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General Review

A Review of the Potential Local Mechanisms by Which Exercise Improves Functional Outcomes in Intermittent Claudication

Amy-Elizabeth Harwood, Thomas Cayton, Romesh Sarvanandan, Risha Lane, and Ian Chetter, Hull, United Kingdom

Background: Intermittent claudication (IC) is a common condition which is associated with significant quality of life limitation. National Institute for Health and Care Excellence guidelines recommend a group-based supervised exercise program 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 IC.

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 nonsupervised exercise program 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 IC. Supervised exercise programs improve walking distances, endothelial and mitochondrial function, muscle strength, and endurance. Furthermore, it leads to a generalized improvement in cardiovascular fitness and overall quality of life.

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

INTRODUCTION

Intermittent claudication (IC)—ischemic 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 occurs at rest, (4) must make the person stop, (5) disappears on a majority of occasions in 10 min or less, and (6) never disappears 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 56 to 309 m before starting an exercise treatment.[11] The data regarding patient recovery

Vascular Department, Hull Royal Infirmary, University of Hull, Hull, UK.

Correspondence to: Amy-Elizabeth Harwood, PhD, Vascular Department, Hull Royal Infirmary, University of Hull, Anlaby Road, Hull HU32JZ, UK; E-mail: Amy.Harwood@hey.nhs.uk

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time is limited; however, it appears that on average patients require 3-min 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 programs have inferior outcomes in comparison with supervised programs in terms of improvements in walking distance, claudication onset, and adherence to treatment. Therefore, National Institute for Health and Care Excellence clinical guideline 147 recommends a group-based supervised exercise program (SEP) as the first-line treatment for patients with IC.[6,14] Consequently, SEPs 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 programs resulting in significant variability between studies. There is a general consensus that exercise programs should be supervised—comprise of intermittent walking to near maximal pain at least 3 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 hemodynamic 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 IC.

METHODS

Search Strategy

All randomized and nonrandomized trials included 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 were undertaking an unsupervised exercise program were excluded. Any intervention that included an exercise program was included and the inclusion was not affected by the duration, length, or time of the program. This review will also consider any differences because of 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 that 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 nonsupervised exercise program or home exercise program was excluded.[20–23] Abstracts identified by the database search were interrogated for relevance by 2 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 studies were duplicates. Of the remaining 70, 47 studies were deemed appropriate for inclusion in the review. Of the specific exercise papers, 40 used aerobic conditioning and 7 studies included some form of resistance training (Fig. 1).

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 IC, specifically in studies involving SEPs 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 fibers (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