Title: Cardiovascular and Musculoskeletal Response to Supervised Exercise in Patients with Intermittent Claudication (PREDICT).

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ABSTRACT

Objective

Intermittent claudication occurs in 20 % of the population over 70 and treatment includes a supervised exercise programme (SEP). Whilst there is evidence demonstrating walking improvements following a SEP there is conflicting data on the physiological changes behind this; therefore this study aimed to explore and identify the potential cardiovascular and musculoskeletal changes with exercise.

Methods

This was a single centre study at a vascular unit in England. Following written informed consent 109 patients were recruited for a SEP, 3 times per week for 12 weeks. Outcome measures included; walking distances, quality of life, cardiorespiratory fitness , flow mediated dilatation and muscle strength and endurance.. For normal data paired sample t-tests were performed to compare baseline data to all time points for significance. For non-parametric data Wilcoxon signed rank tests were performed. Significance was set at $p<0.05$. The association between functional improvement (i.e walking distance at 3 months post SEP and metabolic response and patient characteristics was determined by multivariable regressions.

Results

Maximum walking distance was significantly improved from baseline by 117% at week one, 143% at weeks 4 and 143% at 12 weeks post exercise. Claudication distance was also significantly improved from baseline by 222% at week one, 393% at week 4 and 452% at week 12 (post exercise). Quality of life was significantly improved at all time points in 7/9 and 2/5 domains of the SF36 and VascuQol respectively. Markers of cardiorespiratory fitness were significantly improved at all time points. Flow mediated dilation demonstrated at 50 % improvement but was not statistically significant. Muscle strength and muscle endurance was significantly improved at all time points. Multivariate regression demonstrated that the ventilatory anaerobic threshold and the physical summary score for quality of life were the candidate variables for determining improvements in 12 week walking distance.

Conclusions

Exercise is the recommended first line treatment for all patients diagnosed with claudication. This study aimed to address multiple physiological candidates in this study to identify variables which may be predictive of patient outcome. This study identified that the ventilatory anaerobic threshold, VEVCO2 and physical summary scores from quality of life to be the most predictive candidates. Future studies should endeavour to prioritise these outcomes and assess whether different exercise programme regimes have similar affects.

Introduction

Intermittent claudication ; ischaemic muscle pain precipitated by exertion, is the most common presenting symptom of peripheral arterial disease, affecting 20% of the population over 70[1-3]. It is frequently associated with reductions in walking ability[4, 5], significant deteriorations in quality of life, balance impairment, and diminished physical function and activity levels[6-9].

The Society for Vascular Surgery (USA), European Society for Vascular Surgery (Europe) and the National Institute for Health and Care Excellence (UK) all recommend a group-based supervised exercise programme (SEP) as first line treatment for patients with claudication[5, 10-12]. This treatment is cost effective in improving walking distances and quality of life[13]. However, the mechanism behind improvements following SEP is poorly understood. A systematic review suggested that potentially important physiological changes may include changes in skeletal muscle metabolism, cardiorespiratory function and endothelial (dys)function[14]. Identifying the most important physiological changes would facilitate targeting SEP treatment to further improve outcomes.

The aim therefore of this prospective cohort study was to explore the relationship between changes in clinical outcomes and the potential underlying candidate cardiovascular and musculoskeletal physiological changes associated with SEP in patients with intermittent claudication.

Methods

Study Design

A single centre prospective cohort study was undertaken in a tertiary vascular surgery unit in the United Kingdom. Ethical approvals were granted by the local research ethics committee (Leeds West –15/YH/0089) and the study was conducted in accordance with the Declaration of Helsinki 1975. The study was prospectively registered with clinicaltrials.gov (NCT02641418). All participants provided informed, written consent prior to any study procedures.

Participants

Patients with a newly confirmed diagnosis of claudication were referred to the programme by consultant vascular surgeons from outpatient clinics. The following inclusion criteria were

used: English speaking adults aged over 45; ankle brachial pressure index < 0.9 at rest or at least a 20 mmHg drop with exercise testing; ability to walk unaided, and able to comply with protocol instructions. Exclusion criteria included: inability to provided informed consent; critical limb ischemia (rest pain or tissue loss); active cancer treatment and severe cardiovascular, musculo-skeletal or pulmonary illness precluding SEP participation.

Supervised Exercise Programme

Participants enrolled on a 12-week hospital based SEP. The SEP entailed three exercise classes per week lasting approximately 60 minutes per session, including a 10-minute warm up and a 5-minute cool down period. The design was a circuit of six exercise stations. Specific exercises were performed at each station for two minutes, separated by a two minute walking interval (figure 1). Participants initially completed six stations in the first six weeks, thereafter increasing by one station per week. At the end of the SEP participants were completing 12 stations per exercise class. Participants were required to attend all 36 exercise classes. Attendance was recorded as the number of classes completed.

[INSERT FIGURE ONE HERE]

Outcome Assessments; clinical indicators of lower limb ischaemia, quality of life (QoL) and physiological changes were assessed at baseline and at 1 week, 4 weeks and at 12 weeks after completion of the exercise programme.

Clinical Indicators of Lower limb ischemia): Resting ankle brachial pressure index (ABPI) was recorded using an aneroid sphygmomanometer (Accoson, A C Cossor & Son Ltd, London, UK) and a hand-held ultrasonic 8.2MHz Doppler (Parks Medical Electronics, Aloha, USA). Following this, participants underwent a fixed-load treadmill test (Marquette 2000 treadmill, Marquette Medical Appliance Ltd, Milwaukee, USA) at an incline of 10% and a speed of 2.5 km/hour for a maximum of 20 minutes. If patients could walk for 20 minutes at baseline they were excluded. The distance to onset of claudication pain, the maximum

walking distance (MWD) and post exercise ABPI (within one minute of cessation of the exercise testing) were recorded.

Quality of life: Participants completed both the SF36v2 and the King's College VascuQol questionnaires for the assessment of generic and disease specific QoL. The SF36v2 measures 8 QoL domains (Physical Function, Physical Role, Social Function, Bodily Pain, Emotional Role, Mental Health, Vitality and General Health). Summary scores can also be calculated for physical and mental quality of life

The VascuQol measures the specific effects of peripheral arterial disease on the domains of pain, activities, symptoms, emotion and social activities. Additionally a total VascuQol score is derived. ***Physiological and Musculoskeletal Assessment***

(1) Cardiorespiratory fitness: A symptom-limited ramp-incremental cycle ergometer cardiopulmonary exercise test (MedGraphics Ultima^{TM} CardioO_2, Medical Graphics, St Paul, MN, USA) was performed. Patients were asked to maintain a cycle speed of between 60 – 70 revolutions per minute to maintain consistency. Symptom limited time to volitional fatigue was defined as the point at which the patient could no longer maintain 60 rpm. Continuous heart rate monitoring was performed during the test and recovery phase. The test was terminated early if the patient reported chest pain, chest tightness or severe dyspnoea or if more than 2 mm ST depression was seen in any lead. Gas exchange variables were determined via breath-by-breath analysis with erroneous breaths excluded and averages of 15 seconds were applied. The main variables recorded for each assessment were as follows; peak oxygen consumption (VO_{2peak}) [within the last 15 seconds of exercise], ventilatory anaerobic threshold (VAT), total time to exhaustion and ventilatory equivalents for oxygen (V_E/VO_2) and carbon dioxide (V_E/VCO_2). All variables were calculated automatically with the exception of VAT which was determined by the V-slope method. This is achieved by plotting VCO_2 against VO_2; linear regression

lines are drawn through the upper and lower curve and the point of intersection indicates where VCO_2 increased disproportionately to VO_2 (hence is estimated to be the AT) [15].

(2) Endothelial function: Endothelial function was measured by flow mediated dilatation (FMD) on cardio suite software (Medical Graphics, Gloucestershire, UK). A linear 8 Mhz probe (Toshiba Medical Ultrasound, Toshiba Medical, UK) was used to image a segment of the brachial artery with clear anterior and posterior intimal interfaces between the lumen and the vessel wall, above the antecubital fossa in the longitudinal plane. In addition an automatic inflation cuff was placed above the antecubital fossa. A baseline image during diastole at rest was obtained and arterial diameter measured. After which arterial occlusion was created via cuff inflation to a suprasystolic pressure. The longitudinal image was recorded continuously for two minutes after cuff deflation. FMD was characterised as the change in post stimulus diameter in comparison to the baseline dimeter, for which the following equation was used;

$$\textbf{FMD} = [(\textbf{POBAD} - \textbf{BBAD})/\textbf{BBAD}] \times 100$$

Where POBAD is equal to the post occlusion brachial artery diameter and the BBAD is equal to the baseline brachial artery diameter.

(3) Muscle architecture: Patients lay prone on a medical couch with the knee fully extended and the ankle approximately flexed to 90º. Sagittal B-mode ultrasound scans (Toshiba Medical Ultrasound, Toshiba Medical, UK) of the gastrocnemius belly were conducted with an 8 Mhz linear transducer (Toshiba Medical Ultrasound, Toshiba Medical, UK). Pre-sets were standardized with a frequency of 8 Mhz and a depth of 3cm. To ensure a standard location of the probe on the muscle belly, the distance from the lateral knee to joint to the lateral malleolus was measured. The probe was then placed at one-third of this distance distally from the knee joint space. The muscle thickness, fascicle length and pennation angle were measured in order to analyse the muscle architecture. Muscle

thickness was measured as the distance between the upper and lower aponeuroses. As fascicle length is longer than the probe (i.e. the fascicle extended the field of view on sonography), it was necessary to calculate this parameter using the following equation;

$$FL2 = \frac{h}{\sin \mu'}$$

Where *FL2* is equal to the calculated fascicle length, *h* is the distance between the aponeuroses and μ is the inferior pennation angle. All images were stored and analysed using ImageJ software version 1.46k23 (National Institute of Health, Bethesda, MD).

(4) Muscle strength and endurance: After warmup (using the standard exercise programme warm-up) and demonstration of the lifting technique, familiarisation trials were performed to ensure proper execution of the exercise protocol and limit any learning effects. Patients were seated on the leg press with knees at 90º flexion and the adjustable seat back was positioned so that the patients' femoral lateral epicondyle was aligned with axis of rotation of the machine's lever arm. Patients were then instructed to extend their knee through a full range of motion. The maximum amount of repetition measured for a certain load was used to estimate the 1 repetition maximum based on the following equation [16];

1RM = load/1.0278 – (0.0278*repetitions)

This estimate was then used to determine the load for the actual 1 rep max test test. For the actual 1 rep max testing it was measured using the protocol described by Kraemer and Fry (1995) [17]. Here patients were asked to begin at 90% of the 1 rep max based on the above equation and was increased 2.5 – 5.5% after each successful lift until failure. Resting periods of two minutes in duration were allowed between successive attempts. It was expected that patients would achieve their maximum attempt within 3-4 lifts, with the optimal range between 3-5.

Following adequate rest, patients were seated back on the leg press in the same position as above. Patients were then instructed to extend their knee through their full range of motion as fast as possible at a resistance equal to 40% of their 1 rep max. Patients continued to perform this movement until fatigue, with the total number of repetitions being recorded.

Sample Size

The software package nQuery was used to calculate sample size. With 100 participants and three base independent factors (age, gender, baseline MWD) that are assumed to explain approximately half of the total variance in MWD at 3 months (twelve weeks post exercise completion) in a multivariable regression, there would be a 90% power to detect an additional increase in variability explained by each candidate test predictor of 4.8% at the 5% significance level.

Statistical Analysis

All analyses were conducted in SPSS (version 23, IBM Software, USA) using two-sided significance at the 5% level unless otherwise stated. Baseline data is summarised descriptively (mean and standard deviation) at all time points where normally distributed. If data was non-parametric median and interquartile range was used.

Primary analysis: Clinical and metabolic endpoints are summarised descriptively (mean and standard deviation) at all time points where normally distributed. For normal data paired sample t-tests were performed to compare baseline data to all time points for significance. For non-parametric data Wilcoxon signed rank tests were performed. Significance was set at $p<0.05$.

Secondary analysis: The association between functional improvement in MWD at 3 months (twelve weeks post SEP), metabolic response and patient characteristics was determined by

multivariable regressions. In a base analysis model, MWD at three months (twelve weeks post SEP) was predicted by participants' age, gender and baseline MWD. Correlations between all independent variables were assessed to avoid issues of multicollinearity. Any test variables that significantly predicted MWD as part of the primary analysis were entered into a combined multiple regression.

Results

Patients

Between May 2015 and May 2017, 776 patients were assessed for study inclusion, of which 602 (78%) were eligible to participate according to the pre-specified criteria. 109 (18%) eligible patients consented to participate, and 55 participants completed all classes indicating a compliance rate of 50% (Figure 2). Three participants died during the course of the study, 2 from lung cancer and 1 from pancreatic cancer. Of participants completing the SEP, three were lost to follow up (between weeks four and twelve). Participants' baseline characteristics are presented in table 1.

Walking Improvements:

Patients' maximum walking distance improved significantly compared to baseline at all time points (117%, 143% and 143%). Claudication distance also improved significantly at all time points following SEP (222%, 393% and 452%). There were no significant improvements in resting or exercise ABPI at any time point following exercise (Table 2).

Quality of Life: The SF-36v2 domains of physical function, role physical, bodily pain, general health, mental health and vitality were all significantly improved compared to baseline at all time points. Social function was significantly improved at 1 week but not at 4 and 12 weeks post exercise. Role emotional was significantly improved at weeks 1 and 4 but not at week 12. Overall physical quality of life was significantly improved at all time points

post SEP. The mental summary score was significantly improved at weeks 1 and 4 weeks post exercise completion but not at three months (Table 3).

VascuQol domains of pain, activities, symptom and emotional were significantly improved compared to baseline at all time points. The social domain was significantly improved at week 1 (post exercise) but not at weeks 4 and 12 (post exercise). The VascuQol total score was significantly improved at all time point (Table 3).

Cardiorespiratory Fitness: There were no statistically significant improvements in VO_{2peak} . VAT demonstrated a trend to increase when compared to baseline (Table 4). V_EVCO_2 was significantly improved at all time points when compared to baseline. V_EVO_2 was not significantly improved. Despite a mean increase in the total time on the bike this was not statistically significant, nor was the respiratory exchange ratio or the rating of perceived exertion (table 4).

Endothelial Function

Return to normal arterial diameter was significantly faster one-week post intervention compared to baseline 4.2±2.7 seconds to 3.5±1.8 seconds (p = .05 CI - 3.0,4.1) but this was not sustained at 4 or 12 weeks (post exercise class completion). With regard to baseline arterial diameter, maximum arterial diameter, FMD and reactive hyperaemia (r-wave) these were not significantly different at any time point.

Muscle Architecture

Data from the most symptomatic leg demonstrates that fascicle length in the gastrocnemius lateralis at 12 weeks was significantly different (p = 0.007 CI 18.0, 20.4). Thickness (1 week) (p = .05 CI -17.3, 19.5) and pennation angle (4 week) (p = .04 CI - 17.8, 19.9) in the gastrocnemius medialis were also significantly different. Full data available in supplementary material A.

Muscle Strength and Endurance

Both the 1 rep max and the 40% rep marker of endurance both demonstrated statistically significant improvements at all time points following SEP. Overall there was a mean increase of 26kg in leg strength and a mean increase of 10 repetitions at 40%. This was sustained from one week post SEP to 12 weeks post SEP.

Secondary Analysis Outcomes

Collective Effects of Predictors

Claudication distance, the ventilatory anaerobic threshold and the physical summary score were found to be significant predictors of outcome. Claudication distance demonstrated a significant positive effect indicating that those with higher initial claudication distance were expected to have greater improvements in three month post exercise MWD. . The physical summary score and VAT demonstrated a significant negative effect on three month post exercise MWD. Therefore patients with higher physical summary score and VAT at baseline demonstrated a smaller improvement in MWD (at 12 weeks); or patients who are the least fit have greater improvements following an exercise intervention.

Discussion

SEP for claudication improves clinical outcomes such as time to walking pain and maximum walking distance, however the underlying physiological changes are poorly understood. To our knowledge no single study assessed multiple potential changes in one cohort.

Walking Improvements:

Both the time to pain and the MWD were significant improved at all time points following the exercise programme in line with previous research studies [17, 18]. Furthermore, improvements were sustained up to the three month follow up; indicating that patients continued to progress. This may be due to patients doing their own exercises following completion of the SEP. Indeed, many participants reported that they were still exercising, had joined a gym, or simply walked further on a day-to-day basis at their follow-up visits. Future

studies might consider using pedometers to record daily activity levels to accurately quantify changes in exercise behaviours and highlight patients failing to maintain their activities facilitating further intervention or support.

Quality of life

SEP treatment aims to improve both walking distances and QoL [19-21]. Seven of eight SF36 domains demonstrated a significant improvement at all time points (physical function, role physical, bodily pain, general health, vitality, role emotional and mental health) with social function significantly improved at 1 week post SEP. Additionally the physical and mental summary scores demonstrated a significant improvement at all time points post SEP (with the exception of the mental summary score at three months). This is in keeping with results from previous randomised controlled trials that reported improvements in these scores following an exercise programmes[22-26]. Results from the VascuQol demonstrated significant improvement in pain, activities, symptom and emotional domains at all time points. The social domain score was significantly improved one week post SEP intervention. The total VascuQol score was also significantly improved at all time points.

Cardio-respiratory fitness

A cardiopulmonary exercise test provides an assessment of the integrative response to exercise and involves the measurement of respiratory data[27]. Variables than can be measured include VO_{2peak} (reflects the maximal ability of a person to take in, transport and use oxygen) and the ventilatory anaerobic threshold (the point in time where anaerobic metabolism occurs due to the mismatch between oxygen demand and supply.

This study demonstrated minimal significant improvements in key outcome measures. Only the minute ventilation of carbon dioxide – (V_EVCO_2) was significantly improved at all time points.. The V_EVCO_2 has been demonstrated to be an important marker of mortality in a

number of clinical conditions such as heart failure [28], pulmonary hypertension [29], coronary heart disese [30] and chronic obstructive pulmonary disease [31]. Furthermore V_EVCO_2 has been demonstrated to be superior gas exchange parameters in comparison to the traditionally reported parameters such as VO_{2peak} and VAT [32]. Our results demonstrate that ventilatory efficiency was significantly improved with SEP (i.e. patients had a more efficient lung capacity), and is a unique finding to this study. This highlights the need to further quantify these measures in IC patients to understand the clinical significance. These measures could be prioritised in future studies.

In spite of the lack of significant changes VAT was demonstrated to be important in predicting three month post SEP maximum walking distance when controlling for all other variables. VAT was found to be a suppressor variable for three month post MWD. Therefore it appears that those with higher baseline VAT may have less to gain (in terms of distances as measured by a treadmill walk) in comparison to those with lower VAT; or those patients who are least fit. Speculatively, it is possible that those with low VAT scores have to work at a much higher relative intensity in comparison to their peers but have the most to gain from SEP in terms of physiological response.

Endothelial Function

The vascular endothelium plays a critical role in vascular homeostasis. It regulates vascular tone, coagulation and inflammatory cell adhesion. Endothelial dysfunction occurs in the early development of atherosclerotic lesion and it is a predictor of future events[33]. As it plays an important role in the pathogenesis of atherosclerosis it is a potential mechanism by which exercise may improve function. Brachial artery FMD has been found to be well correlated to peripheral and coronary function and is therefore a good surrogate test to perform[34, 35].The results from this study demonstrated no statistically significant improvements in any of the markers of endothelial function . There was a trend for a mean increase of 50% in FMD

between baseline and week 1, which was maintained at week 4 and week 12 post SEP. However the large standard deviations and low patient numbers most probably account for the non-significance, i.e. type 2 statistical error. Other measures of FMD such as using a device called endoPAT (whereby endothelial function is inferred from finger pulse changes) may have been better tolerated but have high variability and low reliability when compared to brachial FMD occlusion[36]. There is a definitive lack of data surrounding endothelial function in this population and the results from this study demonstrate that there does appear to be an improvement as measured by FMD. However it was not found to be predictive for three month post exercise MWD indicating that it may not be a mechanism of action in improving MWD with SEP. Furthermore there is limited evidence to suggest mild improvements in FMD confer long term health benefits related to a reduction in cardiovascular risk[33].

Muscle Architecture

Changes in lower limb muscle architecture may be responsible for improved walking distances in patients with claudication, with purported changes occurring to fibre type[37] and disease atrophy[38]. This study demonstrated only sporadic significant improvements in muscle architecture (pennation angle, fascicle length and muscle thickness) but no deterioration. It has previously been thought that treadmill-based or walking exercise, which is associated an increase in calpain proteolytic activity, may cause a relative reduction in the skeletal muscle size[39]. However measurements of skeletal muscle mass size following the SEP in this study demonstrated no change. The importance of preserving muscle mass is well documented and is important in balance[40], functional daily activities and overall quality of life [41].

Muscle Strength and Endurance

This study demonstrated a significant improvement in both muscle strength and muscle endurance. Overall, there was a mean increase of 26kg in leg strength and mean number of repetitions from 21 to 32. Clearly this is a dramatic improvement and highlights this as

distinct area of mechanistic focus for future research studies. This study supports those findings by Wang *et al* (2010) following an 8-week course of SEP and supports the notion that SEP provides functional gains, which may lead to improvements in tasks such as rising from chairs, walking and maintaining balance[42]. In turn this could improve likelihood of maintaining physical activity behaviors and a reduction in mortality. In addition resistance training should be added to compliment traditional walking programmes.

Limitations

This study was a single centre prospective observational study at a vascular unit in the UK. Due to the funding and nature of the project patient blinding was not possible. Patients were not informed of the outcome of their tests until the end of their final visit, so as not to influence results. In addition all cardiopulmonary exercise tests were re-analysed by an independent investigator to ensure validity and reliability.

Whilst 109 patients were recruited, many patients dropped out of the exercise programme (including 3 deaths). This means that with 52 participants at week 12, the primary analysis could only detect an additional increase in variability of 8.7%. However, there were no significant differences between those that dropped out and those that completed the exercise programme in terms of gender, age, baseline MWD, exercise test parameters or severity of initial limb ischemia (ABPI)

It is well acknowledged that studies investigating the role of SEP in claudication have substantial attrition rates and low compliance[43]. Finally as the missing data rate was between 40 – 50 % it was not possible to carry out multiple imputation analysis[44].

Finally, exercise interventions are well known to attract motivated individuals who understand clearly the benefits of exercise in general and the nature of the proposed intervention. Those who agreed to participate and complete the exercise are likely to be a

subgroup of claudicants with a higher level of motivation or willingness to change, and more willing to overlook the perceived negatives of attending such a programme (therefore selection bias)[45].

Conclusion

Supervised exercise programmes are the recommended first line treatment for all patients diagnosed with intermittent claudication and there have been several purported physiological changes in the literature that may lead to improvements following a programme. We aimed to address candidates in this study to identify variables which may be predictive of patient outcome. This study identified that the ventilatory anaerobic threshold, VEVCO2 and the physical summary score from the SF36 are the most likely candidates.. Furthermore current vascular guidelines only recommend walking to the point of maximal pain. However, given the results of this study resistance training should be incorporated to compliment traditional walking programmes.

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