Limb-specific and cross-transfer effects of arm-crank exercise training in patients with symptomatic peripheral arterial disease

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Clinical Science Immediate Publication. Published on 23 Apr 2009 as manuscript CS20080688

Limb-Specific and cross-transfer effects of arm-crank exercise training in patients with symptomatic peripheral arterial disease

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Running head: Arm-crank exercise for intermittent claudication

Key Words: Intermittent claudication, upper-limb exercise, near-infrared spectroscopy

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ABSTRACT

Arm-cranking is a useful alternative exercise modality for improving walking performance in patients with intermittent claudication. However, the mechanisms of such an improvement are poorly understood. The main aim of this study was to investigate the effects of arm-crank exercise training on lower-limb oxygen delivery in patients with intermittent claudication. Fifty-seven claudicants (age 70 ± 8 y; mean ± SD) were randomised to an arm-crank exercise group or a non-exercise control group. The exercise group trained twice weekly for 12 weeks. At baseline and 12 weeks, patients completed incremental tests to maximum exercise tolerance on both an arm-crank ergometer and on a treadmill. Respiratory variables were measured breath-by-breath to determine peak oxygen uptake (peak $\dot{V}O_2$) and ventilatory threshold. Near-infrared spectroscopy was used in the treadmill test to determine changes in calf muscle oxygen saturation (StO_2). Patients also completed a square-wave treadmill-walking protocol to determine $\dot{V}O_2$ kinetics. Fifty-one patients completed the study. In the exercise group, higher maximum walking distances (496 ± 250 m to 661 ± 324 m) and peak $\dot{V}O_2$ values (17.2 ± 2.7 $mL \cdot kg^{-1} \cdot min^{-1}$ to 18.2 ± 3.4 $mL \cdot kg^{-1} \cdot min^{-1}$) were recorded in the incremental treadmill test ($P < 0.05$). After training, there was also an increase in time to minimum StO_2 (268 ± 305 s to 410 ± 366 s), a speeding of $\dot{V}O_2$ kinetics (44.7 ± 10.4 s to 41.3 ± 14.4 s), and an increase in sub-maximal StO_2 during treadmill walking ($P < 0.05$). There were no significant changes in the control group. The results suggest that the improvement in walking performance after arm-crank exercise training in claudicants is attributable, at least in part, to improved lower-limb O_2 delivery.

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INTRODUCTION

The main symptom of lower-limb peripheral arterial disease (PAD), intermittent claudication, is prevalent in around 5% of people aged 55-74 years in Western societies [1,2]. Intermittent claudication is a cramp-like leg pain that occurs during walking, when the ability to deliver and utilize oxygen is inadequate to meet the metabolic requirement of the active skeletal muscles [3]. Intermittent claudication reduces walking performance to about 50% of that seen in healthy individuals of a similar age [4], and this impairment can cause a marked reduction in quality of life [5].

Regular walking exercise has consistently been shown to improve walking performance in claudicants [6-8]. However, since walking can be painful, the desire and ability of these patients to perform such activity might be limited. Indeed, in clinical practice, there is evidence that nearly half of patients refrain from regular walking exercise [9]. As upper-limb arterial disease is over 20 times less frequent than lower-limb arterial disease [10], patients are less likely to experience claudication pain during arm exercise. Evidence from our laboratory has shown that arm-crank exercise training is well tolerated by claudicants and can improve walking performance to a similar extent as lower-limb cycle ergometry training [11]. While this improvement seems at least partially attributable to an alteration in exercise pain tolerance [11], the contribution of physiological adaptations remains unclear.

The cross-transfer effect of aerobic exercise training (i.e., increased exercise performance during exercise with the untrained limbs) has generally been explained in terms of central and/or peripheral circulatory adaptations [12-14]. Such changes could enhance oxygen delivery to untrained exercising skeletal muscles and underpin improvements in cardiopulmonary fitness variables (i.e., peak oxygen uptake [peak $\dot{V}O_2$], ventilatory threshold [VT], $\dot{V}O_2$ kinetics) and skeletal muscle oxygenation recorded during exercise. The physiological cross-transfer effects of aerobic exercise training have not previously been investigated in patients with intermittent claudication, and the extent to which physiological adaptations account for the improvement in walking performance after arm-crank exercise training is unknown. Hence, the aim of this study was to test the hypothesis that the improvements in walking performance resulting from arm-crank exercise training are attributable, at least in part, to enhanced lower-limb O_2 delivery.

METHODS

Participants

Fifty seven patients with stable intermittent claudication were recruited from the Sheffield Vascular Institute at the Northern General Hospital, Sheffield, UK. Written informed consent was obtained before patients entered the study. Patients were included if they had Fontaine stage II PAD [15] defined by the following criteria: (a) ≥12 month history of stable intermittent claudication, (b) ambulation during an incremental treadmill test limited by intermittent claudication, and (c) an ankle-brachial pressure index (ABPI) at rest ≤0.90 in their most symptomatic leg. Seven patients meeting the clinical criteria who had an ABPI of >0.9 and showed a clinically important decrease of ≥0.15 after maximal walking exercise [16] were also included in the study. Exclusion criteria included: (a) absence of PAD, (b) inability to obtain an ABPI measurement due to non-compressible vessels, (c) asymptomatic PAD (Fontaine stage I), (d) rest pain due to PAD (Fontaine stage III), (e) exercise tolerance limited by factors other than claudication (e.g., dyspnoea, angina, arthritic pain), (f) history of intermittent claudication <12 months, and (g) re-vascularisation or other major surgery within the previous 12 months. No patients were receiving pharmacological therapy specifically for intermittent claudication (e.g., cilostazol) and no patient changed their medication during the study. This research was carried out in accordance with the

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Declaration of Helsinki of the World Medical Association, and was approved by the North Sheffield Research Ethics Committee.

Assessment procedures and randomization

Patients were fully accustomed with the assessment protocols prior to baseline data collection. Outcome measures were assessed over three separate days at baseline and 12 weeks. Patients were instructed not to perform any vigorous exercise in the 24 hours before an assessment and to abstain from caffeine and nicotine intake for at least 2 hours before an assessment. On day 1, patients underwent a medical examination (including measurement of ABPI) and then performed an incremental arm-crank exercise assessment. On day 2, patients completed an incremental treadmill-walking test. On day 3, patients completed a multiple square-wave transition protocol to allow determination of $\dot{V}O_2$ kinetics.

After completion of the baseline assessments, patients were randomised, using a computer programme (nQuery Advisor 6.0, Statistical Solutions, Ireland), to either an arm-crank exercise group or a non-exercise control group.

Incremental arm-cranking assessment

Patients completed an incremental arm-cranking test to maximum exercise tolerance using an electronically braked cycle ergometer (Lode Excalibur Sport, Netherlands) positioned specifically for arm-cranking. Patients were asked to maintain a cadence of 50 rev·min^{-1}. Following a 2-min warm-up against no resistance (0 W), the work rate was increased by 7 W·min^{-1}. Heart rate was recorded continuously by electrocardiogram (Cardioperfect, Welch Allyn, USA). Perceived exertion (RPE; Borg 6-20 scale) and arm pain (Borg CR-10 scale) [17] were recorded at 1-min intervals. Capillary blood lactate concentration was assessed before and after exercise using a portable lactate analyser (YSI 1500 Sport, Ohio, USA). $\dot{V}O_2$, CO_2 production, minute ventilation, and other respiratory variables were measured and recorded breath-by-breath with an on-line expired gas analysis system (MedGraphics Ultima Cardio$_2$, Minnesota, USA). The system O_2 and CO_2 analysers were calibrated before each test using gases of known concentrations. Inspired and expired volumes were also calibrated using a 3-L syringe. Ventilatory threshold was identified using the *V*-slope method [18] and peak $\dot{V}O_2$ was recorded as the highest value over any 20-s averaged period. At maximum exercise tolerance, the peak levels of all variables were recorded.

Incremental treadmill-walking assessment

Patients performed an incremental treadmill-walking test (3.2 km·h^{-1}, 0% grade with 1% increase every 1 min) to volitional exhaustion, during which pain-free and maximum walking distances were recorded (PWD and MWD, respectively). In our laboratory, the technical errors of measurement (TEM) for these measures are 22% and 6%, respectively. Heart rate, RPE, leg pain, blood lactate concentration, and gas exchange variables were recorded as in the incremental arm-cranking test.

Calf muscle oxygen saturation (StO_2) was recorded at a frequency of 1 Hz at rest and throughout the walking test using continuous-wave near-infrared spectroscopy (NIRS; NIRO-300, Hamamatsu Photonics, Japan). The theory of NIRS has been described in detail elsewhere [19]. Briefly, optodes were placed on the lateral head of the gastrocnemius muscle of the leg with the lowest ABPI. The optodes were housed in an optically dense rubber holder, thus ensuring that the position of the optodes, relative to each other, was fixed and invariant. Source-detector separation was 5 cm. The optode assembly was secured on the skin surface using tape and then covered using Coban band (3M Health Care Inc., USA) to minimize the intrusion of extraneous light and loss of NIR transmitted light.

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The variables assessed by NIRS were StO_2 at absolute (e.g., rest, 1 min, 2 min) and relative (e.g., MWD) time points, and time to minimum StO_2. As the exact contribution from intracellular myoglobin is unclear [20], calf muscle StO_2 changes were used as an index of the balance between O_2 delivery and O_2 utilization; a mismatch being reflected by a drop in StO_2 relative to baseline. Time to minimum StO_2 is thought of as a key measure of calf muscle StO_2 in claudicants because it is strongly correlated with treadmill walking performance in these patients [21,22]. This suggests that patients with faster deoxygenation of the active musculature (probably because of an inadequate blood supply) have greater impairment in exercise performance. This variable has a TEM of 8% in our laboratory. Typical StO_2 profiles are depicted in Figure 1.

Pulmonary $\dot{V}O_2$ kinetics

For the determination of pulmonary $\dot{V}O_2$ kinetics, patients completed a multiple square-wave transition protocol. This involved measurement of breath-by-breath $\dot{V}O_2$ at rest (2 min standing) and during 6 min constant, moderate-intensity walking. The treadmill speed and gradient were individually set to elicit either 90% VT recorded in the incremental walking test or an RPE of 'light' to 'somewhat hard' if the VT could not be detected (n = 22). The majority of patients completed the exercise transitions at a speed of 3.2 $km \cdot h^{-1}$ and gradient of 0 to 2%, and the same settings were used in the post-intervention assessment. The transition from standing to walking was performed three times with a 20-min seated rest period between each exercise transition [23]. $\dot{V}O_2$ data were processed for each exercise transition using a custom-made software programme, described previously [23]. Data points were removed if greater than 3 standard deviations from the local, 5-point mean [24], interpolated to 1-s intervals, and then ensemble-averaged to yield a single response for each patient. The first 30 s of data after the onset of exercise (i.e., phase 1) were deleted. Phase 2 kinetics were then assessed by non-linear least squares regression to a mono-exponential model incorporating a time delay. The exponential model was of the form:

$$Y(t) = Y(b) + A \cdot [1 - e^{-(t\text{-}TD)/\tau}]$$

where Y represents pulmonary $\dot{V}O_2$ at any time (t), b represents baseline, A is the amplitude of the increase in Y above the baseline value, τ is the time constant defined as the duration of time through which Y increases to a value equivalent to 63% of A, and TD is the time delay. The τ has a TEM of 18%. The mean response time (MRT) was also calculated as:

$$MRT = TD + \tau$$

The τ and MRT were used to estimate exercise training-induced changes in muscle $\dot{V}O_2$ kinetics.

Exercise programme

Patients allocated to the exercise group were invited to complete twice weekly supervised arm-crank exercise training sessions for 12 weeks. This exercise regimen has previously been shown to improve walking performance in claudicants and is a manageable training program for these patients [11]. The intensity of exercise was set at 60 to 70% of the peak work rate achieved in the initial incremental arm-crank assessment. During each session, patients trained in cycles of 2 min exercise at a crank rate of 50 $rev \cdot min^{-1}$, followed by 2 min rest, for a total exercise time of 20 min in a 40-minute session. Heart rate, RPE, and arm pain were monitored throughout each session and the intensity of exercise was individually

progressed over the 12 weeks to maintain RPE around 13 ('somewhat-hard'). Patients allocated to the control group were informed of the benefits of an active lifestyle but did not undertake any supervised exercise. Physical activity levels were assessed in both groups at baseline and 12 weeks using the peripheral arterial disease-physical activity recall (PAD-PAR) questionnaire [25].

Statistical analysis

Outcome measures were first tested for normal distribution using the Kolmogorov-Smirnov goodness of fit test. On the whole, as the data were not normally distributed, they were first normalised using logarithmic transformation before further analysis. Differences in group characteristics were assessed using independent *t*-tests and Chi-squared tests. Mixed-model (group by time) analyses of covariance were used to detect changes in outcome measures between groups, with baseline data used as the covariate [26]. Paired-samples *t*-tests were used to interpret significant interaction effects. Bivariate relationships were assessed using the Pearson product-moment correlation coefficient (*r*). Only data for patients who completed the study were included in the analyses and no adjustments were made for multiple comparisons. Statistical significance was set at $P \leq 0.05$ and data are expressed as mean ± SD unless otherwise stated.

RESULTS

Of the 57 patients recruited, two withdrew from the exercise group, and four withdrew from the control group: one patient died of a heart attack; one developed a lower-limb ulcer that required revascularisation surgery; one was identified as having a popliteal artery aneurysm; and, one returned to full-time employment. The remaining two patients cited lack of time as their reason for withdrawal. Demographic data for the two study groups are shown in Table 1. Compliance to the supervised exercise program was 97%. Training intensity increased from 39 ± 8 W at baseline to 55 ± 11 W at 12 weeks ($P < 0.001$). There were no injuries or adverse events resulting from the exercise training or physiological assessments.

Resting ABPI and body mass were unchanged from baseline in both groups ($P = 0.124$ and $P = 0.770$, respectively). At baseline, resting ABPI (lowest value between both legs) was 0.68 ± 0.13 vs. 0.69 ± 0.12 in the exercise and control groups, respectively. At 12 weeks, resting ABPI was 0.71 ± 0.13 vs. 0.69 ± 0.15 in the exercise and control groups, respectively. Free-living physical activity levels (as assessed by the PAD-PAR) were well-balanced between the groups and remained unchanged during the study period (data not presented; $P \geq 0.211$).

The incremental arm-cranking test data are shown in Table 2. Peak values of work rate, $\dot{V}O_2$, and blood lactate were increased in the exercise group compared to the control group. However, there were no changes in either group for VT, or peak values of heart rate, RPE and arm pain.

The incremental treadmill test data are shown in Table 3 and Figure 2. Pain-free and maximum walking distances were increased in the exercise group compared to the control group. At 12 weeks, PWD and MWD had improved in the exercise group by 53% and 33%, respectively, in comparison to only slight increases in the controls. Peak values of $\dot{V}O_2$ and blood lactate, and time to minimum StO_2 were also increased in the exercise group compared to the control group. In addition, StO_2 was increased at 30, 60, 120, and 180 s after exercise training (Figure 2A), with the change in MWD correlated with the change in StO_2 at 180 s ($r = 0.524$, $P = 0.009$) and 240 s ($r = 0.486$, $P = 0.022$). There were no changes in either group for minimum StO_2, end-exercise StO_2, VT, or peak values of heart rate, RPE, and leg pain.

The pulmonary $\dot{V}O_2$ kinetics data are shown in Table 4. The τ and MRT were reduced in the exercise group compared to the control group. In the exercise group, the change in τ was not correlated with the change in MWD (r = -0.164, P = 0.423). There were no changes in either group for the time delay, resting heart rate and $\dot{V}O_2$, or steady state heart rate and $\dot{V}O_2$.

DISCUSSION

The main purpose of this study was to investigate functional and physiological cross-transfer effects of arm-crank exercise training in patients with intermittent claudication. In accordance with previous evidence [11,27], arm-crank training improved walking performance in this patient group. A novel finding was that the improvement in walking performance was accompanied by enhanced lower-limb O_2 delivery during standardised walking exercise, as evidenced by increases in time to minimum StO_2 and sub-maximal StO_2, and a speeding of $\dot{V}O_2$ kinetics. These findings, together with the excellent training adherence, low drop-out rate, and lack of exercise-related complications, lend further support to the use of supervised arm-crank exercise training for improving walking performance and cardiopulmonary fitness in patients with intermittent claudication.

The baseline cardiopulmonary fitness values recorded in the exercise tests were similar to those reported previously for claudicants [11,23], and lower than those reported for healthy males of a similar age [14,23]. The improvements in upper-limb peak work rate (27%) and peak $\dot{V}O_2$ (13%) in the exercise group were also similar to those observed previously after arm-crank exercise training in a similar group of claudicants (22% and 13%, respectively) [11]. These improvements occurred in the absence of changes in the peak values of heart rate, RPE, and pain, suggesting that patients exerted themselves to a similar degree at both assessment time points.

The relative improvements in PWD and MWD in the exercise group of 53% and 33%, respectively, were consistent with those reported previously following arm-crank exercise training (51% and 29%, respectively) [11]. Again, these improvements occurred in the absence of changes in the peak values of heart rate, RPE, and pain. The improvements in walking distances are about half the magnitude of those reported following 12-weeks treadmill-walking exercise training in claudicants (100% and 66%, respectively) [28] and these differences are probably explained by the absence of lower-limb skeletal muscle metabolic adaptations after upper-limb training. Nevertheless, an improvement in MWD of 33% on an incremental walking test is considered clinically meaningful [29], and in our patient cohort equated to an absolute improvement of 165 m.

The results from this study support our hypothesis that there is an improvement in lower-limb O_2 delivery after arm-crank exercise training in claudicants. For example, the exercise group exhibited improvements in peak $\dot{V}O_2$ during the incremental treadmill test and $\dot{V}O_2$ kinetics in the square-wave treadmill test. Broadly speaking, these adaptations can occur in response to enhanced O_2 delivery, enhanced O_2 utilization through localised metabolic adaptations, or a combination of the two. The latter two explanations seem unlikely in this situation because changes in O_2 utilization are generally confined to exercise-trained skeletal muscles [13]. Conversely, an enhancement of O_2 delivery is conceivable, given that reductions in lower-limb muscle blood flow during exercise [30], endothelial vasodilator function [31], and capillary-to-fibre ratio [32] could all contribute to an O_2 delivery limitation in claudicants and are potentially modifiable by exercise training.

The speeding of $\dot{V}O_2$ kinetics is particularly interesting since this is the first study to our knowledge that has reported cross-transfer effects of exercise training on this fitness measure. The training-induced change in τ (mean = 3.4 s) was small compared to previous

Clinical Science Immediate Publication. Published on 23 Apr 2009 as manuscript CS20080688

exercise training studies involving other participant groups. For example, Berger *et al.* [33] reported an 8 to 10 s improvement in τ following 6 weeks of lower-limb exercise training in previously sedentary young adults. This discrepancy is probably largely explained by the fact that cross-transfer effects of exercise training on cardiopulmonary fitness are smaller than limb-specific effects [13,14]. The functional significance of this finding is questionable given that the change in τ did not correlate with the change in MWD (r = -0.164, P = 0.423). However, this lack of association might be explained by the small sample size (n = 27) or the small magnitude of change in τ. Alternatively, a speeding of $\dot{V}O_2$ kinetics via improvements in lower-limb O_2 utilization (not apparent after upper-limb exercise training) might be necessary to have a meaningful impact upon walking performance in this patient group. In any case, although a speeding of $\dot{V}O_2$ kinetics after arm-crank exercise training is a favourable physiological adaptation (and evidence of improved lower-limb O_2 delivery), the magnitude of change was probably too small to be of large functional significance.

The increase in time to minimum StO_2 and sub-maximal StO_2 during the incremental walk also support a post-training enhancement of lower-limb O_2 delivery. Calf muscle StO_2 reflects the balance between O_2 delivery and O_2 utilization and time to minimum StO_2 and sub-maximal StO_2 measures are positively associated with walking performance in patients with intermittent claudication [21,22]. The StO_2 data suggest that after training, patients had a better matching of O_2 delivery to O_2 utilization in the early stages of the incremental walking test, which likely facilitated improved walking distances by delaying the accumulation of metabolites that cause claudication pain. The moderate correlations between the change in MWD and the change in StO_2 at 180 s (r = 0.524) and 240 s (r = 0.486) suggest that the improvement in MWD after arm-crank exercise training is explained, at least in part, by an improvement in lower-limb O_2 delivery.

The underpinning mechanisms of improved lower-limb O_2 delivery during walking exercise remain unclear. Various central and peripheral circulatory adaptations might be implicated, including an increased stroke volume (cardiac output) and blood volume, and enhanced blood rheology and endothelial function [34]. Indeed, the former seems particularly likely given that arm-crank exercise training has previously been shown to improve stroke volume in young women [12], and to reduce the heart rate response to sub-maximal lower-limb exercise in patients with intermittent claudication, indicative of an increase in stroke volume [27]. The latter effect was also observed in the early stages of the incremental treadmill test in the present study (data not presented). An enhancement of lower-limb endothelial vasodilator function is also feasible given that aerobic exercise training has been shown to improve conduit vessel endothelial function in untrained limbs in patients with intermittent claudication [35]. Furthermore, recent evidence suggests that arm-crank exercise training can have an attenuating effect on systemic inflammatory markers [36], which could have a positive impact on systemic endothelial function [37,38]. Further research is needed to clarify the existence and contribution of these potential mechanisms.

Limitations

There are a number of limitations to the present study. Firstly, the precise mechanisms underpinning the observed changes in walking performance and other physiological variables cannot be determined from our data. Further research is needed to establish the role of enhanced stroke volume and lower-limb endothelial function in the improved walking distances observed after a program of arm-crank exercise training. Secondly, methodological limitations need to be considered. Regarding the NIRS data, the exact contribution of intracellular myoglobin to the StO_2 signal is unclear [20], and subcutaneous fat thickness changes might have influenced our findings. However, the latter is unlikely because no relationship exists between calf skinfold and calf muscle StO_2 during walking in

claudicants [39] and significant changes in lower-limb sub-cutaneous fat after a short-term (12-week) program of upper-limb aerobic exercise are unlikely. A limitation of our approach to assessing $\dot{V}O_2$ kinetics was the failure to include a second term in the model that describes the 'slow component'. We could not model a slow component of $\dot{V}O_2$ because the breath-by-breath noise was too high relative to the amplitude of the response. Failure to account for presence of a slow component could lead to an overestimate of τ but inspection of the $\dot{V}O_2$-time plots and steady state $\dot{V}O_2$ values for the constant-intensity walking tests suggests that a slow component was not present for the majority of assessments. Finally, the results of the study are only applicable to male claudicants with mild-to-moderate symptomatology and thus might not be generalizable to females or patients with different symptomatology.

In conclusion, **t**he results of this study support the hypothesis that the improvement in walking performance resulting from arm-crank exercise training in patients with intermittent claudication is explained, at least in part, by enhanced lower-limb O_2 delivery. These findings lend further support to the use of alternative exercise rehabilitation strategies (that avoid the ischemic pain associated with lower-limb exercise) for improving walking performance and cardiopulmonary fitness in this patient group.

ACKNOWLEDGEMENTS

We would like to thank the technical support staff from the Centre for Sport and Exercise Science at Sheffield Hallam University for their support during the assessment sessions. We are also grateful to Dr Timothy Bauer for providing the $\dot{V}O_2$ kinetics averaging and interpolation software. Finally, we are indebted to the patients for their effort and enthusiastic cooperation throughout the study.

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FIGURE LEGENDS

Figure 1. Calf muscle oxygen saturation (StO_2) data before and during the incremental treadmill walking test for patients with different walking abilities. The vertical line represents exercise onset and the arrows indicate the time at which StO_2 reaches its minimum value. Note that, for the poorer performer, there is a very early mismatch between O_2 delivery and O_2 utilization, reflected by a sharp drop in StO_2 relative to baseline, and a low time to minimum StO_2 value. MWD indicates maximum walking distance.

Figure 2. Calf muscle oxygen saturation (StO_2) data during the incremental treadmill walking test for A, the exercise training group, and B, the control group. Min indicates minimum StO_2 value. *Significantly different from baseline value ($P < 0.05$).

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Table 1. Demographics of the two study groups

Variable	Exercise group (n = 27)	Control group (n = 24)	P
Age (y)	69 ± 9	70 ± 8	0.671[a]
Body mass (kg)	81.3 ± 11.5	78.4 ± 13.9	0.431[a]
Stature (cm)	174.2 ± 4.4	173.8 ± 5.7	0.779[a]
Body mass index ($kg \cdot m^{-2}$)	26.8 ± 3.5	25.9 ± 3.7	0.377[a]
Resting ABPI	0.68 ± 0.13	0.69 ± 0.12	0.875[a]
Duration of claudication (months)	76 ± 92	44 ± 40	0.114[a]
Previous MI (%)	19	21	1.000[b]
Previous stroke (%)	11	17	0.693[b]
Diabetes (%)	30	8	0.081[b]
Smoking status (%)			0.545[b]
Current	26	33	
Previous	56	58	
Never	18	9	
Medication (%)			
Beta-blockers	15	17	0.578[b]
ACE-inhibitors	33	21	0.248[b]
Calcium blockers	19	25	0.412[b]
Diuretics	19	33	0.187[b]
Nitrates	26	25	0.598[b]
Anti-platelet agents	96	96	1.000[b]
Statins	100	92	0.216[b]

ABPI indicates ankle-brachial pressure index; MI, myocardial infarction. ABPI data represent the lowest value of both legs.

[a]Independent t-test; [b]Chi-squared test.

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Table 2. Incremental arm-crank exercise test data

	Exercise group		Control group		*P**
	Baseline	12 weeks	Baseline	12 weeks	
Peak work rate (W)	62 ± 14	79 ± 16†	61 ± 18	60 ± 18	<0.001
Peak $\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	13.5 ± 2.7	15.2 ± 2.7†	13.3 ± 3.5	13.1 ± 4.4	0.006
Ventilatory threshold ($mL \cdot kg^{-1} \cdot min^{-1}$)	8.4 ± 1.2	8.3 ± 1.4	8.8 ± 1.5	8.0 ± 1.9	0.108
Peak heart rate ($beats \cdot min^{-1}$)	121 ± 23	124 ± 21	116 ± 24	121 ± 21	0.986
Peak blood lactate (mM)	3.94 ± 1.34	4.34 ± 1.12†	3.63 ± 1.28	3.63 ± 0.94	0.011
Peak RPE	15.7 ± 2.4	15.0 ± 2.6	15.6 ± 2.3	15.3 ± 3.0	0.614
Peak arm pain	4.1 ± 2.6	4.8 ± 2.6	3.8 ± 2.8	4.5 ± 2.5	0.972

$\dot{V}O_2$ indicates oxygen consumption; RPE, rating of perceived exertion.

*Significance of the group by time interaction term.

†Significantly difference from baseline value ($P < 0.05$).

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Table 3. Incremental walking test data

	Exercise group		Control group		*P**
	Baseline	12 weeks	Baseline	12 weeks	
Pain-free walking distance (m)	147 ± 125	225 ± 167†	177 ± 160	192 ± 195	0.035
Maximum walking distance (m)	496 ± 250	661 ± 324†	600 ± 300	626 ± 266	0.011
Peak $\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	17.2 ± 2.7	18.2 ± 3.4†	18.6 ± 5.1	18.0 ± 4.9	0.038
Ventilatory threshold ($mL \cdot kg^{-1} \cdot min^{-1}$)	11.6 ± 2.3	12.0 ± 2.3	12.5 ± 2.6	11.5 ± 1.7	0.172
Peak heart rate ($beats \cdot min^{-1}$)	115 ± 22	117 ± 20	116 ± 19	112 ± 20	0.100
Peak blood lactate (mM)	2.80 ± 1.24	3.14 ± 1.25†	2.66 ± 0.99	2.51 ± 1.02	0.048
Peak RPE	16.0 ± 2.7	15.0 ± 3.0	16.5 ± 2.7	16.2 ± 2.8	0.210
Peak leg pain	6.7 ± 3.0	5.7 ± 2.2	6.7 ± 2.3	6.1 ± 2.9	0.405
Time to minimum StO_2 (s)	268 ± 305	410 ± 366†	497 ± 372	466 ± 379	<0.001
End-exercise StO_2 (%)	39 ± 14	39 ± 15	38 ± 10	35 ± 11	0.186

$\dot{V}O_2$ indicates oxygen consumption; RPE, rating of perceived exertion; StO_2, calf muscle oxygen saturation.

*Significance of the group by time interaction term.

†Significantly difference from baseline value ($P < 0.05$).

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Table 4. Pulmonary $\dot{V}O_2$ kinetics data

	Exercise group		Control group		*P**
	Baseline	12 weeks	Baseline	12 weeks	
Resting $\dot{V}O_2$ ($mL \cdot min^{-1}$)	307 ± 43	320 ± 41	292 ± 46	277 ± 38	0.190
End-exercise $\dot{V}O_2$ ($mL \cdot min^{-1}$)	915 ± 138	923 ± 179	855 ± 168	822 ± 145	0.144
Time delay (s)	13.1 ± 5.9	12.4 ± 6.6	12.9 ± 4.9	11.0 ± 3.5	0.304
τ (s)	44.7 ± 10.4	41.3 ± 14.4†	44.2 ± 11.1	45.3 ± 11.2	0.032
MRT (s)	57.8 ± 11.6	53.7 ± 13.5†	57.1 ± 9.4	56.3 ± 10.5	0.048
Resting heart rate ($beats \cdot min^{-1}$)	75 ± 13	73 ± 14	71 ± 14	66 ± 10	0.146
Steady state heart rate ($beats \cdot min^{-1}$)	95 ± 20	91 ± 17	87 ± 15	86 ± 15	0.942

$\dot{V}O_2$ indicates oxygen uptake; τ, phase 2 time constant; MRT, mean response time.

*Significance of the group by time interaction term.

†Significantly difference from baseline value ($P < 0.05$).

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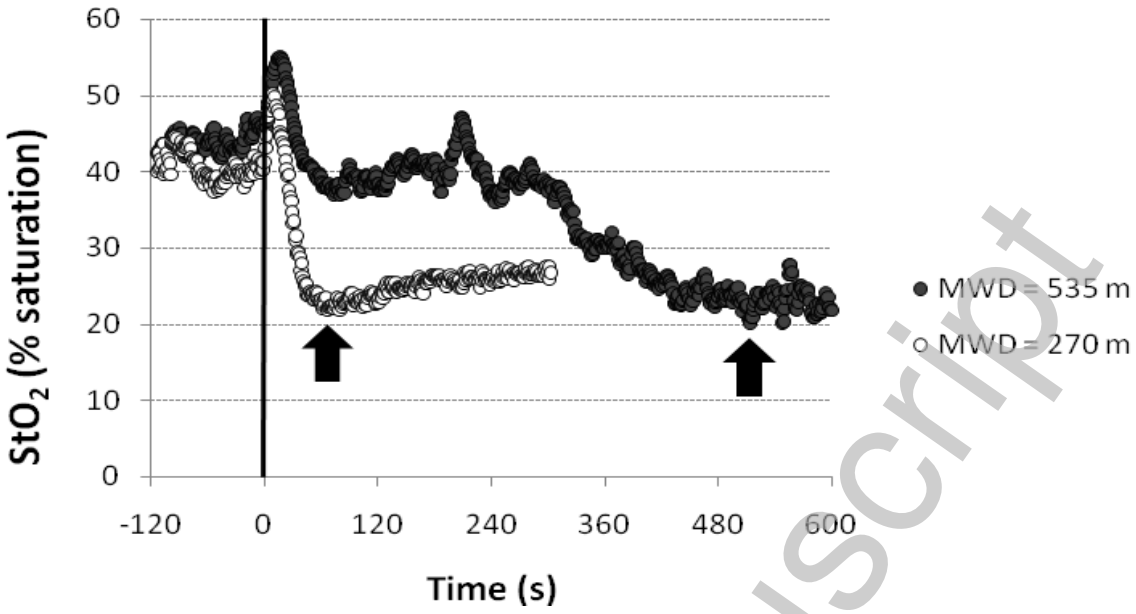

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