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Short-term effects of cycle and treadmill training on exercise tolerance in peripheral arterial disease

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## **Abstract**

To explore the efficacy of cycle training in the treatment of intermittent claudication, the present study compared performance and physiological effects of cycle training with more conventional treadmill walking training in a group of claudicants. Forty two individuals with peripheral arterial disease and intermittent claudication (24 males, 18 females) were stratified on the basis of gender and the presence or absence of type 2 diabetes mellitus, and then randomized to a treadmill (n = 13), cycle (n = 15) or control group (n = 14). Treadmill and cycle groups trained three times a week for six weeks; whereas the control group did not train over this period. Maximal and pain-free exercise times were measured on graded treadmill and cycle tests before and after training. Treadmill training significantly improved maximal and pain-free treadmill walking times; but it did not improve cycle performance. Cycle training significantly improved maximal cycle time; but it did not improve treadmill performance. However, there was evidence of a stronger cross-transfer effect between the training modes for patients who reported a common limiting symptom during cycling and walking at baseline. There was also considerable variation in the training response to cycling, and a subgroup of 'responsive' patients in the cycle group improved their walking performance by more than the average response observed in the treadmill group. These findings suggest that cycle exercise is not effective in improving walking performance in all claudicants; but that it might be an effective alternative to walking in those claudicants who exhibit similar limiting symptoms during both types of exercise.

Key words: intermittent claudication, training, cycle, treadmill, walking performance, O<sub>2</sub> uptake, muscle pain

# Journal of Vascular Surgery

Review Response Form

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Response to Reviewers

Reviewer #4:

**Comment 1.** On page 8 of the revised manuscript under Treadmill test the authors state that the MWT improved significantly in the treadmill group but not in the other two groups (Figure 1). A non-savvy reader might well imply from this that the mean change from baseline was greater in the treadmill group than in the other two groups, since only in the treadmill group was there a significant change from baseline. In order to avoid possible misinterpretation and/or confusion, it would be important to tell the reader if the groups in fact differed on the change from baseline (i.e., is the change in the treadmill group larger than the change in the other groups). The authors have clarified this issue for the next outcome described, depicted in Figure 2.

**Response to 1:** We have added a sentence in the Results to clarify this (see Redline version).

**Comment 2.** On page 9 of the revised manuscript, the same idea as expressed in #1 (reporting whether the groups differ or not on change from baseline) applies to the Cycle test depicted in Figure 3.

**Response to 2:** We have added a sentence in the Results to clarify this (see Redline version).

## Introduction

Improving exercise tolerance through supervised exercise training is an important part of the medical treatment of peripheral arterial disease (PAD) and intermittent claudication<sup>1</sup>. Walking has been the centerpiece of exercise training programs for several decades<sup>2,3</sup>, and it is seen to be essential to maximizing the efficacy of training<sup>4</sup>. However, adherence to walking can be difficult for many claudicants, as reflected in relatively high drop-out rates (~ 30 %) from walking programs<sup>5</sup>, and so alternative modes of exercise might be useful for patients and treating clinicians alike. The effectiveness of other modes of exercise such as cycling<sup>6</sup>, resistance training<sup>2,7</sup>, stairclimbing<sup>8</sup> and arm cranking<sup>6</sup> has been studied to a very limited extent. Of these alternative modes of exercise, cycling is attractive to study because it is a relatively easy, inexpensive and safe exercise to perform, as well as being a popular mode of transport in some countries. We have previously shown that the acute physiological responses to stationary cycling and treadmill walking are similar in patients with intermittent claudication<sup>9</sup>. Although a recent study demonstrated some degree of benefit of cycling in the treatment of intermittent claudication<sup>6</sup>, the relative effectiveness of cycle training compared with the more conventional treadmill training is not known. Establishing this is important to the on-going process of improving the prescription of exercise for intermittent claudication.

Therefore, the aim of this preliminary study was to compare the short-term effects of cycle training with treadmill training on exercise tolerance and physiological responses to exercise in claudicants. Performance and physiological responses to both treadmill and cycle exercise were assessed so that the cross-transfer of effects between exercise modes could also be determined.

## **Methods**

*Subject Identification* Six-hundred-and-ninety-four (694) patients with a reduced ABI (<0.9) in at least one limb and a documented history (>1 year) of intermittent claudication were consecutively identified over a 17-month recruitment period. The majority of excluded patients either lived further than 50 km from the research venue (n=340), did not respond to the invitation to participate (n=88), or were unable to participate for personal reasons (n=87). Other patients deemed ineligible included those with reduced cardiac function or unstable angina (n=60), rest pain (n=18), recently undergoing surgery or suffering a cardiovascular event (n=20), or other medical conditions for which exercise testing and training were contraindicated (n=9).

*Subject Screening and Randomization* Seventy-two (72) patients were identified for further screening and gave their written informed consent to the experimental procedures, which were approved by the ethics committees of the Royal Brisbane and Women's Hospital, University of Queensland and Queensland University of Technology. The pre-study screening test was a maximal graded treadmill test with ECG monitoring and pre- and post-exercise ABI measurements. Five (5) patients were subsequently excluded as they were not primarily limited by claudication, and a further 19 patients were excluded because of ischemic ECG changes or uncontrolled hypertension. The remaining 43 patients were limited by claudication, displayed a positive ABI response during walking (20 mmHg fall), and were therefore eligible for randomization.

Subjects were stratified on the basis of gender and the presence or absence of diabetes to ensure an equal distribution of these characteristics among the experimental groups. That is, prior to randomization, subjects were allocated to the following groups: male diabetic, male non-diabetic, female diabetic, or female non-diabetic. From these stratified groups, subjects were then randomized to a control group, a cycle-training group or a treadmill-training group using a closed envelope system. One subject randomized to the treadmill-training group withdrew from the study after one week of training due to work-related commitments and their baseline data has been omitted. Body weight and heart rate were measured during quiet rest prior to baseline treadmill testing and across the training period. Baseline characteristics of the 42 claudicants are shown in Table 1.

*Sample Size and Statistical Power*                      Maximal walking performance was the variable about which estimates of the current sample sizes ( $n \geq 13$  per group) and statistical power ( $> 0.8$ ) were made. In designing this study we were most concerned with detecting changes in walking performance in response to treadmill training (compared with control) and cycle training (compared with control). Coefficients of variation for walking performance (c.v. = 13-17%), as well as the mean pre-training values, were used to determine the SD for repeated measurements on each variable. The minimum “meaningful change” or difference in the variable is equal to two SDs, a very conservative value that served as the difference score used to compute the corresponding effect sizes. All SDs of difference scores were imputed from averaged SDs of the pre-and post-training scores found in another study (20) that used similar measurement techniques to those adopted in the present study.

*Control Group*                      Claudicants in the control group were managed with standard cardiovascular risk factor modification – that is, the appropriate antiplatelet therapy and

pharmacotherapy for hypertension, diabetes and hypercholesterolaemia, as well as advice concerning the need to stop smoking and to exercise.

*Training Groups* Claudicants in the treadmill and cycle training groups were also managed with standard cardiovascular risk factor modification, and in addition they performed three supervised training sessions per week for a period of six weeks. Prior to and following each exercise session patients completed a series of lower limb stretching exercises. During each training session subjects completed ten, two minute bouts of exercise with each bout separated by two minutes of rest. Walking was performed on motorized treadmills (Cybex Trotter 700T, Medway MA, U.S.A) and cycling was performed on cycle ergometers (Monark 818 Ergomedic, Vansbro, Sweden). The training intensity corresponded to a workload that elicited an O<sub>2</sub> uptake (VO<sub>2</sub>) equal to 80% of the peak value measured during the baseline incremental walking or cycling tests (see below). This workload was maintained during the first three weeks of the supervised program, and then during the last three weeks of training the intensity was increased to the maximum workload achieved during the baseline test. Heart rate (Polar Electro-Oy Fitwatch, Kempele, Finland) and patient-reported claudication pain severity (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = maximal pain) were recorded during each exercise bout.

*Exercise Testing* Prior to training, all subjects performed an initial screening treadmill test to maximum claudication and then a separate session aimed at familiarizing them with all the testing apparatus and exercise protocols. Subjects then completed at least two maximal graded treadmill walking tests and two maximal graded cycle tests over a 2-week period on four separate days. A third test was conducted if there was more than a 25 % difference in maximum walking



or cycling times between the two tests<sup>10</sup>. Performance on the last tests was taken to represent a pre-training score.

The maximal graded walking test was performed on a motorized treadmill (TrackMaster TMX425CP, Newton, KS, U.S.A.) at a constant speed of 2.7 km h<sup>-1</sup>. The treadmill gradient was initially set at 0 % for the first five minutes of the test, and then it was increased by 2 % every three minutes until the patient failed to sustain the task. Pain-free walking time (PFWT) and the total time spent walking (MWT) were recorded. This protocol is similar to that used previously by our group<sup>9,11-14</sup> and it is highly reproducible (average CV = 6 %) when conducted after the above-mentioned familiarization routine<sup>12</sup>. The maximal graded cycle test was performed on an electrically-braked cycle ergometer (Lode Rehcort; Groningen, Netherlands) at a cadence of 60 rpm. For the first five minutes of the test the power output was set at 30 W, and thereafter it was increased 10 W each three minutes until the subject failed to sustain the required cadence. Pain-free cycling time (PFCT) and the total time spent cycling (MCT) were recorded. During the treadmill and cycle tests, the site(s) and severity of claudication pain were assessed every 60 s and at the end of exercise using the above-mentioned scale.

*Physiological Measurements* Heart rate and pulmonary gas exchange data were collected for two minutes prior to exercise, while the subject was seated on the cycle ergometer or standing on the treadmill, as well as throughout exercise. Heart rate (HR) was measured with a portable heart rate monitor (Polar Electro-Oy S610i, Kempe, Finland) and averaged over 5 second intervals. Minute ventilation ( $V_E$ ), rates of oxygen consumption ( $V_{O_2}$ ) and carbon dioxide production ( $V_{CO_2}$ ), and the respiratory exchange ratio ( $RER = V_{CO_2}/V_{O_2}$ ) were measured breath-by-breath and averaged over 5 second intervals (MedGraphics CPX/D, St. Paul, MN, USA).

Submaximal gas exchange and HR values were calculated by averaging all 5 second samples recorded between the 3 min 50 s and 4 min 45 s period of the first five minute exercise stage. To identify peak values, HR and gas exchange variables were averaged over 15 second intervals and the highest values recorded during the last three minutes of the exercise test were taken as the peak values.

The ankle:brachial index (ABI) was measured in triplicate at rest, after 20 minutes of lying quietly, in both legs. The ABI was calculated using the systolic pressures of the highest brachial artery and the higher of the dorsalis pedis or posterior tibial arteries, all of which were measured within 60 s of each other. An average resting ABI value for each leg was obtained by averaging the closest two of the triplicate measures. Immediately after each exercise test, subjects returned to a supine position and single measures of the ABI of both legs were repeated at 2, 4, 6, 8 and 10 minutes after exercise. The same ankle and brachial arteries used to calculate the resting ABI were measured during the post-exercise period. Ankle pressures were measured with an inflatable cuff and Doppler ultrasound (8MHz) probe (Huntleigh Muti-Doplex, Cardiff, UK), while brachial pressures were measured with an automated pressure monitor (Criticon Dinamap, Florida, U.S.A).

*Data Analysis* Only values of variables measured during the last of the baseline tests and the post-training test were included in the analyses described below. Difference or “change” scores were calculated as the difference between the last of the baseline test and post-training test scores. All variables were tested for normality using the Kolmogorov-Smirnov test, and in cases where variables were not normally distributed a log transformation was applied to stabilise the variance. A three-way repeated measures ANOVA (group; time; limb) was used to detect main

effects and interactions for the resting and post-exercise (minimum value) ABI data. A two-way repeated measures ANOVA was used to detect main effects (group; time) and interactions (group  $\times$  time) for all other variables. The “time” factor represents the six week period of training.

Tukey’s HD test was used to locate differences when an ANOVA result was significant.

Relationships between variables were established using Pearson’s correlation coefficient. All data are expressed as means and SDs, unless otherwise stated. Statistical significance was set at  $p < 0.05$ .

## **Results**

Baseline characteristics of the 42 claudicants are shown in Table 1. Patients were well matched for age, gender and cardiovascular risk factors. Smoking behaviour and exercise behaviour beyond the supervised training were assessed using validated questions from the National Health Survey of Australia, and these behaviours remained unchanged in all subjects over the training period. The lack of change in exercise behaviour was also confirmed by the results of physical activity surveys that were conducted before and after training. There were no significant main effects (group or time) or interaction for resting and post-exercise (treadmill and cycle) ABI responses, body weight and resting heart rate, suggesting these responses were similar before and after training.

*Training Sessions* Subjects in the treadmill group completed a similar number of training sessions ( $16.6 \pm 1.0$ ) as those in the cycle group ( $17.0 \pm 2.3$ ), and the total dose of training was not different ( $p = 0.37$ ) between the treadmill ( $22.04 \pm 7.64$  MET hours) and cycle ( $22.64 \pm 7.46$  MET hours) groups. The heart rate at the end of each exercise bout, averaged over all training sessions, was not significantly different ( $p = 0.14$ ; student's t-test) between the cycle ( $114 \pm 24$  bpm) and treadmill ( $101 \pm 19$  bpm) groups. Mean claudication pain severity during cycle training was  $1.2 \pm 0.7$  in the high ABI leg and  $1.6 \pm 0.5$  in the low ABI leg. These values were significantly higher ( $p < 0.05$ ) than the corresponding values observed in the treadmill training group ( $0.5 \pm 0.5$  and  $1.0 \pm 0.7$  respectively).

*Treadmill Test* Prior to training, neither MWT nor PFWT were different between the groups. As shown in Figure 1, MWT was significantly increased by training in the treadmill group (mean difference = 240 s; 95% CI = 119-361 s); whereas there was no significant change in the cycle (mean difference = 48 s; 95% CI = -22 – 117 s) or control group (mean difference = -10 s; 95 % CI = -90 – 71 s). This change in MWT in the treadmill group was significantly greater than the corresponding change scores in the cycle and control groups. This outcome was not affected by the exclusion of two claudicants who reported only mild or moderate claudication during the baseline treadmill test. As shown in Figure 2, following training PFWT was significantly longer ( $p < 0.05$ ) for the treadmill group ( $412 \pm 251$  s to  $607 \pm 369$  s) compared with the cycle group ( $271 \pm 289$  s to  $263 \pm 293$  s) and control group ( $391 \pm 411$  s to  $446 \pm 442$  s). Submaximal and peak responses for heart rate and pulmonary gas exchange measurements during the treadmill test are shown in Tables 2 and 3. In the treadmill group, the change in MWT was significantly correlated ( $p < 0.05$ ) with the training-induced changes in submaximal heart rate (r

= -0.55; 95 % CI = -0.73 - -0.30), peak  $\text{VO}_2$  ( $\text{l min}^{-1}$ ;  $r = 0.77$ ; 95 % CI = 0.61 – 0.87) and peak heart rate ( $r = 0.54$ ; 95 % CI = 0.28 – 0.72).

*Cycle Test* Prior to training, MCT was not significantly different between the groups. As shown in Figure 3, MCT was significantly increased by training in the cycle group (mean difference = 93 s; 95 % CI = 45 - 132 s); whereas it was not significantly increased in the treadmill (mean difference = 45 s; 95 % CI = -60 – 149 s) or control group (mean difference = 51 s; 95 % CI = -128 – 230 s) (Figure 3). This change in MCT in the cycle group was significantly greater than the corresponding change score in the control group; but it was not significantly greater than the change score in the treadmill group. PFCT was also not different between the groups prior to training, and it was not affected by training (Figure 4). Submaximal and peak responses for heart rate and pulmonary gas exchange measurements during the cycle test are shown in Tables 2 and 3. In the cycle group, the change in MCT was not correlated with any other measured variable.

*Cycle versus Walking Tests* For the entire cohort, pain-free times on the baseline cycle and treadmill tests were not significantly different from each other; whereas MWT was significantly larger than MCT (difference =  $179 \pm 410$  s; 95 % CI = 51.7 to 307.5 s; paired t-test). Submaximal and peak physiological responses were not different between these cycle and treadmill tests. Many of these responses to both baseline exercise tests (i.e. cycle vs treadmill) were significantly correlated ( $p < 0.05$ ), particularly maximal exercise time ( $r = 0.75$ ), peak  $\text{VO}_2$  ( $r = 0.91$ ) and ABI two minutes after exercise in the low ABI ( $r = 0.83$ ) and high ABI leg ( $r = 0.86$ ). The number of symptoms that limited performance and were cited as the reasons for

stopping exercise varied between one and three and there was some variation in the anatomical location of these symptoms. For the baseline treadmill test these symptoms included pain in the calves ( $n = 33$ ), gluteals ( $n = 8$ ), hamstrings ( $n = 7$ ) and quadriceps ( $n = 4$ ), as well as dyspnoea ( $n = 5$ ) and 'general fatigue' ( $n = 5$ ). Six subjects did not cite claudication as a main reason for stopping treadmill exercise, although four of them reported maximal claudication pain during the test. Two of these subjects reported only mild or moderate pain during baseline treadmill testing, despite the fact that they reported maximal claudication during the screening treadmill test prior to baseline testing. For the baseline cycle test the limiting symptoms included pain in the quadriceps ( $n = 27$ ), calves ( $n = 16$ ), hamstrings ( $n = 2$ ) and gluteals ( $n = 1$ ), as well as dyspnoea ( $n = 8$ ) and general fatigue ( $n = 4$ ). Five subjects did not cite claudication as a main reason for stopping cycle exercise, and two of them did not experience claudication during the test. Half of the subjects ( $n = 21$ ) shared at least one similar limiting symptom between the baseline cycle and treadmill tests.

Treadmill training had a significantly larger effect ( $p < 0.05$ ) on MWT ( $240 \pm 178$  s) than cycle training had on MCT ( $93 \pm 98$  s). Training pain level in the low ABI limb tended to be correlated ( $p = 0.06$ ) with the effect of treadmill training on MWT ( $r = -0.54$ ;  $n = 13$ ; 95 % CI =  $-0.84 - 0.02$ ); but it was not correlated ( $r = -0.2$ ) with the effect of cycle training on MCT. In all trained subjects, training pain level in the low ABI limb was inversely correlated to the specific effect of training on maximal exercise time ( $r = -0.53$ ;  $n = 28$ ; 95 % CI =  $-0.75 - -0.20$ ). With respect to the effects of training on cycle and treadmill performance in all trained subjects ( $n = 28$ ), there were no significant correlations between the changes in maximal cycling and treadmill times ( $r = 0.01 - 0.27$ ). However, there was a significant correlation between the training-induced changes in

maximal cycle and treadmill times in those subjects who reported at least one limiting symptom that was in the same anatomical location during treadmill and cycle exercise before training (Fig. 5A); but there was no correlation in those who reported limiting symptoms in a different anatomical location during treadmill and cycle exercise (Fig. 5B). Age was also significantly correlated with the effect of cycle training on MWT ( $r = 0.62$ ;  $p < 0.05$ ).

*Responders versus Non-responders* For each subject who trained, a positive response to training occurred if the effect of training on maximal exercise time exceeded the difference between the last two baseline tests (i.e. MWT for treadmill group; MCT for cycle group). According to this criterion, 11 out of the 13 subjects in the treadmill group and 8 out of the 15 subjects in the cycle group responded positively to training. A similar analysis in the control group (i.e. post-pre scores versus baseline variation) revealed three responders for MWT and one responder for MCT. Comparisons of baseline characteristics, baseline performances and training variables between responders ( $n = 19$ ) and non-responders ( $n = 9$ ) were performed. Only training pain severity in the low ABI leg was significantly different ( $p < 0.05$ ) between the responders ( $1.1 \pm 0.7$ ) and non-responders ( $1.8 \pm 0.6$ ).

## **Discussion**

Optimising the exercise program for claudicants depends on knowing the effects of the various dimensions of training, such as intensity, duration and mode. A metaanalysis of training studies performed up until the mid-1990s suggested that an optimal exercise program aimed at improving walking performance should use walking as the mode of exercise<sup>4</sup>. This suggestion, however, was based on studies that did not systematically compare the effects of alternative

modes of exercise with walking. The present study is the first to contrast cycle with treadmill training, controlling for all other major dimensions of training, and it is one of only eight randomized controlled exercise trials to have studied more than 40 patients. Six weeks of treadmill training improved graded walking performance by, on average, 25 %. In contrast, cycle training did not improve graded walking performance, despite the finding that it significantly improved graded cycle performance. In addition, although treadmill training improved walking performance, it failed to increase cycle performance. These preliminary findings suggest that the training effects induced by cycling or walking are specific to the mode of exercise used during training and that there is no “cross-training” benefit.

In the treatment of walking intolerance, the efficacy of alternative modes of exercise requires that there is a significant transfer of physiological adaptation to walking. The findings of our study suggest that this is generally not the case for cycling, despite the strong associations between cycling and walking performance before and after training ( $r = 0.72 - 0.75$ ). Claudication in the calf and quadriceps muscles were the most frequently cited symptoms during treadmill walking and cycling respectively. It is perhaps this difference in the location of claudication between the two modes of exercise that has led some to suggest that cycling would not be beneficial to PAD patients who most frequently claudicate in the calf<sup>15</sup>. However, the number of limiting symptoms during both modes of exercise varied between one and three (see Results), and 50 % of the subjects reported a similar limiting symptom during cycling and treadmill exercise. Among the two groups of claudicants that trained ( $n = 28$ ) and who had a similar limiting symptom between cycling and walking ( $n = 12$ ), evidence of a cross-training effect was observed in the form of a significant association between the training effects on maximum walking and cycle times (Figure 5). Seven of these claudicants were in the cycle group, and five of them improved their maximum



walking time (mean increase = 35 %) beyond the baseline variation in this measurement and by more than the mean response seen in the treadmill group. These data suggest that the similarity of symptoms between cycling and walking might help determine the effect of cycle training on walking performance. However, age was also positively related to the effect of cycle training on maximum walking time, and so we cannot exclude the possibility that age affects the responsiveness to training. Further research is clearly required to explore if the similarity of symptoms between exercise modes and/or age influences the performance benefit obtained from cycle training.

A novel finding of the present study was the larger effect of treadmill training on maximal walking time compared with the effect of cycle training on maximal cycle time. This larger, specific effect of treadmill training (mean increase = 24 vs 10 %) could not be attributed to differences in any of the measured baseline characteristics (Table 1) or other dimensions of training, which were similar between the training programs. Excluding nonresponders from analyses had little effect on this difference in training effect. In contrast, levels of training pain in both limbs were significantly higher in the cycle than the treadmill group, and training pain level in the low ABI limb was inversely related to the specific effect of training on maximal exercise time. These data raise the possibility that the smaller training response to cycling might be related to the significantly higher pain levels reported by the cycle group. Moreover, they suggest that in response to both forms of training a greater improvement in exercise tolerance occurred in those subjects who experienced lower and mild levels of claudication pain during the training sessions. This conflicts with the suggestion that an optimal training program for claudicants consists of exercise to near-maximal pain<sup>4</sup>. Further study of this link between training pain and

physiological adaptation to training is required because the present data suggest that high levels of claudication pain might not be optimal.

Although a number of studies have examined the training effects of cycling combined with other forms of exercise, only one other study has tested the effects of cycle training alone <sup>6</sup>. That study reported that walking performance was improved significantly by cycle training. In trying to explain how this effect differs from that observed in the present study, several factors need to be considered. First, it is unlikely that the training stimulus was relatively lower in the present study because the training program was modeled on that used by Walker et al. <sup>6</sup> and training was performed more frequently (3 vs 2 sessions per week). Moreover, the increase in cycle performance and peak VO<sub>2</sub> demonstrates that it provided a significant physiological stimulus. Second, our familiarization routine of several baseline testing sessions <sup>9,11-14,16</sup> might help reduce the confounding influence that task learning and lowered anxiety makes to the so-called training responses, and it is not clear what familiarisation was provided in the other study <sup>6</sup>. Third, in contrast to the treadmill testing of one patient at a time, these investigators used an indoor shuttle walk test where ‘more than one patient’ was tested simultaneously. All but one of the 24 subjects in their cycle training group appeared to improve their maximum walking distance, and this relatively homogenous response raises the question as to the psychological influence of training and performing tests together on an individual’s walking performance after training. Fourth, one subject in their study appeared to improve their performance by more than 1000 %, and while this wouldn’t affect the significance of the group effect it would greatly inflate the average size of the effect reported (i.e. 50 %). Fifth, the symptoms that limited walking performance were not reported in this study, and the heart rates measured during exercise (~160 bpm) far exceed the maximal heart rates of 110-120 bpm observed in the present and other studies <sup>2,9,20</sup>. This raises

the possibility that cardiac dysfunction and symptoms other than claudication contributed more to exercise limitations than was the case in the present study.

Over several decades there has been considerable interest in the physiological mechanisms that underpin the training effect on exercise tolerance in PAD<sup>3,17,18</sup>; yet despite this and the large number of factors suggested to be involved in the training response this problem is not well understood<sup>19</sup>. An improvement in performance might be underpinned by an improvement in exercise time in the absence and/or presence of pain, as well as the physiological responses associated with these two phases of exercise. In the present study, pain-free time during the treadmill test was improved significantly by treadmill training, and this improvement explained more than 80 % of the increase in maximal time on this test. In contrast, cycle training had no significant effect on pain-free time during the cycle test and, thus, made very little contribution to the increase in maximal cycle time. Thus, the specific effect of training differs markedly between cycling and walking: the improvement in maximal performance induced by both modes of training is linked mainly to a delay in the onset of pain for walking, and an extension of the time spent exercising with pain for cycling. This novel finding raises the possibility that the physiological adaptations to training also differ between cycling and walking.

In the present study, we used a graded exercise protocol with an initial stage of 5 min duration that enables physiological responses to reach a steady-state in most patients<sup>12,13,16</sup>. For treadmill exercise, there was a tendency towards a significant interactive effect on submaximal  $\text{VO}_2$  (group-by-test:  $p = 0.07$ ), where  $\text{VO}_2$  was lowered by training in the treadmill, but not cycle, group. These data are consistent with the above-mentioned effects of treadmill training on pain-free time during treadmill walking, demonstrating a link between increased time without pain and

a lowered  $O_2$  cost of exercise during this mode of exercise. These findings are similar to those observed after the same<sup>6,20</sup> or longer periods of training<sup>2,5,20</sup>, where  $VO_2$  and blood lactate concentration during treadmill exercise were reduced by treadmill training. However, neither of these studies nor the present study shed light on how the oxygen cost of exercise was lowered; but it might relate to improved walking technique, recruitment of a smaller number of motor units and/or recruitment of less economical type II muscle fibres<sup>11</sup>. In contrast to the submaximal  $VO_2$  response, peak  $VO_2$  was not significantly increased during treadmill exercise by treadmill training, a finding consistent with the only other training study of the same duration to have made these measurements<sup>20</sup>. However, peak  $VO_2$  during cycle exercise was significantly increased by cycle training. This suggests that the improvement in cycle performance in the cycle group, which was underpinned by an increase in the time spent exercising with pain, was linked to increases in the peak rates of  $O_2$  delivery to, and/or  $O_2$  consumption by, working muscles.

Some limitations of this study should be considered. Although the sample size of this study compares favourably with other randomized controlled exercise training studies, small effects might go undetected and a type II error might have occurred. This probably applies most to the effect of cycle training given that it increased walking performance by an average of ~5 % more than the effect observed in the control group. Whether or not such an effect on a graded test translates into a clinically relevant effect in the life of a patient is difficult to determine at present. The study was powered to detect larger differences (~10 %) in graded treadmill performance than were observed for the control group; but given the natural variation in exercise performance as measured in our hands (CV~5-10 %), improvements less than this are of questionable significance, from a physiological and clinical perspective. Given the number of comparisons made in this study and the fact that we did not adjust the level of significance accordingly, we

acknowledge that we might have committed a type I error for any of the significant effects or correlations we observed . The duration of the study was restricted to 6 weeks, and given that longer training programs will elicit larger increases in performance, it is possible that the present study underestimates the training benefit that might be obtained with cycling. However, the duration of the training program studied here is consistent with the trend in some countries, such as Australia and the U.S., of providing relatively short periods of supervised intervention that are then followed by longer periods of home-based intervention and allied health support.

In conclusion, this is the first study to compare the effect on walking performance induced by cycle or treadmill training in PAD patients with claudication. On average, cycle training over a six week period did not significantly improve walking performance. There was, however, considerable variation in the response to cycle training, with five out of the 15 claudicants in the cycle group improving their walking performance. This responsiveness to training might be influenced by age, the severity of muscle pain during training and/or the similarity of symptoms between cycling and walking. These preliminary findings deserve further study before cycle training is abandoned as a potential exercise prescription for selected patients with claudication.

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## Figure Captions

Figure 1. Maximum walking times before and after training for patients in the treadmill, cycle and control groups. Figure shows individual walking times (—) and mean values (●). \* Indicates a significant change in MWT from pre-training to post-training in the treadmill group.

Figure 2. Pain-free walking times before and after training for patients in the treadmill, cycle and control groups. Figure shows individual walking times (—) and mean values (●). † a significant main effect where the treadmill group was greater than the cycle group. ‡ a significant main effect where post-training values were greater than pre-training values.

Figure 3. Maximum cycling times before and after training for patients in the treadmill, cycle and control groups. Figure shows individual walking times (—) and mean values (●). \* a significant effect of training on MCT in the cycle group.

Figure 4. Pain-free cycling time before and after training for patients in the treadmill, cycle and control groups. Figure shows individual walking times (—) and mean values (●).

Figure 5. The relationship between the training-induced changes in maximal treadmill and cycle times in claudicants who reported at least one exercise-limiting symptom that was in the same anatomical location (A) or exercise-limiting symptoms that were in a different anatomical location (B) during baseline treadmill and cycle tests.



## Introduction

Improving exercise tolerance through supervised exercise training is an important part of the medical treatment of peripheral arterial disease (PAD) and intermittent claudication<sup>1</sup>. Walking has been the centerpiece of exercise training programs for several decades<sup>2,3</sup>, and it is seen to be essential to maximizing the efficacy of training<sup>4</sup>. However, adherence to walking can be difficult for many claudicants, as reflected in relatively high drop-out rates (~ 30 %) from walking programs<sup>5</sup>, and so alternative modes of exercise might be useful for patients and treating clinicians alike. The effectiveness of other modes of exercise such as cycling<sup>6</sup>, resistance training<sup>2,7</sup>, stairclimbing<sup>8</sup> and arm cranking<sup>6</sup> has been studied to a very limited extent. Of these alternative modes of exercise, cycling is attractive to study because it is a relatively easy, inexpensive and safe exercise to perform, as well as being a popular mode of transport in some countries. We have previously shown that the acute physiological responses to stationary cycling and treadmill walking are similar in patients with intermittent claudication<sup>9</sup>. Although a recent study demonstrated some degree of benefit of cycling in the treatment of intermittent claudication<sup>6</sup>, the relative effectiveness of cycle training compared with the more conventional treadmill training is not known. Establishing this is important to the on-going process of improving the prescription of exercise for intermittent claudication.

Therefore, the aim of this preliminary study was to compare the short-term effects of cycle training with treadmill training on exercise tolerance and physiological responses to exercise in claudicants. Performance and physiological responses to both treadmill and cycle exercise were assessed so that the cross-transfer of effects between exercise modes could also be determined.

## **Methods**

*Subject Identification* Six-hundred-and-ninety-four (694) patients with a reduced ABI (<0.9) in at least one limb and a documented history (>1 year) of intermittent claudication were consecutively identified over a 17-month recruitment period. The majority of excluded patients either lived further than 50 km from the research venue (n=340), did not respond to the invitation to participate (n=88), or were unable to participate for personal reasons (n=87). Other patients deemed ineligible included those with reduced cardiac function or unstable angina (n=60), rest pain (n=18), recently undergoing surgery or suffering a cardiovascular event (n=20), or other medical conditions for which exercise testing and training were contraindicated (n=9).

*Subject Screening and Randomization* Seventy-two (72) patients were identified for further screening and gave their written informed consent to the experimental procedures, which were approved by the ethics committees of the Royal Brisbane and Women's Hospital, University of Queensland and Queensland University of Technology. The pre-study screening test was a maximal graded treadmill test with ECG monitoring and pre- and post-exercise ABI measurements. Five (5) patients were subsequently excluded as they were not primarily limited by claudication, and a further 19 patients were excluded because of ischemic ECG changes or uncontrolled hypertension. The remaining 43 patients were limited by claudication, displayed a positive ABI response during walking (20 mmHg fall), and were therefore eligible for randomization.

Subjects were stratified on the basis of gender and the presence or absence of diabetes to ensure an equal distribution of these characteristics among the experimental groups. That is, prior to randomization, subjects were allocated to the following groups: male diabetic, male non-diabetic, female diabetic, or female non-diabetic. From these stratified groups, subjects were then randomized to a control group, a cycle-training group or a treadmill-training group using a closed envelope system. One subject randomized to the treadmill-training group withdrew from the study after one week of training due to work-related commitments and their baseline data has been omitted. Body weight and heart rate were measured during quiet rest prior to baseline treadmill testing and across the training period. Baseline characteristics of the 42 claudicants are shown in Table 1.

*Sample Size and Statistical Power*                      Maximal walking performance was the variable about which estimates of the current sample sizes ( $n \geq 13$  per group) and statistical power ( $> 0.8$ ) were made. In designing this study we were most concerned with detecting changes in walking performance in response to treadmill training (compared with control) and cycle training (compared with control). Coefficients of variation for walking performance (c.v. = 13-17%), as well as the mean pre-training values, were used to determine the SD for repeated measurements on each variable. The minimum “meaningful change” or difference in the variable is equal to two SDs, a very conservative value that served as the difference score used to compute the corresponding effect sizes. All SDs of difference scores were imputed from averaged SDs of the pre-and post-training scores found in another study (20) that used similar measurement techniques to those adopted in the present study.

*Control Group*                      Claudicants in the control group were managed with standard cardiovascular risk factor modification – that is, the appropriate antiplatelet therapy and

pharmacotherapy for hypertension, diabetes and hypercholesterolaemia, as well as advice concerning the need to stop smoking and to exercise.

*Training Groups* Claudicants in the treadmill and cycle training groups were also managed with standard cardiovascular risk factor modification, and in addition they performed three supervised training sessions per week for a period of six weeks. Prior to and following each exercise session patients completed a series of lower limb stretching exercises. During each training session subjects completed ten, two minute bouts of exercise with each bout separated by two minutes of rest. Walking was performed on motorized treadmills (Cybex Trotter 700T, Medway MA, U.S.A) and cycling was performed on cycle ergometers (Monark 818 Ergomedic, Vansbro, Sweden). The training intensity corresponded to a workload that elicited an O<sub>2</sub> uptake (VO<sub>2</sub>) equal to 80% of the peak value measured during the baseline incremental walking or cycling tests (see below). This workload was maintained during the first three weeks of the supervised program, and then during the last three weeks of training the intensity was increased to the maximum workload achieved during the baseline test. Heart rate (Polar Electro-Oy Fitwatch, Kempele, Finland) and patient-reported claudication pain severity (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = maximal pain) were recorded during each exercise bout.

*Exercise Testing* Prior to training, all subjects performed an initial screening treadmill test to maximum claudication and then a separate session aimed at familiarizing them with all the testing apparatus and exercise protocols. Subjects then completed at least two maximal graded treadmill walking tests and two maximal graded cycle tests over a 2-week period on four separate days. A third test was conducted if there was more than a 25 % difference in maximum walking

or cycling times between the two tests<sup>10</sup>. Performance on the last tests was taken to represent a pre-training score.

The maximal graded walking test was performed on a motorized treadmill (TrackMaster TMX425CP, Newton, KS, U.S.A.) at a constant speed of 2.7 km h<sup>-1</sup>. The treadmill gradient was initially set at 0 % for the first five minutes of the test, and then it was increased by 2 % every three minutes until the patient failed to sustain the task. Pain-free walking time (PFWT) and the total time spent walking (MWT) were recorded. This protocol is similar to that used previously by our group<sup>9,11-14</sup> and it is highly reproducible (average CV = 6 %) when conducted after the above-mentioned familiarization routine<sup>12</sup>. The maximal graded cycle test was performed on an electrically-braked cycle ergometer (Lode Rehcort; Groningen, Netherlands) at a cadence of 60 rpm. For the first five minutes of the test the power output was set at 30 W, and thereafter it was increased 10 W each three minutes until the subject failed to sustain the required cadence. Pain-free cycling time (PFCT) and the total time spent cycling (MCT) were recorded. During the treadmill and cycle tests, the site(s) and severity of claudication pain were assessed every 60 s and at the end of exercise using the above-mentioned scale.

*Physiological Measurements* Heart rate and pulmonary gas exchange data were collected for two minutes prior to exercise, while the subject was seated on the cycle ergometer or standing on the treadmill, as well as throughout exercise. Heart rate (HR) was measured with a portable heart rate monitor (Polar Electro-Oy S610i, Kempe, Finland) and averaged over 5 second intervals. Minute ventilation ( $V_E$ ), rates of oxygen consumption ( $V_{O_2}$ ) and carbon dioxide production ( $V_{CO_2}$ ), and the respiratory exchange ratio ( $RER = V_{CO_2}/V_{O_2}$ ) were measured breath-by-breath and averaged over 5 second intervals (MedGraphics CPX/D, St. Paul, MN, USA).

Submaximal gas exchange and HR values were calculated by averaging all 5 second samples recorded between the 3 min 50 s and 4 min 45 s period of the first five minute exercise stage. To identify peak values, HR and gas exchange variables were averaged over 15 second intervals and the highest values recorded during the last three minutes of the exercise test were taken as the peak values.

The ankle:brachial index (ABI) was measured in triplicate at rest, after 20 minutes of lying quietly, in both legs. The ABI was calculated using the systolic pressures of the highest brachial artery and the higher of the dorsalis pedis or posterior tibial arteries, all of which were measured within 60 s of each other. An average resting ABI value for each leg was obtained by averaging the closest two of the triplicate measures. Immediately after each exercise test, subjects returned to a supine position and single measures of the ABI of both legs were repeated at 2, 4, 6, 8 and 10 minutes after exercise. The same ankle and brachial arteries used to calculate the resting ABI were measured during the post-exercise period. Ankle pressures were measured with an inflatable cuff and Doppler ultrasound (8MHz) probe (Huntleigh Muti-Doplex, Cardiff, UK), while brachial pressures were measured with an automated pressure monitor (Criticon Dinamap, Florida, U.S.A).

*Data Analysis* Only values of variables measured during the last of the baseline tests and the post-training test were included in the analyses described below. Difference or “change” scores were calculated as the difference between the last of the baseline test and post-training test scores. All variables were tested for normality using the Kolmogorov-Smirnov test, and in cases where variables were not normally distributed a log transformation was applied to stabilise the variance. A three-way repeated measures ANOVA (group; time; limb) was used to detect main

effects and interactions for the resting and post-exercise (minimum value) ABI data. A two-way repeated measures ANOVA was used to detect main effects (group; time) and interactions (group  $\times$  time) for all other variables. The “time” factor represents the six week period of training.

Tukey’s HD test was used to locate differences when an ANOVA result was significant.

Relationships between variables were established using Pearson’s correlation coefficient. All data are expressed as means and SDs, unless otherwise stated. Statistical significance was set at  $p < 0.05$ .

## **Results**

Baseline characteristics of the 42 claudicants are shown in Table 1. Patients were well matched for age, gender and cardiovascular risk factors. Smoking behaviour and exercise behaviour beyond the supervised training were assessed using validated questions from the National Health Survey of Australia, and these behaviours remained unchanged in all subjects over the training period. The lack of change in exercise behaviour was also confirmed by the results of physical activity surveys that were conducted before and after training. There were no significant main effects (group or time) or interaction for resting and post-exercise (treadmill and cycle) ABI responses, body weight and resting heart rate, suggesting these responses were similar before and after training.

*Training Sessions* Subjects in the treadmill group completed a similar number of training sessions ( $16.6 \pm 1.0$ ) as those in the cycle group ( $17.0 \pm 2.3$ ), and the total dose of training was not different ( $p = 0.37$ ) between the treadmill ( $22.04 \pm 7.64$  MET hours) and cycle ( $22.64 \pm 7.46$  MET hours) groups. The heart rate at the end of each exercise bout, averaged over all training sessions, was not significantly different ( $p = 0.14$ ; student's t-test) between the cycle ( $114 \pm 24$  bpm) and treadmill ( $101 \pm 19$  bpm) groups. Mean claudication pain severity during cycle training was  $1.2 \pm 0.7$  in the high ABI leg and  $1.6 \pm 0.5$  in the low ABI leg. These values were significantly higher ( $p < 0.05$ ) than the corresponding values observed in the treadmill training group ( $0.5 \pm 0.5$  and  $1.0 \pm 0.7$  respectively).

*Treadmill Test* Prior to training, neither MWT nor PFWT were different between the groups. As shown in Figure 1, MWT was significantly increased by training in the treadmill group (mean difference = 240 s; 95% CI = 119-361 s); whereas there was no significant change in the cycle (mean difference = 48 s; 95% CI = -22 – 117 s) or control group (mean difference = -10 s; 95 % CI = -90 – 71 s). This change in MWT in the treadmill group was significantly greater than the corresponding change scores in the cycle and control groups. This outcome was not affected by the exclusion of two claudicants who reported only mild or moderate claudication during the baseline treadmill test. As shown in Figure 2, following training PFWT was significantly longer ( $p < 0.05$ ) for the treadmill group ( $412 \pm 251$  s to  $607 \pm 369$  s) compared with the cycle group ( $271 \pm 289$  s to  $263 \pm 293$  s) and control group ( $391 \pm 411$  s to  $446 \pm 442$  s). Submaximal and peak responses for heart rate and pulmonary gas exchange measurements during the treadmill test are shown in Tables 2 and 3. In the treadmill group, the change in MWT was significantly correlated ( $p < 0.05$ ) with the training-induced changes in submaximal heart rate (r



= - 0.55; 95 % CI = -0.73 - -0.30), peak  $\text{VO}_2$  ( $\text{l min}^{-1}$ ;  $r = 0.77$ ; 95 % CI = 0.61 – 0.87) and peak heart rate ( $r = 0.54$ ; 95 % CI = 0.28 – 0.72).

*Cycle Test*                      Prior to training, MCT was not significantly different between the groups. As shown in Figure 3, MCT was significantly increased by training in the cycle group (mean difference = 93 s; 95 % CI = 45 - 132 s); whereas it was not significantly increased in the treadmill (mean difference = 45 s; 95 % CI = -60 – 149 s) or control group (mean difference = 51 s; 95 % CI = -128 – 230 s) (Figure 3). This change in MCT in the cycle group was significantly greater than the corresponding change score in the control group; but it was not significantly greater than the change score in the treadmill group. PFCT was also not different between the groups prior to training, and it was not affected by training (Figure 4). Submaximal and peak responses for heart rate and pulmonary gas exchange measurements during the cycle test are shown in Tables 2 and 3. In the cycle group, the change in MCT was not correlated with any other measured variable.

*Cycle versus Walking Tests*                      For the entire cohort, pain-free times on the baseline cycle and treadmill tests were not significantly different from each other; whereas MWT was significantly larger than MCT (difference =  $179 \pm 410$  s; 95 % CI = 51.7 to 307.5 s; paired t-test). Submaximal and peak physiological responses were not different between these cycle and treadmill tests. Many of these responses to both baseline exercise tests (i.e. cycle vs treadmill) were significantly correlated ( $p < 0.05$ ), particularly maximal exercise time ( $r = 0.75$ ), peak  $\text{VO}_2$  ( $r = 0.91$ ) and ABI two minutes after exercise in the low ABI ( $r = 0.83$ ) and high ABI leg ( $r = 0.86$ ). The number of symptoms that limited performance and were cited as the reasons for

stopping exercise varied between one and three and there was some variation in the anatomical location of these symptoms. For the baseline treadmill test these symptoms included pain in the calves ( $n = 33$ ), gluteals ( $n = 8$ ), hamstrings ( $n = 7$ ) and quadriceps ( $n = 4$ ), as well as dyspnoea ( $n = 5$ ) and 'general fatigue' ( $n = 5$ ). Six subjects did not cite claudication as a main reason for stopping treadmill exercise, although four of them reported maximal claudication pain during the test. Two of these subjects reported only mild or moderate pain during baseline treadmill testing, despite the fact that they reported maximal claudication during the screening treadmill test prior to baseline testing. For the baseline cycle test the limiting symptoms included pain in the quadriceps ( $n = 27$ ), calves ( $n = 16$ ), hamstrings ( $n = 2$ ) and gluteals ( $n = 1$ ), as well as dyspnoea ( $n = 8$ ) and general fatigue ( $n = 4$ ). Five subjects did not cite claudication as a main reason for stopping cycle exercise, and two of them did not experience claudication during the test. Half of the subjects ( $n = 21$ ) shared at least one similar limiting symptom between the baseline cycle and treadmill tests.

Treadmill training had a significantly larger effect ( $p < 0.05$ ) on MWT ( $240 \pm 178$  s) than cycle training had on MCT ( $93 \pm 98$  s). Training pain level in the low ABI limb tended to be correlated ( $p = 0.06$ ) with the effect of treadmill training on MWT ( $r = -0.54$ ;  $n = 13$ ; 95 % CI =  $-0.84 - 0.02$ ); but it was not correlated ( $r = -0.2$ ) with the effect of cycle training on MCT. In all trained subjects, training pain level in the low ABI limb was inversely correlated to the specific effect of training on maximal exercise time ( $r = -0.53$ ;  $n = 28$ ; 95 % CI =  $-0.75 - -0.20$ ). With respect to the effects of training on cycle and treadmill performance in all trained subjects ( $n = 28$ ), there were no significant correlations between the changes in maximal cycling and treadmill times ( $r = 0.01 - 0.27$ ). However, there was a significant correlation between the training-induced changes in

maximal cycle and treadmill times in those subjects who reported at least one limiting symptom that was in the same anatomical location during treadmill and cycle exercise before training (Fig. 5A); but there was no correlation in those who reported limiting symptoms in a different anatomical location during treadmill and cycle exercise (Fig. 5B). Age was also significantly correlated with the effect of cycle training on MWT ( $r = 0.62$ ;  $p < 0.05$ ).

*Responders versus Non-responders* For each subject who trained, a positive response to training occurred if the effect of training on maximal exercise time exceeded the difference between the last two baseline tests (i.e. MWT for treadmill group; MCT for cycle group). According to this criterion, 11 out of the 13 subjects in the treadmill group and 8 out of the 15 subjects in the cycle group responded positively to training. A similar analysis in the control group (i.e. post-pre scores versus baseline variation) revealed three responders for MWT and one responder for MCT. Comparisons of baseline characteristics, baseline performances and training variables between responders ( $n = 19$ ) and non-responders ( $n = 9$ ) were performed. Only training pain severity in the low ABI leg was significantly different ( $p < 0.05$ ) between the responders ( $1.1 \pm 0.7$ ) and non-responders ( $1.8 \pm 0.6$ ).

## **Discussion**

Optimising the exercise program for claudicants depends on knowing the effects of the various dimensions of training, such as intensity, duration and mode. A metaanalysis of training studies performed up until the mid-1990s suggested that an optimal exercise program aimed at improving walking performance should use walking as the mode of exercise<sup>4</sup>. This suggestion, however, was based on studies that did not systematically compare the effects of alternative

modes of exercise with walking. The present study is the first to contrast cycle with treadmill training, controlling for all other major dimensions of training, and it is one of only eight randomized controlled exercise trials to have studied more than 40 patients. Six weeks of treadmill training improved graded walking performance by, on average, 25 %. In contrast, cycle training did not improve graded walking performance, despite the finding that it significantly improved graded cycle performance. In addition, although treadmill training improved walking performance, it failed to increase cycle performance. These preliminary findings suggest that the training effects induced by cycling or walking are specific to the mode of exercise used during training and that there is no “cross-training” benefit.

In the treatment of walking intolerance, the efficacy of alternative modes of exercise requires that there is a significant transfer of physiological adaptation to walking. The findings of our study suggest that this is generally not the case for cycling, despite the strong associations between cycling and walking performance before and after training ( $r = 0.72 - 0.75$ ). Claudication in the calf and quadriceps muscles were the most frequently cited symptoms during treadmill walking and cycling respectively. It is perhaps this difference in the location of claudication between the two modes of exercise that has led some to suggest that cycling would not be beneficial to PAD patients who most frequently claudicate in the calf<sup>15</sup>. However, the number of limiting symptoms during both modes of exercise varied between one and three (see Results), and 50 % of the subjects reported a similar limiting symptom during cycling and treadmill exercise. Among the two groups of claudicants that trained ( $n = 28$ ) and who had a similar limiting symptom between cycling and walking ( $n = 12$ ), evidence of a cross-training effect was observed in the form of a significant association between the training effects on maximum walking and cycle times (Figure 5). Seven of these claudicants were in the cycle group, and five of them improved their maximum

walking time (mean increase = 35 %) beyond the baseline variation in this measurement and by more than the mean response seen in the treadmill group. These data suggest that the similarity of symptoms between cycling and walking might help determine the effect of cycle training on walking performance. However, age was also positively related to the effect of cycle training on maximum walking time, and so we cannot exclude the possibility that age affects the responsiveness to training. Further research is clearly required to explore if the similarity of symptoms between exercise modes and/or age influences the performance benefit obtained from cycle training.

A novel finding of the present study was the larger effect of treadmill training on maximal walking time compared with the effect of cycle training on maximal cycle time. This larger, specific effect of treadmill training (mean increase = 24 vs 10 %) could not be attributed to differences in any of the measured baseline characteristics (Table 1) or other dimensions of training, which were similar between the training programs. Excluding nonresponders from analyses had little effect on this difference in training effect. In contrast, levels of training pain in both limbs were significantly higher in the cycle than the treadmill group, and training pain level in the low ABI limb was inversely related to the specific effect of training on maximal exercise time. These data raise the possibility that the smaller training response to cycling might be related to the significantly higher pain levels reported by the cycle group. Moreover, they suggest that in response to both forms of training a greater improvement in exercise tolerance occurred in those subjects who experienced lower and mild levels of claudication pain during the training sessions. This conflicts with the suggestion that an optimal training program for claudicants consists of exercise to near-maximal pain<sup>4</sup>. Further study of this link between training pain and

physiological adaptation to training is required because the present data suggest that high levels of claudication pain might not be optimal.

Although a number of studies have examined the training effects of cycling combined with other forms of exercise, only one other study has tested the effects of cycle training alone <sup>6</sup>. That study reported that walking performance was improved significantly by cycle training. In trying to explain how this effect differs from that observed in the present study, several factors need to be considered. First, it is unlikely that the training stimulus was relatively lower in the present study because the training program was modeled on that used by Walker et al. <sup>6</sup> and training was performed more frequently (3 vs 2 sessions per week). Moreover, the increase in cycle performance and peak VO<sub>2</sub> demonstrates that it provided a significant physiological stimulus. Second, our familiarization routine of several baseline testing sessions <sup>9,11-14,16</sup> might help reduce the confounding influence that task learning and lowered anxiety makes to the so-called training responses, and it is not clear what familiarisation was provided in the other study <sup>6</sup>. Third, in contrast to the treadmill testing of one patient at a time, these investigators used an indoor shuttle walk test where ‘more than one patient’ was tested simultaneously. All but one of the 24 subjects in their cycle training group appeared to improve their maximum walking distance, and this relatively homogenous response raises the question as to the psychological influence of training and performing tests together on an individual’s walking performance after training. Fourth, one subject in their study appeared to improve their performance by more than 1000 %, and while this wouldn’t affect the significance of the group effect it would greatly inflate the average size of the effect reported (i.e. 50 %). Fifth, the symptoms that limited walking performance were not reported in this study, and the heart rates measured during exercise (~160 bpm) far exceed the maximal heart rates of 110-120 bpm observed in the present and other studies <sup>2,9,20</sup>. This raises

the possibility that cardiac dysfunction and symptoms other than claudication contributed more to exercise limitations than was the case in the present study.

Over several decades there has been considerable interest in the physiological mechanisms that underpin the training effect on exercise tolerance in PAD<sup>3,17,18</sup>; yet despite this and the large number of factors suggested to be involved in the training response this problem is not well understood<sup>19</sup>. An improvement in performance might be underpinned by an improvement in exercise time in the absence and/or presence of pain, as well as the physiological responses associated with these two phases of exercise. In the present study, pain-free time during the treadmill test was improved significantly by treadmill training, and this improvement explained more than 80 % of the increase in maximal time on this test. In contrast, cycle training had no significant effect on pain-free time during the cycle test and, thus, made very little contribution to the increase in maximal cycle time. Thus, the specific effect of training differs markedly between cycling and walking: the improvement in maximal performance induced by both modes of training is linked mainly to a delay in the onset of pain for walking, and an extension of the time spent exercising with pain for cycling. This novel finding raises the possibility that the physiological adaptations to training also differ between cycling and walking.

In the present study, we used a graded exercise protocol with an initial stage of 5 min duration that enables physiological responses to reach a steady-state in most patients<sup>12,13,16</sup>. For treadmill exercise, there was a tendency towards a significant interactive effect on submaximal  $\text{VO}_2$  (group-by-test:  $p = 0.07$ ), where  $\text{VO}_2$  was lowered by training in the treadmill, but not cycle, group. These data are consistent with the above-mentioned effects of treadmill training on pain-free time during treadmill walking, demonstrating a link between increased time without pain and

a lowered  $O_2$  cost of exercise during this mode of exercise. These findings are similar to those observed after the same<sup>6,20</sup> or longer periods of training<sup>2,5,20</sup>, where  $VO_2$  and blood lactate concentration during treadmill exercise were reduced by treadmill training. However, neither of these studies nor the present study shed light on how the oxygen cost of exercise was lowered; but it might relate to improved walking technique, recruitment of a smaller number of motor units and/or recruitment of less economical type II muscle fibres<sup>11</sup>. In contrast to the submaximal  $VO_2$  response, peak  $VO_2$  was not significantly increased during treadmill exercise by treadmill training, a finding consistent with the only other training study of the same duration to have made these measurements<sup>20</sup>. However, peak  $VO_2$  during cycle exercise was significantly increased by cycle training. This suggests that the improvement in cycle performance in the cycle group, which was underpinned by an increase in the time spent exercising with pain, was linked to increases in the peak rates of  $O_2$  delivery to, and/or  $O_2$  consumption by, working muscles.

Some limitations of this study should be considered. Although the sample size of this study compares favourably with other randomized controlled exercise training studies, small effects might go undetected and a type II error might have occurred. This probably applies most to the effect of cycle training given that it increased walking performance by an average of ~5 % more than the effect observed in the control group. Whether or not such an effect on a graded test translates into a clinically relevant effect in the life of a patient is difficult to determine at present. The study was powered to detect larger differences (~10 %) in graded treadmill performance than were observed for the control group; but given the natural variation in exercise performance as measured in our hands (CV~5-10 %), improvements less than this are of questionable significance, from a physiological and clinical perspective. Given the number of comparisons made in this study and the fact that we did not adjust the level of significance accordingly, we



acknowledge that we might have committed a type I error for any of the significant effects or correlations we observed . The duration of the study was restricted to 6 weeks, and given that longer training programs will elicit larger increases in performance, it is possible that the present study underestimates the training benefit that might be obtained with cycling. However, the duration of the training program studied here is consistent with the trend in some countries, such as Australia and the U.S., of providing relatively short periods of supervised intervention that are then followed by longer periods of home-based intervention and allied health support.

In conclusion, this is the first study to compare the effect on walking performance induced by cycle or treadmill training in PAD patients with claudication. On average, cycle training over a six week period did not significantly improve walking performance. There was, however, considerable variation in the response to cycle training, with five out of the 15 claudicants in the cycle group improving their walking performance. This responsiveness to training might be influenced by age, the severity of muscle pain during training and/or the similarity of symptoms between cycling and walking. These preliminary findings deserve further study before cycle training is abandoned as a potential exercise prescription for selected patients with claudication.

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## Figure Captions

Figure 1. Maximum walking times before and after training for patients in the treadmill, cycle and control groups. Figure shows individual walking times (—) and mean values (●). \* Indicates a significant change in MWT from pre-training to post-training in the treadmill group.

Figure 2. Pain-free walking times before and after training for patients in the treadmill, cycle and control groups. Figure shows individual walking times (—) and mean values (●). † a significant main effect where the treadmill group was greater than the cycle group. ‡ a significant main effect where post-training values were greater than pre-training values.

Figure 3. Maximum cycling times before and after training for patients in the treadmill, cycle and control groups. Figure shows individual walking times (—) and mean values (●). \* a significant effect of training on MCT in the cycle group.

Figure 4. Pain-free cycling time before and after training for patients in the treadmill, cycle and control groups. Figure shows individual walking times (—) and mean values (●).

Figure 5. The relationship between the training-induced changes in maximal treadmill and cycle times in claudicants who reported at least one exercise-limiting symptom that was in the same anatomical location (A) or exercise-limiting symptoms that were in a different anatomical location (B) during baseline treadmill and cycle tests.

Table 1. Baseline characteristics of the entire cohort of claudicants and the three experimental groups.

	<i>Entire cohort</i>	<i>Treadmill</i>	<i>Cycle</i>	<i>Control</i>
<b>Number</b>	42	13	15	14
<b>Males</b>	24	8	8	8
<b>Females</b>	18	5	7	6
<b>Age (y)</b>	63 (9)	62 (6)	65 (10)	61 (10)
<b>Weight (kg)</b>	74.9 (14.6)	76.5 (17.2)	72.2 (12.7)	76.5 (14.6)
<b>Heart Rate (bpm)</b>	70 (11)	68 (13)	72 (11)	69 (10)
<b>Systolic Blood Pressure (mmHg)</b>	139 (16)	142 (16)	141 (19)	134 (13)
<b>Diastolic Blood Pressure (mmHg)</b>	69 (8)	69 (8)	68 (8)	72 (7)
<b>ABI</b>				
High ABI leg	0.96 (0.26)	0.97 (0.25)	0.84 (0.27)	1.08 (0.20)*
Low ABI leg	0.69 (0.16)	0.67 (0.11)	0.64 (0.18)	0.77 (0.14)
<b>Clinical History</b>				
Stroke	9	2	3	4
MI	8	3	4	1
Diabetes	12	4	4	4
<b>Medications</b>				
Antihypertensives	22	9	7	6
Lipid lowering	28	7	10	11
Anticoagulants & antithrombotics	33	10	12	11
Hypoglycaemic agents	7	3	3	1
Insulin	4	2	2	0
Beta blockers	9	3	3	3
Antiangina	7	3	3	1
Asthma medication	3	1	0	2
<b>Smoking</b>				
Current	11	4	1	6
Reformed	24	7	11	6

\* a significant difference between the control and cycle groups.

Table 2. Submaximal physiological responses during the maximal exercise tests in the three experimental groups. Comparisons have only be made between values pertaining to a given exercise test. "Pre" refers to the last of the baseline tests, and "post" refers to the test performed at the end of six weeks of training.

	Treadmill Test		Cycle Test	
	Pre	Post	Pre	Post
<b>HR</b> (bpm)	†			
Treadmill	89 (14)	88 (13)	93 (15)	95 (14)
Cycle	104 (21)	103 (18)	106 (23)	104 (27)*
Control	93 (12)	92 (11)	93 (13)	94 (17)
<b>VO<sub>2</sub></b> (ml min <sup>-1</sup> )	‡			
Treadmill	726 (185)	689 (234)	693 (134)	687 (163)
Cycle	741 (205)	752 (211)	692 (90)	673 (100)
Control	695 (190)	669 (157)	674 (77)	666 (72)
<b>VO<sub>2</sub></b> (ml kg <sup>-1</sup> min <sup>-1</sup> )				
Treadmill	9.6 (1.6)	9.0 (1.6)	9.2 (1.3)	9.1 (1.4)
Cycle	10.1 (1.5)	10.3 (1.7)	9.5 (1.0)	9.4 (1.1)
Control	9.0 (1.2)	8.7 (1.1)	9.0 (1.4)	8.9 (1.1)
<b>RER</b>				
Treadmill	0.96 (0.09)	0.96 (0.08)	1.07 (0.09)	1.08 (0.09)
Cycle	0.98 (0.06)	0.97 (0.07)	1.12 (0.13)	1.08 (0.11)
Control	0.95 (0.09)	0.96 (0.08)	1.05 (0.11)	1.07 (0.10)
<b>V<sub>E</sub></b> (l min <sup>-1</sup> )				
Treadmill	23.6 (6.7)	22.2 (7.2)	24.5 (4.9)	24.3 (5.9)
Cycle	24.2 (6.3)	24.4 (5.7)	24.9 (3.0)	24.1 (3.7)
Control	22.5 (7.5)	22.0 (6.3)	22.7 (3.0)	23.5 (2.5)

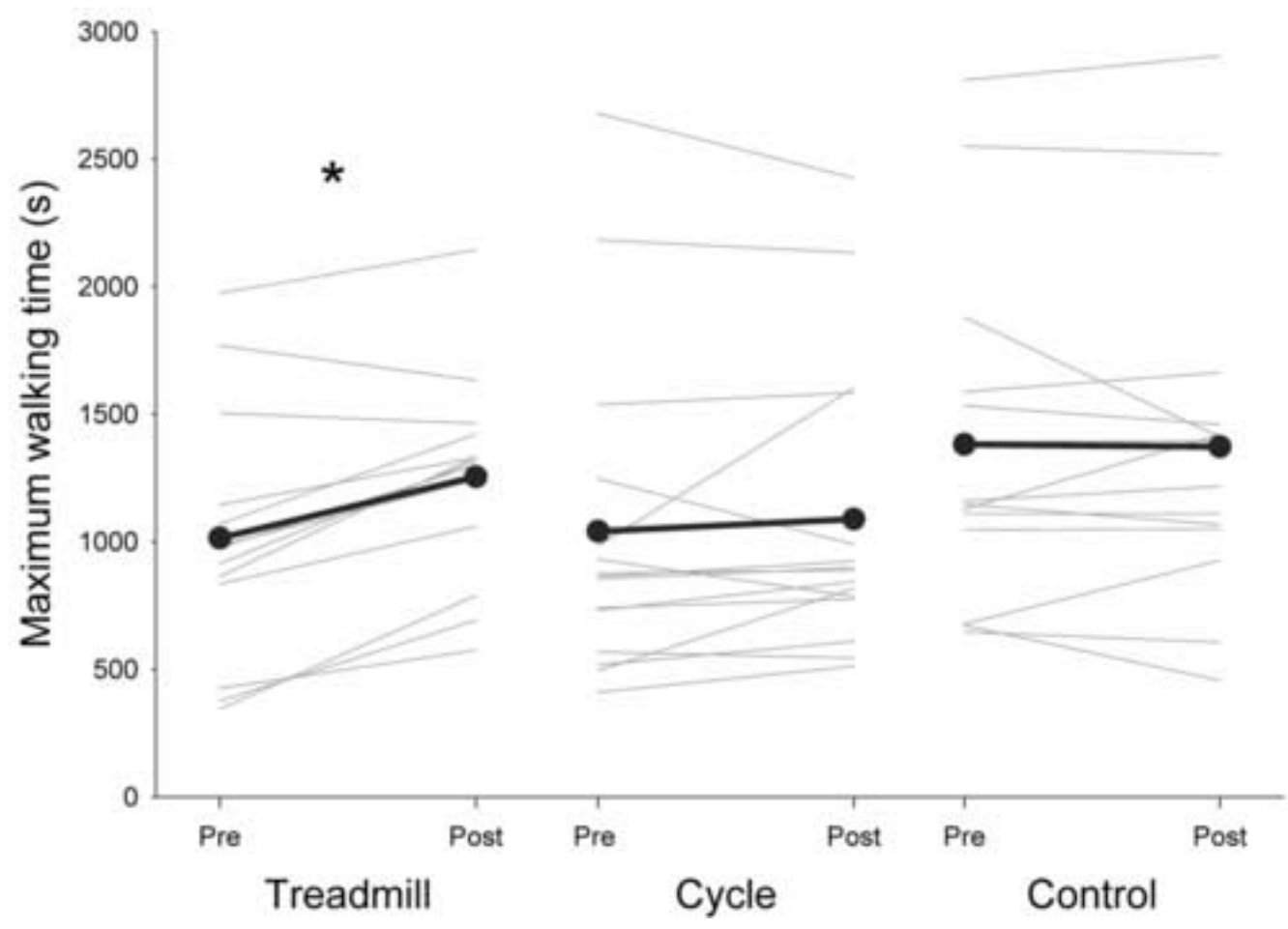
\* a significant effect of training in the cycle group. † a main effect where the cycle group is greater than the treadmill group. ‡ a main effect where the cycle group is greater than the control group.

Table 3. Peak physiological responses during the maximal exercise tests in the three experimental groups. Comparisons have only be made between values pertaining to a given exercise test. "Pre" refers to the last of the baseline tests, and "post" refers to the test performed at the end of six weeks of training.

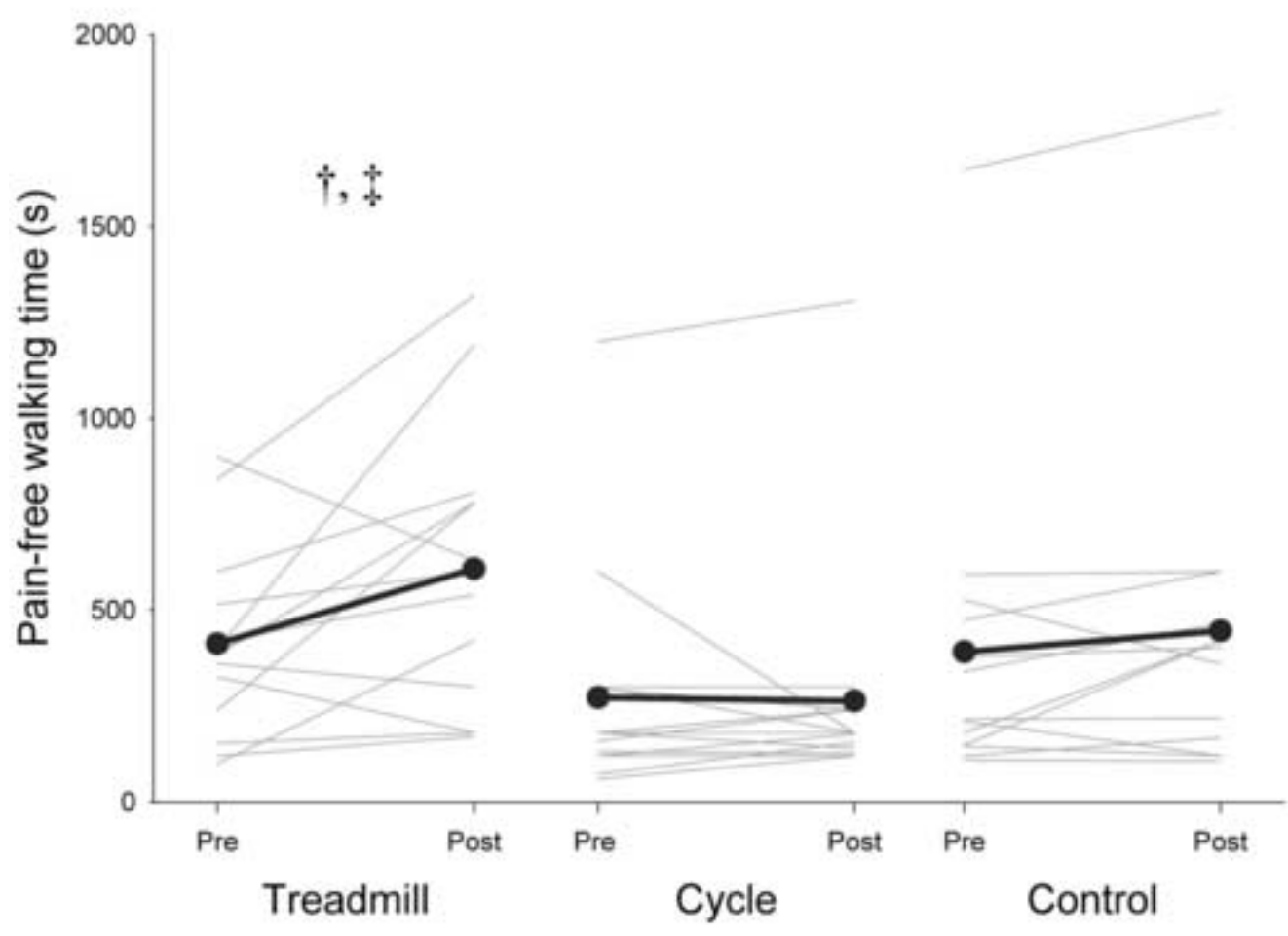
	Treadmill Test		Cycle Test	
	Pre	Post	Pre	Post
<b>HR</b> (bpm)				
Treadmill	115 (23)	118 (20)	123 (25)	125 (24)
Cycle	122 (19)	123 (19)	131 (25)	131 (26)
Control	127 (27)	127 (24)	128 (26)	127 (24)
<b>VO<sub>2</sub></b> (ml min <sup>-1</sup> )	†		†	
Treadmill	1140 (307)	1202 (308)	1126 (291)	1166 (337)
Cycle	1052 (384)	1154 (406)	1041 (370)	1115 (395)
Control	1263 (418)	1251 (435)	1236 (446)	1221 (423)
<b>VO<sub>2</sub></b> (ml kg <sup>-1</sup> min <sup>-1</sup> )	†			
Treadmill	15.2 (4.0)	15.8 (2.3)	15.0 (3.7)	15.6 (4.0)
Cycle	14.4 (4.4)	15.8 (4.8)	14.4 (4.6)	15.4 (4.9)*
Control	16.6 (4.9)	16.4 (4.9)	16.2 (4.9)	16.1 (4.7)
<b>RER</b>			†	
Treadmill	1.15 (0.09)	1.19 (0.09)	1.29 (0.10)	1.29 (0.11)
Cycle	1.17 (0.10)	1.18 (0.10)	1.34 (0.11)	1.30 (0.11)
Control	1.22 (0.07)	1.20 (0.11)	1.32 (0.09)	1.28 (0.11)
<b>V<sub>E</sub></b> (l min <sup>-1</sup> )	†			
Treadmill	41.7 (12.2)	44.8 (9.8)	49.2 (11.9)	49.2 (12.4)
Cycle	40.5 (12.9)	44.1(12.3)	46.7 (10.7)	48.9 (10.6)
Control	49.1 (18.6)	49.1 (21.6)	56.0 (25.8)	53.0 (22.5)

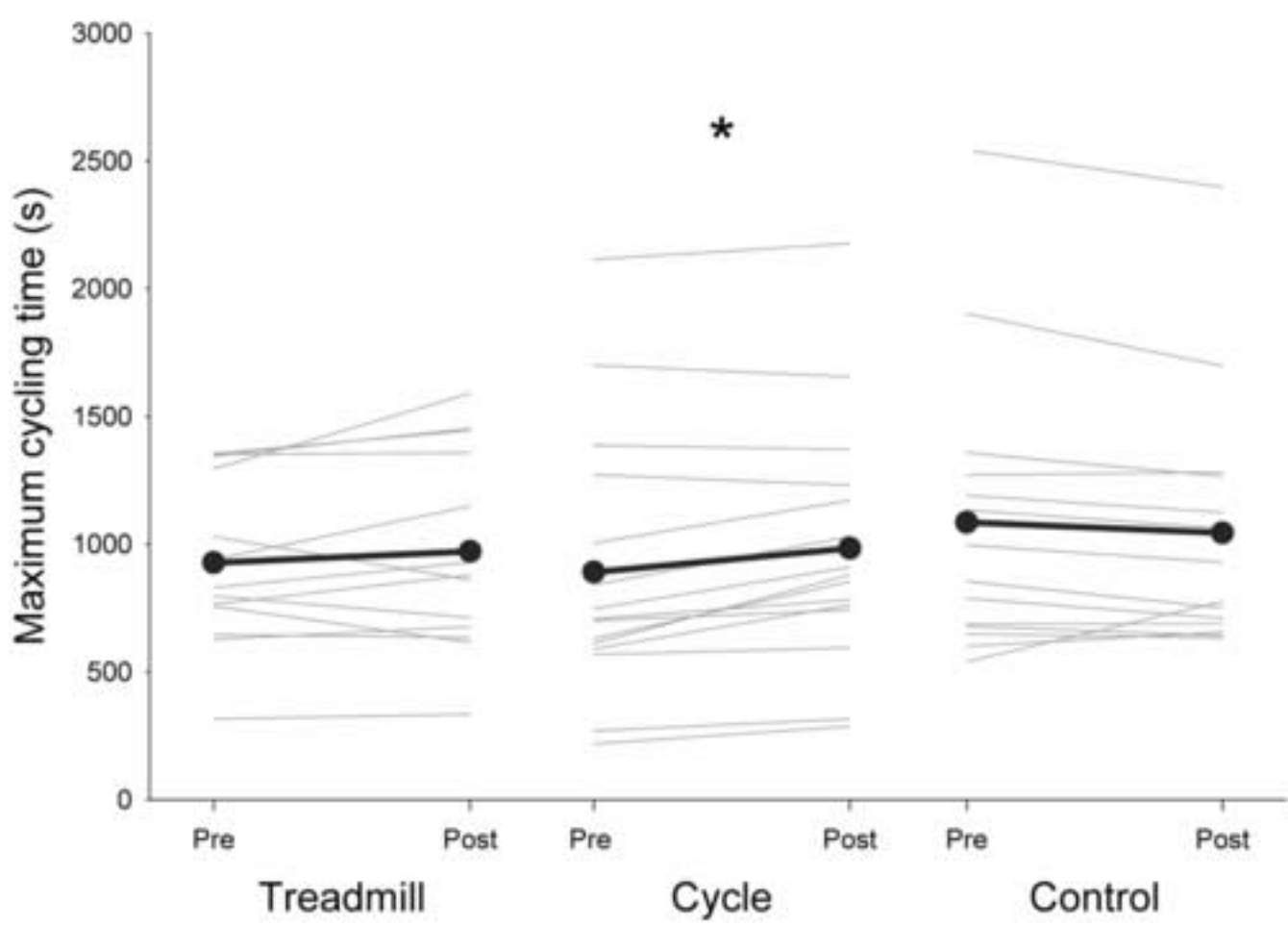
\* a significant effect of training in the cycle group for the treadmill and cycle test.

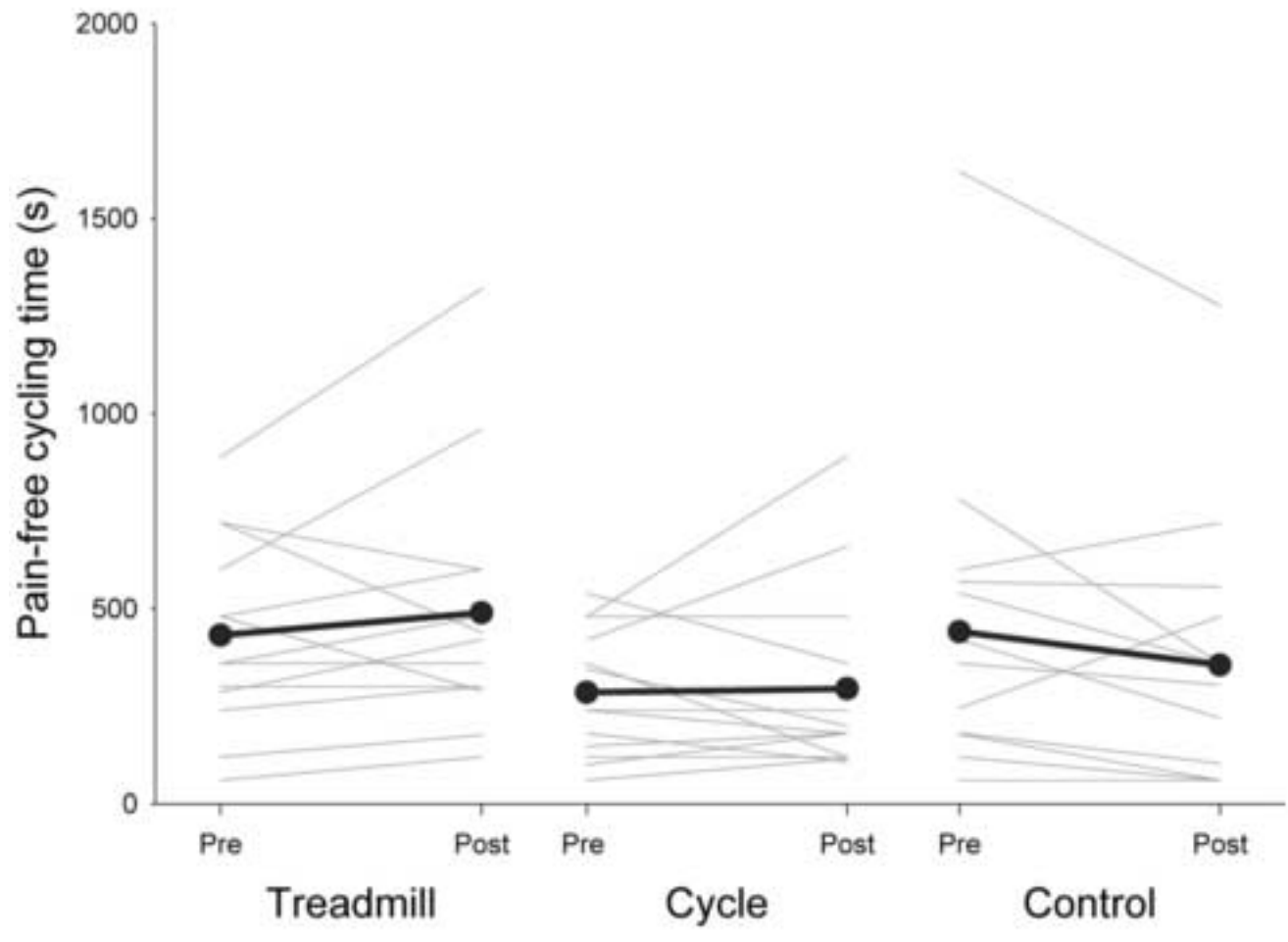
† a main effect where post-training values are significantly different from pre-training values for the test (treadmill and/or cycle) indicated.



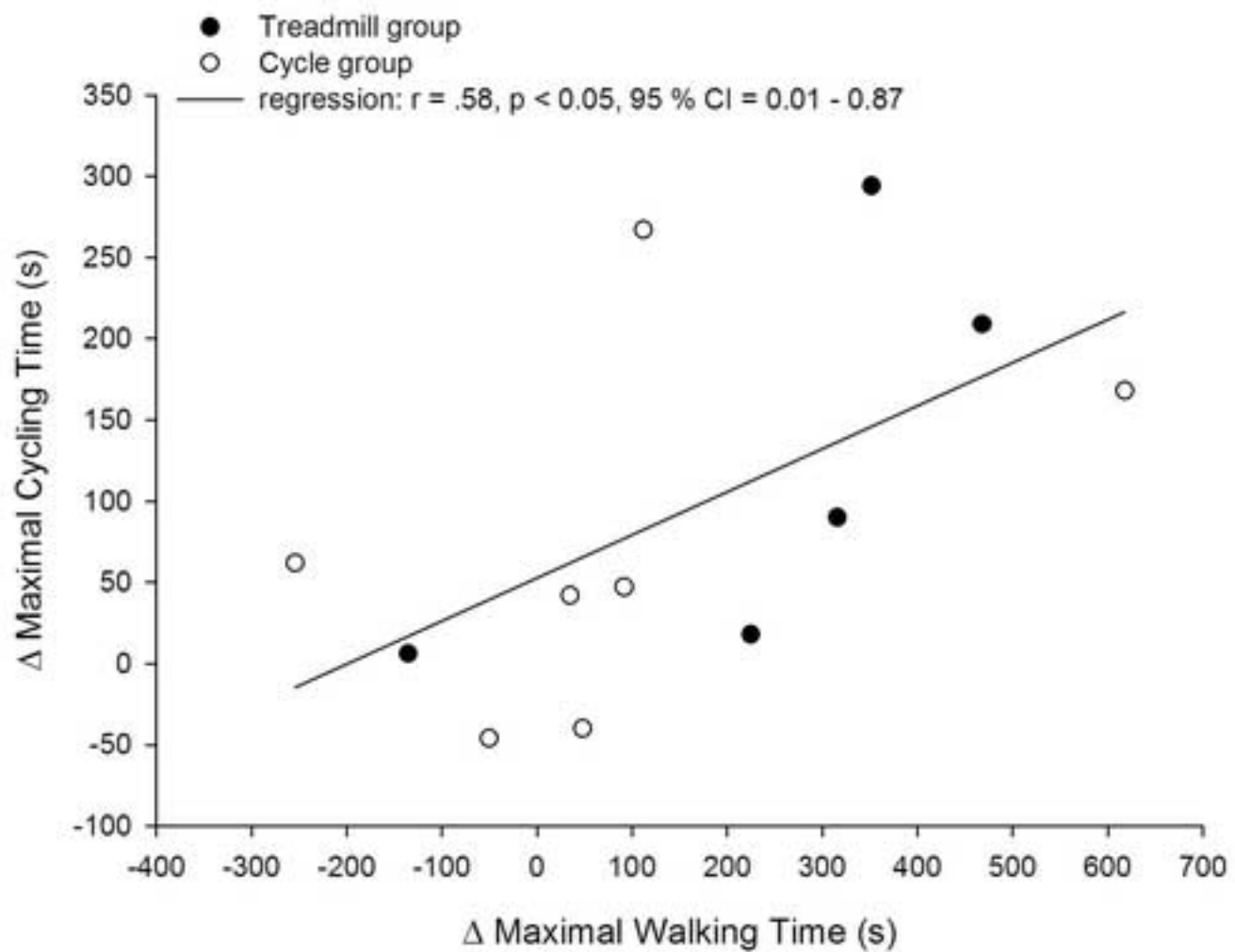


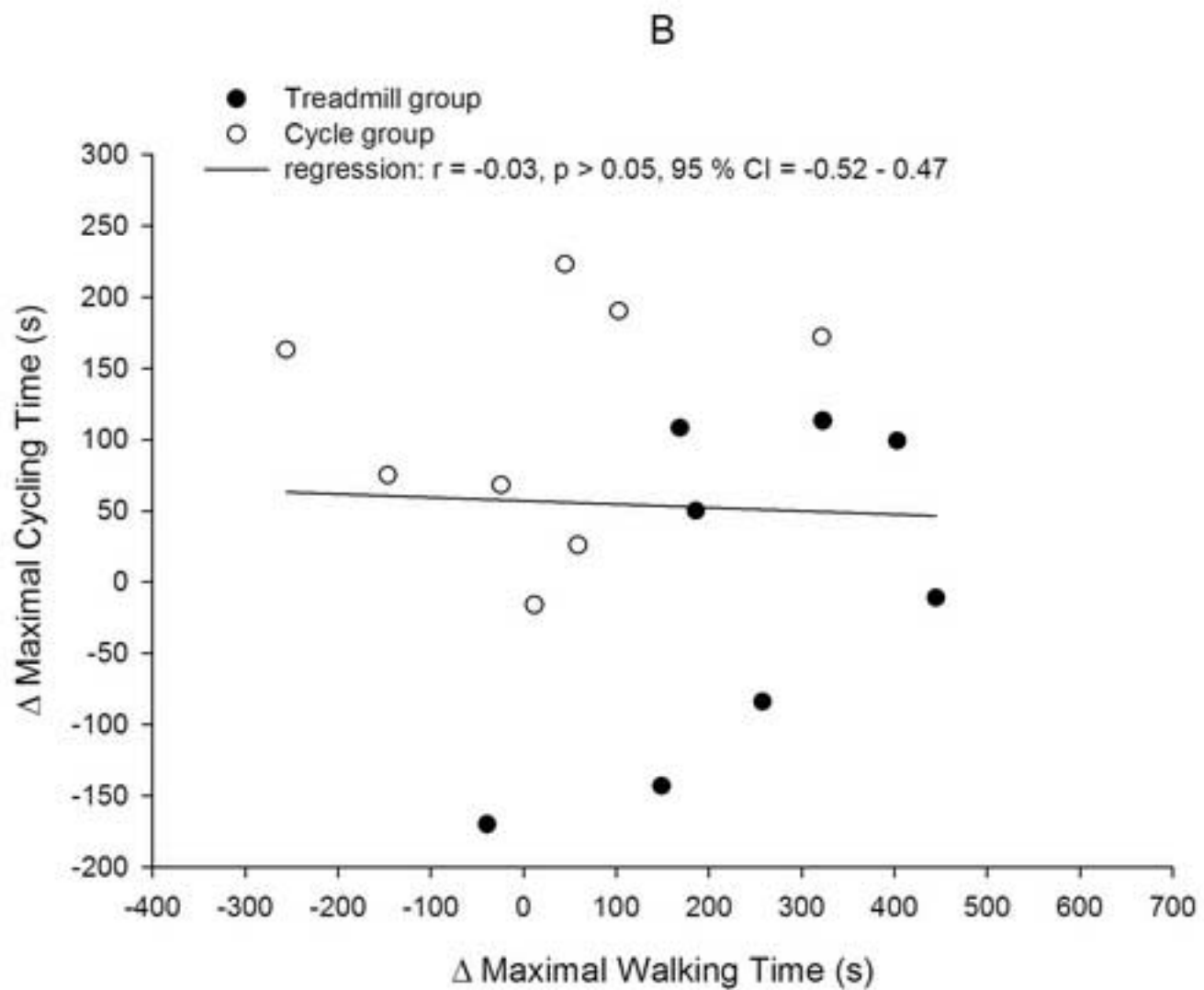






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