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Comparison of Upper-Limb and Lower-Limb Exercise Training in Patients with Intermittent Claudication

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Dedication

This thesis is primarily dedicated to the life and memory of Professor Richard F.M. Wood (1943-2003), for his relentless work with patients with intermittent claudication.

Professor Richard F.M. Wood, or "Prof" as he was known, was Professor of Vascular Surgery, at the University of Sheffield (1994-2002), and was a key member of my PhD supervisory team. His vision, professionalism, intellect, support and kindness will always be remembered with great fondness. His unfortunate passing in April 2003, prior to study completion, meant that the study outcomes were unknown to him. His work however, lives on in the lives of so many that he encouraged, inspired and supervised, of which I am but one. I feel very honoured and proud to have known him.

This thesis is also dedicated to the other two gentlemen of my PhD supervisory team, namely; Dr John M. Saxton (Director of Studies and Exercise Physiologist, Sheffield Hallam University) and Professor A. Graham Pockley (Professor of Immunobiology, University of Sheffield).

Gentlemen, I shall always be grateful to you for your inspiration, vision, support and encouragement throughout this study, which deserves special recognition. I feel privileged and honoured to have been chosen to conduct this prestigious research, and to work alongside such expertise. I hereby formally acknowledge my unreserved gratitude to you, for allowing me to be a part of your team. This study changed the lives of so many patients, this was your conception and I am grateful to bear its fruits.

The work submitted herewith is in recognition of these gentlemen's endeavours.

To my parents, family and dear friends, too numerous to mention individually. For all your support throughout the years during this study, I shall forever be indebted. Your kindness and love was felt throughout the years, this gave me strength. My deepest affection is extended to you all now and forever.

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Statement of Originality

The strategy of using upper-limb exercise training to improve walking performance in patients with peripheral arterial disease (PAD) has previously only been described during a preliminary six-week study conducted by members of our investigatory team (Walker *et al.* 2000).

Following this preliminary work, a larger-scale six-month randomised controlled trial (RCT) was needed to prove that upper-limb exercise training can evoke positive health outcomes and to further understand the mechanisms of action. Patients' perception of community-based walking ability and quality of life following such an exercise strategy also necessitated investigation. In addition, long-term (48-weeks) post-intervention follow-up was essential to compare patients walking ability, functional capacity, community-based walking ability and quality of life, after undertaking such a structured upper-limb exercise regimen. Such a robustly designed trial has never been performed previously.

All of the recruitment, initial consultations and approximately 99.9% of all assessment and training sessions were performed by myself. Mr. Jonathan Male provided technical assistance in the majority of assessment and training sessions. Statistical analysis was performed by myself, with guidance and verification of findings confirmed by Dr. John. M. Saxton.

With the exception of any statement to the contrary, all the data presented in this report are the result of my own efforts. In addition, no parts of this report have been copied from other sources. I understand that any evidence of plagiarism and/or the use of unacknowledged third party data will be dealt with as a serious matter.

Signed .....

25/05/07

Date .....

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Publications

Zwierska I, Walker RD, Choksy SA, Male JS, Pockley AG, Saxton JM. (2005). Upper- versus lower-limb aerobic exercise rehabilitation in patients with symptomatic peripheral arterial disease: a randomised controlled trial. *J Vasc Surg*, **42**: 1122-1130.

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Abstract

Objectives: To investigate the effects of a 24-week programme of upper- and lower-limb aerobic exercise training on walking performance and quality of life in patients with symptomatic peripheral arterial disease (PAD) and to study the mechanisms, which could influence symptomatic improvement.
Methods: Following approval from the North Sheffield Local Research Ethics Committee, 104 patients (median age 69 y, range 50-85 y) with stable PAD were randomised into an upper- or lower-limb aerobic exercise training group, or to a non-exercise training control group. Training was performed twice weekly for 24-weeks at equivalent relative exercise intensities. An incremental arm- and leg-crank test (ACT and LCT, respectively) to maximum exercise tolerance was performed before and at 6-, 12-, 18- and 24-weeks of the intervention to determine peak oxygen consumption ($\dot{V}O_2$). Walking performance, defined as the claudication and maximum walking distance (CD and MWD respectively) achieved before intolerable claudication pain, was assessed at the same time-points using a shuttle-walk protocol. Peak blood lactate concentration, ratings of perceived exertion (Borg RPE) and pain (Borg CR-10) were recorded during all assessments. Physical activity status, community-based walking ability and quality of life were assessed throughout the intervention period. Assessments were repeated 6-, 12-, 24- and 48-weeks following the intervention period.
Results: Both CD and MWD increased over time ($P < 0.01$) in both training groups. At 24-weeks, CD had improved by 56% and 65% and MWD had improved by 30% and 35% ($P < 0.01$) in the upper-limb and lower-limb exercise groups, respectively. These changes were associated with improvements in community-based walking distance, speed and stair-climbing ability ($P < 0.01$). All patients assigned to exercise training exhibited an increase in LCT peak $\dot{V}O_2$ at the 24-week time-point in relation to baseline measures ($P < 0.01$) and control patients ($P < 0.01$), whereas ACT peak $\dot{V}O_2$ at the 24-week time-point was only improved in the upper-limb exercise training group ($P < 0.05$). An increase in peak blood lactate concentration (1.95 ± 0.14 vs. 2.40 ± 0.17 mM, mean ± SEM; $P < 0.05$) and amount of pain experienced at MWD ($P < 0.05$) was only observed in the upper-limb exercise training group. This suggests that an alteration in exercise pain tolerance accounted, at least in part, for the improvement in MWD in this group. Upon completing the intervention period the general health status of both exercise training groups was improved in relation to the control group ($P < 0.05$). However, improvements in physical functioning and bodily pain in relation to baseline ($P < 0.05$) and energy and vitality in relation to control patients ($P < 0.05$) were only observed in the upper-limb training group. At 48-weeks follow-up, CD remained improved by 39% and 48% ($P < 0.05$) and MWD remained improved by 18% and 26% ($P < 0.05$) in the upper-limb and lower-limb exercise groups, respectively, compared to baseline measures. A retained improvement in walking confidence ($P < 0.01$) and community-based walking distance ($P < 0.05$) was also observed, however global physical activity status in both exercise trained patient groups, returned to baseline.
Conclusions: Both upper- and lower-limb aerobic exercise training can be useful exercise training modalities for improving cardiovascular function, walking performance, exercise pain tolerance and quality of life in patients with symptomatic PAD. This study suggests that a combination of physiological adaptations and altered exercise pain tolerance might account for the improvement in walking performance achieved through upper-limb aerobic exercise training in patients with PAD. This study also indicates that although walking performance remained improved in both exercise trained patients at 48-weeks follow-up, as compared to baseline measures, a progressive dwindling of improvement was observed over this time period. Reluctance for the continuation of exercise in the home-setting was observed.

Chapter 1 - Introduction

1.1 Background information

Peripheral arterial disease (PAD) is a clinical manifestation of atherosclerosis that is prevalent in industrialised societies (Mohler III *et al.* 2003). Epidemiological studies illustrate that PAD is very common when screening is performed in older adults (Newman, 2000). Intermittent claudication is the most common symptomatic manifestation of mild to moderate PAD (Regensteiner *et al.* 1997a), typically occurring in one out of every 20 people over the age of 65 years in the general population (Beebe, 2001). The condition usually results from atherosclerotic narrowing of the lower-limb arteries (Santilli *et al.* 1996) and it is generally characterised by lesions within the aorto-iliac and/or superficial femoral arteries, popliteal arteries or femoropopliteal arterial segments.

In the presence of slowly progressive arterial stenosis, blood flow through collateral channels is usually sufficient to maintain normal metabolic function at rest, but is inadequate to meet an increased metabolic demand during exercise (McCombs and Subramanian, 2002). During ambulation, when the arterial oxygen supply is insufficient to meet the metabolic requirements of the exercising leg muscles (Beebe, 2001; Regensteiner and Hiatt, 1995), the environment for substrate metabolism becomes relatively anaerobic, thereby resulting in the local accumulation of lactic acid and metabolic by-products; this accounts for the development of muscle pain and tightness (claudication) (McCombs and Subramanian, 2002).

The term 'claudication' is derived from the Latin word *claudicare*, meaning to "limp", after the Roman Emperor Claudius who limped - limping is the typical gait pattern observed in patients with claudication (Hiatt and Nehler, 2001). Patients typically walk at a slower pace and exhibit a decreased step length and cadence compared with age-matched healthy individuals and these abnormal gait parameters impair walking ability (Scherer *et al.* 1998). The pain is often described as cramp-like (Beebe, 2001), and although this most commonly affects the calf muscles (Hiatt and Nehler, 2001), it can also affect the thigh and buttock regions in one or both legs during walking (Santilli *et al.* 1996). The pain usually subsides within ten minutes of rest (McDermott *et al.* 2002b) in patients with mild to moderate disease.

Compared with healthy individuals of a similar age, the peak treadmill walking performance of patients with claudication is reduced by 50% to 60% (Hiatt and Nehler, 2001). Furthermore, on the basis of peak oxygen uptake ($\dot{V}O_2$) measurements, these patients exhibit an approximately 50% reduction in peak aerobic exercise capacity compared to healthy age-matched control patients (Hiatt *et al.* 1987; Hiatt *et al.* 1988) - the clinical condition of these patients is therefore of a similar severity as class III heart failure patients (Hiatt, 1999). The condition is also associated with an increased risk of cardiovascular morbidity and mortality (Regensteiner and Hiatt, 2002b).

Intermittent claudication is a relatively common condition (Beebe, 2001), with males developing claudication about twice as frequently as females (McCombs and Subramanian, 2002). Approximately 2% of men aged 45-69 years and 1% of women aged 50-69 years are affected (Hughson *et al.* 1978). The Framingham study estimated the incidence of claudication at 26.6 per 1000 males and 13.3 per 1000 females less than 65 years of age (Kannel and McGee, 1985). The prevalence of claudication increases with age, with up to 1 in 5 patients over the age of 75 years being affected (Spronk *et al.* 2003). When questioned, many older patients consider increased difficulty in walking to be a normal consequence of ageing (Boccalon, 1999) and thus, do not report symptoms to a physician (Beebe, 2001). This might account for the fact that, despite its prevalence, PAD often remains undiagnosed and the risk of cardiovascular ischaemic events, disease progression, functional disability, amputation and death are therefore increased (Treat-Jacobson and Walsh, 2003). An under-representation of the condition might also account for the observed gender differences in its incidence.

1.1.1 Natural history of intermittent claudication

Despite the functional impairment caused by intermittent claudication, its natural history, in terms of the risk of disease progression with respect to disability and eventual limb loss (McCombs and Subramanian, 2002) in the affected limb is relatively benign (Nehler and Hiatt, 1999b). Patients with PAD can often remain at the same level of walking impairment for years if not offered specific treatments (Regensteiner and Hiatt, 1995). Intermittent claudication can, however, progress in five different ways; i) improvement, ii) stabilisation, iii) worsening of the disease, but with no revascularisation required, iv) worsening of the disease with revascularisation required, and v) a requirement for amputation, usually after disease progression (Aquino *et al.* 2001). A large proportion of claudicants (approximately 75%) improve spontaneously

or remain stable (Gardner *et al.* 2004b), particularly those who stop smoking and persevere with walking (Whyman and Ruckley, 1998). If patients with claudication ignore the symptoms, a gradual process of decline usually occurs (Beebe, 2001). It has been estimated that 30% to 40% of patients will experience a symptomatic and/or objective deterioration over time, as measured by the ankle to brachial pressure index (ABPI) (Aquino *et al.* 2001), with approximately 25% of patients experiencing a deterioration in symptoms over five years (Bloor, 1961; Jelnes *et al.* 1986).

Rest pain is indicative of critical limb ischaemia (Creager, 2001), and further deterioration could result in limb loss (Hiatt and Nehler, 2001). The cumulative 10-year risk of developing ischaemic rest pain and ischaemic ulceration is reported to be 23% and 30%, respectively (Aquino *et al.* 2001). Studies during the last 40 years suggest that only about a quarter of patients with intermittent claudication will develop critical limb ischaemia, and this deterioration typically occurs during the first year after diagnosis (Aquino *et al.* 2001). The yearly incidence of amputation is low and reported to be between 1.4% (McCombs and Subramanian, 2002) and 5% (McDaniel and Cronenwett, 1989).

1.1.2 Associated diseases and mortality

Patients with PAD are more likely to report exertional leg symptoms, and musculoskeletal disease than non-PAD patients (McDermott *et al.* 2002a). Population studies of PAD confirm that older adults with PAD are disabled (Newman, 2000). Interestingly, despite the major impact on physical exercise performance, the emotional state and mental health of patients with intermittent claudication has been reported to be relatively normal compared with age-matched healthy controls (Regensteiner *et al.* 1996). However, some patients can feel very negative about their health and their future, and this can lead to unemployment, social isolation and depression (Binnie *et al.* 1999).

Although the prognosis for the claudicating limb is reasonably good (Tisi and Shearman, 1998; Stewart and Lamont, 2001), PAD can be thought of as a marker of advanced systemic atherosclerosis (Beebe, 2001; Newman, 2000), since its identification increases the likelihood of there being co-existent coronary heart (CHD) and cerebrovascular disease (Eberhardt and Coffman, 2004). The prognosis of patients with these risk factors is poor as they are at greater risk of suffering from myocardial infarction (MI), stroke, and cardiovascular death (Creager, 2001). Indeed, patients are

classed as being at a high risk of sustaining such a systemic ischaemic event (Hiatt and Nehler, 2001) and compared with aged-matched controls, patients with intermittent claudication exhibit excess cardiovascular morbidity and mortality rates (Tisi and Shearman, 1998; Stewart and Lamont, 2001).

Population studies confirm that patients with PAD have a high risk of total mortality (Newman, 2000). Epidemiological studies have shown there to be a two to three fold increase in cardiovascular disease (CVD) morbidity and mortality in patients with PAD (Newman, 2000). Mortality has been reported to be 60% over 10 years (Hiatt, 1997a), with most of these deaths resulting from MI, stroke (Regensteiner and Hiatt, 2002b) and other cardiovascular events (Creager, 2001). A four-fold increase in the overall mortality rate among patients with large vessel PAD, as diagnosed by non-invasive testing, and a 15-fold increase in rates of mortality due to CVD and CHD among patients with large-vessel PAD which was both severe and symptomatic has been reported (Criqui *et al.* 1992). The risk of CVD and mortality in patients with PAD is similar to those with a history of MI or stroke, therefore it has been suggested that patients with PAD should be subjected to the same measures as those recommended for secondary prevention in MI and stroke survivors (Newman, 2000).

Intermittent claudication is therefore an important clinical predictor of increased cardiovascular mortality (Boccalon, 1999). Lower ABPI, older age, stroke, and diabetes-requiring medication have been reported to be the four key predictive risk factors for mortality in claudicants (Aquino *et al.* 2001). Cardiovascular mortality correlates inversely with ABPI, and the risk of death is greatest in those patients with most severe PAD (Creager, 2001). Prompt diagnosis and management of the condition are crucial (Olin, 2002), and it is recommended that patients with PAD receive anti-platelet therapy in order to prevent ischaemic events (Regensteiner and Hiatt, 2002b).

1.1.3 Diagnosis of intermittent claudication

PAD is probably the most under-diagnosed and least aggressively managed atherosclerotic disease (Mohler, 2003). Although leg pain which is associated with exercise and relieved by rest is suggestive of intermittent claudication, other conditions such as major venous outflow obstruction, chronic compartment syndrome, nerve root compression, and arthritis can cause similar, confusing symptoms (Beebe, 2001). Claudication pain is associated with the location of the occlusive lesion, hence aorto-

iliac occlusive arteriosclerosis produces pain in the hip, buttocks or thigh, whereas pain associated with more distal femoropopliteal occlusive lesions typically occurs in the muscles of the calf (Beebe, 2001). Non-invasive approaches to locate lesions include magnetic resonance angiography, duplex scanning and haemodynamic localisation (Gey *et al.* 2004).

The diagnosis of intermittent claudication is based on patient history and physical examination. Although these are extremely important, they may prove to be of limited value due to the lack of consistent sensitivity and specificity (Mohler, 2003). The arterial physical examination includes pulse evaluation and careful inspection of the leg. The most important predictor of clinical outcome has been reported to be the severity of objectively determined arterial occlusive disease on initial evaluation (Aquino *et al.* 2001).

Diagnosis is usually confirmed by assessing the ABPI (Santilli *et al.* 1996). In addition, occlusive lesions can be further localised by taking pressure measurements in the upper and lower thigh and calf (Doppler segmental limb pressures) (Hiatt and Nehler, 2001). Thigh pressures are decreased in patients with iliac occlusive disease, whereas patients with disease more distal in the leg may exhibit a normal thigh pressure, but decreased calf and ankle pressures (Hiatt and Nehler, 2001).

1.1.3.1 Ankle to Brachial Pressure Index (ABPI)

The ABPI provides important information regarding the diagnosis and prognosis of PAD (Hiatt and Nehler, 2001). Serial measurements of Doppler ankle pressures have been used extensively to quantify haemodynamic improvements produced by arterial reconstruction and exercise rehabilitation, and to determine the progression of occlusive disease (Baker and Dix, 1981). Screening based on ABPI using Doppler ultrasonography may be more useful than physical examination alone (Gey *et al.* 2004). An ABPI should be performed in all patients suspected of having PAD, including patients at risk by age criteria (older than 70 years) or in younger patients with risk factors. This includes patients between 50 and 69 years of age who smoke or have diabetes (Hiatt and Nehler, 2001). Patients with exertional leg symptoms should also be evaluated with an ABPI (Hiatt and Nehler, 2001).

ABPI is a simple, non-invasive and reliable approach for the measurement of impaired lower-extremity perfusion (McDermott *et al.* 2002b). The ABPI is the ratio of ankle (dorsalis pedis and posterior tibial arteries) to upper arm (brachial artery) systolic blood pressure, and it is determined using a standard blood pressure cuff and a simple, continuous wave Doppler ultrasound instrument (Beebe, 2001). The resting ABPI in most patients who experience intermittent claudication is reduced (Amirhamzeh *et al.* 1997). An ABPI of less than 0.90 is 95% sensitive and 99% specific for PAD (Olin, 1998) and supports the diagnosis of peripheral arterial insufficiency (Amirhamzeh *et al.* 1997). However, multiple baseline determinations should be obtained on patients studied longitudinally (Baker and Dix, 1981).

ABPI is calculated by dividing the ankle systolic pressure in each lower extremity by the brachial systolic pressure (McDermott *et al.* 1998b). Conflicting arguments exist regarding the use of dorsalis pedis or posterior tibial artery pressures. It is important to note that the dorsalis pedis artery may not be palpable in 5% of normal individuals (Beebe, 2001). Previously the highest arm pressure (Baker and Dix, 1981) and the higher of either the posterior tibial or dorsalis pedis systolic pressures in the more severely diseased leg (Izquierdo-Porrera *et al.* 2000) have been recommended for calculation of ABPI.

More recently the association between ABPI and lower-extremity function has been found to be strongest when ABPI is calculated by averaging the values from the dorsalis pedis and posterior tibial arteries (McDermott *et al.* 2000). The brachial arterial pressures in each arm should also be averaged to obtain the upper extremity pressure (McDermott *et al.* 1998b). The higher of the two brachial pressures should only be used if the two brachial pressures differ by more than 10 mm Hg, in which case subclavian stenosis should be suspected (McDermott *et al.* 1998b; McDermott *et al.* 2002a). The lowest ABPI obtained from the right and left legs should be used in all calculations (McDermott *et al.* 2002a).

1.1.3.2 ABPI interpretation

Table 1. ABPI interpretation (Treat-Jacobson and Walsh, 2003).

ABPI	Diagnosis
Above 0.90	Normal
0.71 – 0.90	Mild Obstruction
0.41 – 0.70	Moderate Obstruction
0.00 – 0.40	Severe Obstruction

ABPI values between 0.41 and 0.90 represent mild to moderate PAD, and values of 0.40 or less are consistent with critical leg ischaemia (Hiatt and Nehler, 2001). On the basis of long-term follow-up of 1,244 patients with intermittent claudication having a mean ABPI of 0.78, the average yearly decline in ABPI is 0.014 (Aquino *et al.* 2001).

ABPI has been reported to be highly correlated with lower-extremity functional measures (McDermott *et al.* 2002b). The ankle systolic pressure correlates closely with direct intra-arterial pressure recordings, except at extremes of very high (0.8) or very low (< 0.4) ABPI (Beebe, 2001). It is well correlated with disease severity and can be used to assess disease progression and predict cardiovascular and cerebrovascular mortality (Mohler, 2003). However, ABPI has not shown a good correlation with walking performance in some studies (Beebe, 2001; Leder *et al.* 2002).

An accurate ankle pressure may not always be obtained (Hiatt and Nehler, 2001), especially in patients with long standing diabetes (Beebe, 2001). Patients with diabetes mellitus or end-stage renal disease might have calcified tibial vessels (Hiatt and Nehler, 2001). With incompressible vessels (Blackburn and Peterson-Kennedy, 1994), pressures can be artificially increased (McDermott *et al.* 2002b) and the clinical status consequently appears to be better than it really is (Beebe, 2001). The pressure in these calcified arteries is much greater than in the arm (> 200-250 mm Hg), leading to an ABPI value of greater than 1.30 (Hiatt and Nehler, 2001). However, other reports have found that mean ABPI is similar in PAD patients with and without diabetes (Dolan *et al.* 2002).

Approximately 5% of patients with PAD have a normal ABPI (McDermott *et al.* 2002b). These patients should be referred to a non-invasive laboratory for Doppler

waveform evaluation of the lower-extremity arteries and an exercise test on a treadmill to evaluate post-exercise ABPI (McDermott *et al.* 2002b). A significant decrease in post-exercise ABPI confirms the diagnosis of PAD (Hiatt and Nehler, 2001). With exercise testing it must change by at least 0.15 before it can be considered significant (Baker and Dix, 1981).

1.2 Assessment of functional status

1.2.1 Introduction

Improving walking ability is the primary goal of treating intermittent claudication. The condition is associated with a significant deterioration in functional capacity on exertion (Askew *et al.* 2002). The limitation in exercise capacity reduces a patient's level of everyday physical activity (Barletta *et al.* 1996). Determination of peak $\dot{V}O_2$ is considered to be important for assessing a patient's functional capacity (Womack *et al.* 1998) and is a common physiological variable measured during exercise testing, since its measurement helps to further define the extent of exercise intolerance and sheds light on the underlying causes (Askew *et al.* 2002).

The assessment of both walking ability (Regensteiner *et al.* 1990) and functional status in patients with intermittent claudication in the laboratory and community settings are important, so that the relative efficacies of the various treatments can be judged (Regensteiner, 1997). Quality of life should also be assessed, in order to ascertain the benefit of a given treatment for patients with PAD (Regensteiner, 2004). Treadmill protocols and questionnaire assessments are typically used (Regensteiner *et al.* 1997a), since both provide a high degree of precision and accuracy, and are practical and reproducible (Regensteiner and Hiatt, 1995).

1.2.2 Objective assessment of walking performance

1.2.2.1 Claudication and maximum walking distance

The primary measure of disability in patients with intermittent claudication is walking distance (Watson and Collin, 1998). The arterial insufficiency to the extremities due to the condition results in a mismatch of oxygen supply and demand to the working muscles, causing ischaemic pain (Askew *et al.* 2002). Both claudication distance (CD, distance at which claudication pain first occurs) and maximum walking distance (MWD, maximum distance terminated by intolerable claudication pain) are considered to be clinically relevant parameters (Labs *et al.* 1999a). Any therapy designed to

improve the symptomatic status of patients with claudication will typically result in an increase in CD as well as MWD (Hiatt and Nehler, 2001). Determination of both CD and MWD is part of a routine programme in the angiological examination of patients with PAD (Muller-Buhl *et al.* 1999).

A prerequisite for any test that is used to quantify walking capacity in this patient group is that it displays acceptable test-retest reliability (Labs *et al.* 1998), as defined in terms of the coefficient of variation and intraclass and Pearson product moment correlation coefficients of repeated tests, and that there is no significant difference in the readings obtained from repeated tests. Most treadmill studies have reported coefficients of variation for CD and MWD in the range of 15 - 40% (Cachovan *et al.* 1999; Gardner *et al.* 1991; Labs *et al.* 1999b; Labs *et al.* 1998; Perakyla *et al.* 1998). The variability of test-retest reliability coefficients reported from treadmill studies can probably be explained by differences in the testing protocols used and/or the way in which the test was administered, as well as the level of prior patient familiarisation and characteristics of the sample population (Zwierska *et al.* 2004).

The quantification of CD is the main outcome measure for clinical trials (Labs *et al.* 1998), since the daily activities of patients with PAD are typically governed by the onset of symptoms and not maximally tolerated discomfort (Mohler III *et al.* 2003). It has therefore been suggested that CD should receive greater attention than MWD in everyday clinical practice (Muller-Buhl *et al.* 1999). However, MWD has been found to correlate in a better way than CD with the objective and subjective assessment criteria of PAD (Muller-Buhl *et al.* 1999), since patients' own estimations of their CD are very subjective and in many cases unreliable (Nasr *et al.* 2002). MWD rather than the CD therefore appears to be the most reliable (Chaudhry *et al.* 1997) and important criteria by which to assess these patients (Muller-Buhl *et al.* 1999). The assessment of walking ability is not only an objective measure of the effectiveness of therapy, but it is also a valuable tool for motivating and providing feedback to the patient (Binnie *et al.* 1999).

1.2.2.2 Treadmill tests of walking performance

Walking is the most common mode of assessment of intermittent claudication (Askew *et al.* 2002). Treadmill testing provides an objective measure of walking capacity in PAD (Hiatt and Nehler, 2001). Patients have a reduced treadmill exercise performance

that is associated with severe limitations in physical functioning and ambulatory activity in the community (Regensteiner *et al.* 1996). It is widely believed that treadmill testing is the gold standard means of assessment, since exercise performance can be characterised and changes due to an intervention assessed (Regensteiner *et al.* 1990). A change in treadmill performance in response to therapy is the most commonly used endpoint in clinical claudication trials (Nasr *et al.* 2002). Typically, a 25% to 50% increase in treadmill performance is considered to be of clinical significance (Hiatt *et al.* 1995a; Hiatt, 1999).

There are two internationally accepted treadmill protocols, namely the constant-workload protocol, which uses a constant speed and grade (mostly 2mph or 3.2km.h^{-1} and 12% grade) and the graded (incremental) test, in which the speed is kept constant, but the gradient is varied. This test begins on the horizontal, after which the incline increases in pre-defined increments (e.g. 2%) at pre-defined intervals (e.g. 2 minutes) (Labs *et al.* 1999a).

The time or distance to the onset of claudication pain and maximal walking time or distance are recorded during an assessment (Nehler and Hiatt, 1999b). ABPI, blood pressure and heart rate can also be determined immediately after treadmill testing, while patients rest in the supine position on an examination table in close proximity to the treadmill (Montgomery and Gardner, 1998). The constant-load treadmill test and the graded-exercise treadmill tests show similar reproducibility (Cachovan, 1997). Constant-pace tests are generally easier to administer and do not require a programmable treadmill. In addition, there is a larger historical database derived from constant-pace tests, as many of the earlier published studies have used such protocols.

However, incremental (graded) protocols have the advantage that they can be used to assess walking performance in more heterogeneous patient populations with wide-ranging walking abilities (Hiatt *et al.*, 1995; Regensteiner and Hiatt 1995). In addition, incremental protocols are likely to be more useful for re-assessing patients after a treatment intervention (in which an improvement is expected), as they do not exhibit the 'ceiling' or 'placebo' effects which are more characteristic of constant-pace protocols (Regensteiner and Hiatt, 1995). Incremental treadmill protocols are also generally considered to have higher test-retest reproducibility for MWD than constant-pace treadmill protocols (Hiatt *et al.*, 1995; Labs *et al.*, 1999; Regensteiner and Hiatt 1995).

However, there is some evidence that constant-pace tests exhibit superior reproducibility for those patients with MWD in the range 50 - 150 m (Cachovan, 1997).

1.2.2.3 Alternative testing modalities

There are well documented limitations associated with treadmill testing, in that CD measured during a maximal graded exercise test may not accurately reflect the effect of claudication on everyday physical activities (Montgomery and Gardner, 1998). Furthermore, treadmill testing does not measure the effects of an intervention on the patient's perceived ability to walk or carry out activities in the community setting (Regensteiner *et al.* 1996). The test is costly and time-consuming (Montgomery and Gardner, 1998), since treadmills are expensive and require the presence of trained personnel (Cameron *et al.* 1997). Treadmill testing might not be available, practical or feasible in all clinical and rehabilitation settings e.g. vascular screening clinics, nursing homes, and retirement communities (Montgomery and Gardner, 1998). As a consequence, treadmill testing can be impractical in large epidemiologic studies or primary care settings (Regensteiner *et al.* 1990). Some elderly patients might also find treadmill assessments stressful (Amirhamzeh *et al.* 1997) or impossible to perform due to restricting factors other than claudication pain (Perakyla *et al.* 1999).

In addition to these potential problems, patients with claudication rarely need to walk at the intensity attained during a maximal, graded treadmill test (Gardner *et al.* 2001). Therefore, walking capacity assessed via incline treadmill testing might not accurately reflect the influence of claudication on everyday functional ability (Montgomery and Gardner, 1998; Coughlin *et al.* 2001), particularly walking ability on level ground in the non-laboratory setting (Regensteiner *et al.* 1990). Neither does treadmill testing directly assess a patient's perception of functional impairment, nor whether therapy has resulted in benefit (Nasr *et al.* 2002; Regensteiner *et al.* 1996).

One alternative to treadmill testing is a protocol in which patients walk up and down a 100-foot hallway for 6 minutes (the 6-minute walk protocol), during which they are encouraged to complete as many laps as possible (Guyatt *et al.* 1985). The test is clinically useful because it is less time consuming and exhausting than a treadmill graded exercise test and is less anxiety producing than other tests (Montgomery and Gardner, 1998). When compared to the graded treadmill protocol, the 6-minute walk test yields highly reliable measurements, which are related to the functional and

haemodynamic severity of PAD in patients with intermittent claudication, when compared with a graded treadmill protocol (Montgomery and Gardner, 1998).

Some studies have shown walking performance to improve significantly between the first and second test during the six-minute walk test, but not between the second and third test (Bauman and Arthur, 1997). These findings indicate that, as with treadmill testing, familiarisation is essential prior to data collection during this type of testing. However, in contrast, other studies (Montgomery and Gardner, 1998) have found no significant change between the first and second test, suggesting that accurate results can be obtained in patients with intermittent claudication following only one 6-minute walk test. Compared with the standard graded exercise test, the 6-minute walk test is easy to administer, requires less time, is less expensive, is better tolerated by patients and provides a better approximation of walking ability typically encountered during activities of daily living (Montgomery and Gardner, 1998). However, the 6-minute walk test does have a few disadvantages, in that a walking test that is performed in a 100-foot corridor logistically prevents immediate post-exercise measurements from being obtained because patients are far from an examination table upon test completion (Montgomery and Gardner, 1998). Personnel who administer the test must be trained to provide the same instructions to all patients (Montgomery and Gardner, 1998). Furthermore, the 6-minute walk test may not be as accurate in evaluating ambulatory function in patients who have asymptomatic PAD (Fontaine Stage I), because of a ceiling effect, and in patients with rest pain (Fontaine Stage III) or tissue loss (Fontaine Stage IV), because of a floor effect (Montgomery and Gardner, 1998).

Other alternatives to treadmill testing include cycling. However, currently cycling has little place in the assessment of intermittent claudication or prescription of exercise, which might in some respect be due to the lack of data on the physiological responses to cycling in intermittent claudication that are required to help determine or predict its effectiveness, relative to walking as a mode of exercise assessment or prescription (Askew *et al.* 2002).

An alternative exercise testing modality to treadmill walking for assessing the effect of the disease or treatment intervention on the functional capacity of a patient is a shuttle-walk test such as that developed by Singh *et al.* for patients with chronic airways obstruction (Singh *et al.* 1992). In a shuttle-walk test, patients walk back and forth

between two cones placed a set distance apart on flat ground at a pace which is controlled by audio-tape bleeps. Walking speed is increased incrementally - this gradually stresses the cardio-respiratory system to a symptom-limited maximum (Singh *et al.* 1992) and potentially makes it safer for patients with cardiac and respiratory conditions.

Figure 1. Patient undertaking a shuttle-walk test

The shuttle-walk test has recently been evaluated in patients with intermittent claudication, with respect to test-retest reliability, cardiovascular responses and patient preferences (Zwierska *et al.* 2004). The test exhibited similar test-retest reliability as an internationally accepted treadmill protocol (Labs *et al.* 1999a), but evoked lower levels of cardiovascular stress. Furthermore, compared to the graded treadmill protocol, the incremental shuttle-walk test was the preferred method of assessing walking ability by a large proportion of patients who expressed a definite opinion (Zwierska *et al.* 2004).

1.2.3 Questionnaires used to evaluate functional status

1.2.3.1 Introduction

Initial patient evaluation should consist of a clinical assessment of their disability, including a walking test to maximal claudication pain (Nehler and Hiatt, 1999b). However, in order to comprehensively evaluate functional status, it is important not only to consider laboratory-based measures such as treadmill tests, but also to examine community-based functional status such as can be obtained from questionnaires

(Regensteiner and Hiatt, 1995). Certain well-established questionnaires assess walking capacity (Nehler and Hiatt, 1999b) and provide patient-based information on claudication severity and response to therapy (Hiatt, 1997b). Questionnaires that evaluate functional status may play an important role in describing the benefits of interventions in patients with PAD (Regensteiner *et al.* 1996; Regensteiner and Hiatt, 1995). To evaluate their validity, questionnaire responses have been correlated to objective measures of walking performance and have been shown to have a high degree of precision and accuracy, and to be practical and reproducible (Regensteiner and Hiatt, 1995).

It is important that a questionnaire is easy to administer and evaluate (Regensteiner and Hiatt, 1995) and in the case of patients with intermittent claudication the most important criterion for the quality of life is functional disability (Muller-Buhl *et al.* 2003). The condition impairs patient's general health, and patients exhibit low scores for physical, social and emotional function (Barletta *et al.* 1996). The expected gain in quality of life should therefore be a crucial factor in the choice of treatment for patients with intermittent claudication (de Vries *et al.* 2002). Three such questionnaires that are used to evaluate disease-specific functional status/quality of life, generic health related quality of life and physical activity status are the Walking Impairment Questionnaire (WIQ), the Medical Outcomes Study SF-36 questionnaire and the PAD-Physical Activity Recall (PAD-PAR) questionnaire, respectively (Regensteiner *et al.* 1997a). These questionnaires have been used to quantify improvements in a patient's ability to walk distances and speeds, in the amount of habitual physical activity and in physical functioning after treatment interventions (Regensteiner *et al.* 1997a). The overall impact of a treatment intervention on health status (Hiatt, 1997b) and the overall impact on claudication can be described (Hiatt, 1999). Activity monitors that evaluate functional status can be used in conjunction with questionnaires to more fully describe the benefits of interventions in patients with PAD (Regensteiner *et al.* 1996). The information derived from such questionnaires thus provides a valuable adjunct to laboratory-based measures (Regensteiner and Hiatt, 1995).

1.2.3.2 Walking Impairment Questionnaire (WIQ)

The Walking Impairment Questionnaire (WIQ, Appendix 15) was developed and validated specifically for patients with intermittent claudication by Regensteiner *et al.* (Regensteiner *et al.* 1990). The WIQ is a disease-specific questionnaire (Hiatt *et al.*

1995a) which quantifies patients' self-reported claudication severity, the ability to walk defined distances, speeds and climb stairs (Regensteiner and Hiatt, 1995). It also characterises the symptoms that limit walking ability in patients with PAD (Regensteiner *et al.* 1990; Regensteiner *et al.* 1996) through a series of questions (Hiatt *et al.* 1995a).

The WIQ is simple to administer (Hiatt, 1999) and has been validated for detecting changes in walking impairment due to interventions in patients with intermittent claudication (Regensteiner *et al.* 1990). A treadmill test cannot fully evaluate whether an intervention alters a patient's perceived ability to walk in the community or non-laboratory setting, and might not therefore characterise a patients functional ability (Regensteiner *et al.* 1990). In the WIQ, patients rank their ability to walk specific distances on a 0-4 Likert scale.

The WIQ responses are stable when repeated over time in control patients (Hiatt *et al.* 1995b). The WIQ has been validated by comparison with treadmill walking, peripheral bypass and angioplasty in patients with PAD (Regensteiner *et al.* 1990; Regensteiner *et al.* 1993a). Changes in walking ability with exercise training have also been evaluated (Hiatt *et al.* 1990; Regensteiner *et al.* 1990). Modest correlations ($r = 0.68$) between the WIQ questionnaire and peak treadmill walking time have previously been reported (Regensteiner *et al.* 1990). Following a 3-month randomised controlled trial of exercise conditioning or post-surgery, the WIQ has identified improvements in the walking distance and speed domains, which were corroborated by treadmill performance (Regensteiner *et al.* 1990). An advantage of this questionnaire is that it can be administered and scored in 6-8 minutes (Regensteiner and Hiatt, 1995).

1.2.3.3 Physical activity recall (PAD-PAR) questionnaire

Physical activity status is an important variable to measure in PAD, given the link between inactivity and cardiovascular disease morbidity and mortality (Sieminski *et al.* 1997). The PAD-Physical Activity Recall (PAD-PAR; Appendix 18) has been developed and recommended (Regensteiner *et al.* 1997a; Regensteiner *et al.* 1996) for quantifying the weekly physical activity level of patients with intermittent claudication (Otis *et al.* 2000). The questionnaire has been modified from the original physical activity recall questionnaire developed by Sallis *et al.* (Sallis *et al.* 1985) to be more appropriate for patients with intermittent claudication (Hiatt *et al.* 1995b), since the

condition limits the number and amount of activities of daily living that can be performed by patients (Sieminski *et al.* 1997).

The PAD-PAR provides a global measure of habitual physical activity levels. Patients evaluate time spent over the previous week performing work activities, household tasks/yard work and leisure activities (Otis *et al.* 2000; Hiatt *et al.* 1995b; Sallis *et al.* 1985), classified as heavy, moderate, light and very light on the basis of metabolic equivalents (METs). One MET is equivalent to a resting $\dot{V}O_2$ of $3.5ml.kg^{-1}.min^{-1}$. Global physical activity status is obtained by estimating the total energy expenditure by summing the number of hours of physical activity per week in each of the four categories, which is recorded in MET hours per week ($MET\text{-}h.wk^{-1}$: hours per week multiplied by the MET value of the activity). Although the PAD-PAR must be administered by an interviewer, typically it can be administered and scored in less than 12 min (Regensteiner and Hiatt, 1995).

1.2.3.4 Quality of life assessment - the Medical Outcomes Study SF-36 v2

Intermittent claudication has detrimental effects on quality of life (Oka *et al.* 2003; Treat-Jacobson and Walsh, 2003). Patients are limited in their capacity to exercise and this consequently reduces their level of everyday physical activity (Barletta *et al.* 1996) and functioning (Taft *et al.* 2001). The Medical Outcomes Short Form-36 (MOS SF-36 *v2*; Appendix 13) (Ware and Sherbourne, 1992) is a self-administered health-related quality of life questionnaire that is easy to score (Regensteiner and Hiatt, 1995). The SF-36 assesses multiple aspects of normal life function (Hiatt *et al.* 1995b). It is a non-disease specific questionnaire (Hiatt and Nehler, 2001) and is a reliable and valid generic instrument which includes multi-item scales that assess two components of health, namely physical and mental (Gardner *et al.* 2001). More precisely, physical function and general health and well-being perceptions, as well as limitations due to mental health, social function and vitality (Ware and Sherbourne, 1992; McHorney *et al.* 1993; Regensteiner *et al.* 1997a; Regensteiner, 1997; Tarlov *et al.* 1989; Gardner *et al.* 2001; Stewart *et al.* 1989). Each domain of the SF-36 is scored from 0 (poorest health) to 100 (optimal health; Table 2).

This questionnaire has been used in population studies to evaluate functional status in a number of disease states and healthy persons (Tarlov *et al.* 1989; Stewart *et al.* 1989). It is well-validated and has been widely implemented in PAD studies. Patients with

PAD report profound limitations in all domains of quality of life which are related to their reduced physical health (Dumville *et al.* 2004). The scores from these domains are generally worse than those given by patients with chronic pulmonary disease and moderate to severe heart failure (Oka *et al.* 2003). Patients frequently report a significant impairment in their general health and lower scores for physical function (Barletta *et al.* 1996; Bauman and Arthur, 1997).

The effect of intermittent claudication on social and emotional function is questionable, since some studies have reported an impairment in these domains (Barletta *et al.* 1996), whereas others have not (Dumville *et al.* 2004). Furthermore, conflicting evidence exists regarding the correlation between a patient's quality of life impairment and their exercise capacity as assessed using the treadmill test. Some studies have reported poor correlations (Barletta *et al.* 1996), whereas others have reported correlations with physical domains, but not mental domains (Bauman and Arthur, 1997). The questionnaire is therefore particularly sensitive to detecting treatment effects in the physical functioning realm (Hiatt and Nehler, 2001). Such measurements provide a comprehensive insight into the degree of disability experienced by the patient as a result of the disease (Hiatt *et al.* 1995b).

Intermittent claudication has a greater impact on SF-36 scores in women than on men, which might result from a higher prevalence of mood disturbances and decreased physical functioning and more bodily pain in women compared to men (Oka *et al.* 2003). Training and invasive therapy have been shown to have a similar impact on health related quality of life dimensions (Taft *et al.* 2001), whereas unsupervised exercise programmes are unlikely to significantly improve a patient's quality of life (Currie *et al.* 1995). Ultimately, the success of any treatment or intervention must be judged against a patient's own assessments of change in various aspects of everyday life affected by the illness (Taft *et al.* 2001). For this reason, the SF-36 questionnaire is a useful measure of quality of life. It can be used with other health status questionnaires, such as the European Quality of Life (EuroQol) EQ-5D questionnaire (Appendix 14). The EuroQol has been used in previous studies (de Vries *et al.* 2002), since this questionnaire was best for discriminating among patients with different symptom severity.

Table 2. Definitions of the extreme scores in the MOS SF-36 (Ware, 2004)

Subscales	*Definitions of extreme scores*	
	Lowest possible scores	*Highest possible scores*
Physical functioning	Very limited performance in all physical activities, including bathing and dressing	Performance of all physical activities, including the most vigorous without limitations due to health concerns
Role - physical	Problems with work or activities of daily living as a result of physical health	Indicate no problems with work or other activities of daily living
Bodily pain	Very severe and extremely limiting pain	No pain or limitations due to pain
General health	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent
Vitality	Feel tired and worn out all the time	Full of pep and energy all the time
Social functioning	Extreme and frequent interference with normal social activities due to physical and emotional problems	Performs normal social activities without interference due to physical and emotional problems
Role - emotional	Problems with work or activities of daily living as a result of emotional problems	Indicate no problems with work or other activities of daily living
Mental health	Feelings of nervousness and depression all of the time	Feels peaceful, happy and calm all of the time

1.3 Current management of intermittent claudication

1.3.1 Treatment of intermittent claudication

The primary objectives of treatment for intermittent claudication are to improve walking ability (Hiatt, 1997a) and to reduce cardiovascular morbidity and mortality by treating the systemic atherosclerosis via the modification of risk factors and the use of anti-platelet drugs (Hiatt and Nehler, 2001). It is mandatory for clinicians to treat both PAD-specific symptoms (to decrease functional impairment and thereby improve quality of life, as well as to decrease rates of amputation) and the underlying systemic atherosclerosis (and thereby reduce cardiovascular ischaemic events, especially MI and stroke) (Hirsch and Reich, 2001).

Some patients with claudication are chronically disabled and in these patients the treatment goals are to relieve symptoms and to improve exercise performance and daily functional abilities (Hiatt and Nehler, 2001), predominately walking ability (Hiatt, 1997a). Treatment must be individualised, in that it must be based on the degree of lifestyle-limiting symptoms that are experienced by each patient (Beebe, 2001).

Given the relatively stable natural history of claudication, but severe limitation associated with the condition (Nehler and Hiatt, 1999b), vascular specialists typically recommend complete smoking cessation and home-based physical exercise as a primary treatment modality (Nehler and Hiatt, 1999b), coupled with vigorous risk factor modification (Santilli *et al.* 1996). Conservative management is advocated as the treatment of choice (Tan *et al.* 2000b), however compliance to these recommendations and ultimate benefit from these lifestyle modifications have not been well documented (Nehler and Hiatt, 1999b).

Further treatment to relieve claudication may include other pharmacological therapies and, occasionally, endovascular or other procedures (Santilli *et al.* 1996). Controversy exists concerning the relative effectiveness of conservative management and invasive therapy (Taft *et al.* 2001). Although many therapies for claudication have been thoroughly investigated, research continues on new treatments (Regensteiner and Hiatt, 2002b).

1.3.2 Intervention therapies

The decision to proceed with interventional surgery in patients with intermittent claudication requires an understanding of the natural history of the disease and an assessment of the patient's quality of life impairment as a result of walking difficulty (Hiatt and Nehler, 2001). Angiography precedes invasive treatment, however currently angiography is often replaced by non-invasive imaging modalities such as magnetic resonance angiography and duplex ultrasonography (de Vries *et al.* 2002). These modalities involve lower costs and risks compared to angiography, however they can lead to false test results (de Vries *et al.* 2002). Catheter-based endovascular treatments which are used in PAD include balloon angioplasty, endoluminal stents, and mechanical atherectomy devices (Beebe, 2001).

A large proportion of balloon angioplasties are technically successful and these improve the resting and post-exercise ankle pressures (Whyman and Ruckley, 1998). Invasive therapy might be more effective than supervised exercise training in alleviating illness-specific symptoms and improving certain aspects of physical functioning (Taft *et al.* 2001). However, many patients with intermittent claudication of relatively short duration can experience an improvement in their ischaemic symptoms without interventional treatment (McCombs and Subramanian, 2002). The choice between exercise training and angioplasty in the treatment of claudication with regards to the functional benefits and quality of life improvements achieved, thus remains controversial (Nehler and Hiatt, 1999b; Lewis *et al.* 1999).

The hazards of percutaneous transluminal angioplasty must also not be overlooked. Despite the reported low incidence of major complications, the occasional patient requires surgical intervention for bleeding, false aneurysm or acute ischaemia (Whyman and Ruckley, 1998). Blood flow may be restored and functional status improved, however for a symptom that has a relatively stable natural history, the associated cost of morbidity and mortality is high (Regensteiner and Hiatt, 1995).

A vascular bypass graft is a further option as this improves the exercise tolerance of claudicants by increasing blood flow to the lower-limbs (Tan *et al.* 2000a). Surgery generally involves two operations, the aortofemoral bypass which has the greatest utility in claudication and involves a single surgical procedure which bypasses diffusely diseased iliac arteries, and the femoral above-knee popliteal bypass (Hiatt and Nehler,

2001). Surgical revascularisation is undertaken on patients with severe aortoiliac disease in whom long-term patency is likely to be achieved (e.g. aorto-bifemoral or femoral-femoral bypass) and in patients who have a low cardiovascular peri-operative ischaemic risk (Hirsch and Reich, 2001). Endovascular revascularisation currently serves as an effective therapy for patients with high grade stenosis of the proximal limb arterial segments (e.g. distal aorta, common iliac artery, or external iliac artery, and occasionally the proximal common femoral artery) (Hirsch and Reich, 2001). In patients primarily considered for surgical treatment, anti-platelet and anticoagulant drug therapy can be used as a means of promoting graft patency, and beta-adrenergic blockers can be used as a means of reducing the perioperative risks associated with vascular surgery (Hiatt, 2002).

Patients with symptoms that limit their lifestyle may benefit from elective invasive revascularisation (Mohler III, 1999). While peripheral bypass surgery is feasible in the majority of patients with claudication, most vascular surgeons wish to delay this option as long as possible (Nehler and Hiatt, 1999b). Revascularisation procedures are therefore generally postponed until initial conservative management fails (de Vries *et al.* 2002). Symptoms consistent with limb-threatening ischaemia (such as rest pain) or a foot ulcer that does not heal (especially in a patient with diabetes) require immediate attention and possibly revascularisation (Mohler III, 1999). Surgery is also reserved for patients with severe, incapacitating claudication (Beebe, 2001; Regensteiner, 2004), those who develop ischaemic pain at rest or limb threatening ischaemia (Tsai *et al.* 2002; Gardner *et al.* 2001), and for those in whom all other therapies have failed (Nehler and Hiatt, 1999b).

All invasive interventions have a finite duration of success (Hiatt and Nehler, 2001) and may be inappropriate or unsuccessful, leaving patients with a significant handicap (Binnie *et al.* 1999). With bypass surgery, problems with graft failure, particularly with femoral above-knee popliteal bypass may arise (Hiatt and Nehler, 2001). This has the potential to convert a patient with claudication into a patient with more severe leg ischaemia, requiring further bypass surgery to avoid limb loss (Nehler and Hiatt, 1999b). The overly liberal use of catheter-based intervention or surgery, without vigorous attempts at risk-factor reduction, and exercise and medical therapy, is misguided and carries the needless potential risk of converting a non-limb-threatening condition into a worse situation should complications occur (Beebe, 2001).

Following failure of angioplasty or bypass surgery, the resultant limb circulation is frequently worse than that encountered before the intervention (Hiatt and Nehler, 2001). This occurs because of division or thrombosis of the collateral circulation at the time of the intervention, or the failure of thrombus propagation or embolisation at the time of reconstruction, or both (Hiatt and Nehler, 2001). These events are more likely to occur in vascular bypass procedures than angioplasty (Hiatt and Nehler, 2001).

Angioplasty performed whenever feasible has been shown to be more effective than exercise alone (de Vries *et al.* 2002). However, invasive treatments can carry economic implications, since percutaneous transluminal angioplasty is expensive both in terms of consumables and staff costs (Whyman and Ruckley, 1998). Considering the limited health care budget, consideration needs to be made regarding whether the gain in quality-adjusted life expectancy justifies the cost involved (de Vries *et al.* 2002). The expected gain in effectiveness achieved with bypass surgery for intermittent claudication is considered to be small compared with the cost involved (de Vries *et al.* 2002), and as such it is recognised as an expensive treatment which is of unproven benefit for claudication (Whyman and Ruckley, 1998).

1.3.3 Pharmacological therapies

Although pharmacological therapies have been developed, the role of drugs in the overall management of the disease needs further study (Regensteiner and Hiatt, 1995). Various classes of drugs have been suggested as possible treatment options for intermittent claudication. In patients with PAD evidence supports the use of statin drugs for lipid management and angiotensin-converting enzyme-1 inhibitors for blood pressure control (Hiatt, 2002). Atorvastatin improves pain-free walking distance and community-based physical activity in patients with intermittent claudication (Mohler III *et al.* 2003). Recently, the Heart Protection Study confirmed that statin treatment reduces the risk of death and adverse cardiovascular events in patients with coronary and non-coronary atherosclerosis, including patients with PAD who had not had a prior cardiovascular event (MRC/BHF Heart Protection Study, 2002).

One possible mechanism of action of how modification of the lipid profile with a statin drug improves symptoms of claudication, might be the reduction in plaque size, thereby improving the blood flow in the large arteries of the lower extremities (Mohler III *et al.* 2003). Another possible mechanism is statin-induced improvement of vasomotor

regulation of blood flow, particularly in the microcirculation or it might affect new blood vessel formation (Mohler III *et al.* 2003). It has been suggested that the timing of clinical improvement for atorvastatin appears to be longer compared with cilostazol, and thus patients with claudication symptoms should not expect symptomatic improvement in pain-free walking time after weeks, but more likely after months of treatment (Mohler III *et al.* 2003).

Furthermore, specific anti-platelet agents (aspirin and clopidogrel), anti-claudicants (cilostazol and pentoxifylline) (Olin, 2002), carnitine (Hiatt, 1997a), vasodilators, anticoagulants, prostaglandins and prostaglandin derivatives, have been recommended, all of which have variable and generally disappointing results (Beebe, 2001). Aspirin should be considered in all patients with PAD, with clopidogrel an alternate (and potentially more effective) agent (Hiatt and Nehler, 2001). Aspirin, is considered valuable because of its impact on vascular events at other sites (Verstraete, 1994), possibly promoting the patency of surgical and angioplasty procedures (Hiatt and Nehler, 2001). It has also been indicated to reduce morbidity and mortality in PAD (Bradberry, 2004). Anti-platelet agents such as clopidogrel and ticlopidine act by blocking adenosine diphosphate (ADP) receptors on the platelet (Hiatt and Nehler, 2001). Clopidogrel reduces the risk of atherothrombotic events such as MI and stroke in these patients (Bradberry, 2004) and may be beneficial in the long-term management of atherosclerotic disorders (Beebe, 2001). Angiotensin-converting enzyme (ACE) inhibitors may confer an additional benefit in terms of reducing the risk of fatal and non-fatal ischaemic events (Hiatt and Nehler, 2001).

Although no studies have shown that these drugs are capable of improving the symptoms of claudication (Beebe, 2001), substantial reductions in cardiovascular morbidity and mortality can be achieved (Creager, 2001). Nevertheless, risk factor modification in conjunction with anti-platelet treatment does decrease the incidence of heart attack, stroke and peripheral vascular events in PAD (Mohler III, 2004) and should be considered in all patients with intermittent claudication (Hiatt, 1997a).

Other drugs such as pentoxifylline, a xanthine derivative, has been shown to reduce blood viscosity (Beebe, 2001). Pentoxifylline exhibits a modest (Hiatt, 1997a) to marginal efficacy in improved treadmill exercise performance (Nehler and Hiatt, 1999b; Girolami *et al.* 1999) and is the only drug approved for the treatment of claudication in

the USA. It has been reported to improve MWD by approximately 20 - 25% (Creager, 2001). However, adverse effects including headache, diarrhoea, abnormal stools and palpitations have been reported with the drug (Chapman and Goa, 2003).

Cilostazol, a phosphodiesterase type 3 inhibitor, approved for the treatment of PAD in 1999 (Jaff, 2002) is currently the most effective drug for claudication (Hiatt and Nehler, 2001). It is significantly more effective than pentoxifylline in improving both pain-free and MWD (Beebe, 2001). Randomised, double-blind, placebo controlled trials in patients with moderate to severe intermittent claudication have demonstrated that cilostazol significantly increases walking distances and improves quality of life compared with placebo (Chapman and Goa, 2003). In clinical trials, MWD has been reported to improve by approximately 40 - 60% (Creager, 2001).

It acts by inhibiting platelet aggregation and increasing vasodilation (Beebe, 2001). It also exhibits anti-proliferative effects on smooth muscle cells and has beneficial effects on high density lipoprotein-cholesterol and triglyceride levels (Chapman and Goa, 2003). Although the drug has been shown to have a good safety and tolerability profile (Collinson and Donnelly, 2004), it does have side effects including headache, transient diarrhoea, abnormal stools, peripheral edema (Chapman and Goa, 2003), palpitations and dizziness. It should not be given to patients with claudication who also have heart failure (Hiatt and Nehler, 2001) and severe hepatic or renal impairment (Chapman and Goa, 2003). In the UK, USA and Japan, cilostazol administered at 100mg twice daily is licensed for symptom relief in patients with stable, moderate-to-severe intermittent claudication and as an adjunct to non-pharmacological approaches such as exercise (Collinson and Donnelly, 2004).

Several other anti-platelet agents, angiogenic growth factors such as vascular endothelial growth factor, basic fibroblast growth factor, propionyl-l-carnitine, vasodilator prostaglandins, L-arginine and lipid-lowering drugs are also being evaluated for the treatment of claudication (Hiatt, 1997a; Creager, 2001). Angiogenic growth factors have shown preliminary success in patients with rest pain and ischaemic ulcers and are being investigated for use in patients with intermittent claudication (Schainfeld, 2001). Drugs such as oxpentifylline and naftidrofuryl may also improve the walking distance in some patients, however they have not been shown to be of long-term value and are infrequently prescribed by vascular surgeons (Whyman and Ruckley, 1998).

Although new pharmacologic therapies are emerging, supervised exercise rehabilitation remains the most effective approach for increasing pain-free walking for patients with intermittent claudication (Mohler III, 1999).

1.3.4 Lifestyle management

Although the treatment of claudication symptoms is important, an improved lifestyle and treatment of risk factors will prolong life (Mohler III, 2004). Hence, epidemiological evidence has led most clinicians in both primary and hospital care to manage intermittent claudication conservatively (Stewart and Lamont, 2001); by advising claudicants of the benefits of taking regular exercise, giving up smoking and when necessary, losing some weight (Binnie *et al.* 1999). The main treatment strategy for symptomatic relief for patients with mild to moderate intermittent claudication in the UK is exercise advice (Cheetham *et al.* 2004). Indeed, the general advice given in the hospital setting is to "stop smoking and keep walking" (Housley, 1988).

The goal of patient education is to increase awareness about the causative relationship between risk factors and poor lifestyle choices and the disease (Beebe, 2001). Simple advice given to walk further, regardless of cessation of smoking and correction of other risk factors, can improve walking ability remarkably and the improvements can be sustained at two years, possibly even in the presence of a worsening disease profile (Whyman and Ruckley, 1998). Unfortunately, a major problem for clinicians is motivating targeted individuals to begin and adhere to an exercise regimen and to stop smoking (Christman *et al.* 2001), since many patients find it difficult to translate this general advice into specific practical strategies for achieving, and sustaining, appropriate changes in behaviour (Binnie *et al.* 1999). Furthermore, patients are reluctant to understand that various interventions, including limb bypass and angioplasty, do not cure PAD (Beebe, 2001).

Nursing intervention can improve the functional ability and the general well-being of many patients (Binnie *et al.* 1999). In the hospital setting vascular nurses practicing in a multitude of inpatient and outpatient settings can play an important role during exercise therapy, by developing and providing a personalised home-based exercise programme, and the nurses can care and motivate patients during follow-up periods (Spronk *et al.* 2003). Vascular nurses can also assist patients with risk factor modifications (Treat-Jacobson and Walsh, 2003). Substantial data exists proving the benefit of life-style

modification in improving mortality and reducing cardiovascular events in patients with PAD (Khan *et al.* 2005). There exists compelling evidence to support smoking cessation, to increase exercise capacity and improve diet in these patients (Khan *et al.* 2005). Counselling sessions about nutrition, exercise, risk factors for atherosclerosis, and potential complications of cardiovascular disease have been administered in conjunction with supervised exercise therapy (Menard *et al.* 2004). Smoking cessation, blood pressure control, lipid modification and strict control of diabetes mellitus will reduce the risk of both macro- and microvascular disease progression (Mohler III, 2004) and this should be the first choice approach for the treatment for PAD (Beebe, 2001).

A combination of health education and exercise for claudicants with high cholesterol, could lower the total cholesterol, possibly reducing the need for additional treatment (Tan *et al.* 2000a). However, deficiencies in physician knowledge and attitudes regarding atherosclerotic risk factor reduction in PAD contribute to lower rates of risk factor reduction in these patients (McDermott *et al.* 2002c). Maintaining glycaemic control, and ensuring the initiation of lifelong anti-platelet therapy and participation in exercise rehabilitation programmes, will all promote positive outcomes for patients with intermittent claudication (Treat-Jacobson and Walsh, 2003).

1.3.5 Risk factor modification

The risk factors that contribute to PAD are similar to those associated with systemic atherosclerosis, namely, cigarette smoking and diabetes mellitus (both of which pose the greatest risk for disease progression) (Aquino *et al.* 2001; Creager, 2001), hypertension, hypercholesterolemia, hyperhomocysteinemia (Creager, 2001), dyslipidaemia and age (Treat-Jacobson and Walsh, 2003). Elevated levels of plasma homocysteine are an independent risk factor for PAD, although to date no clinical trials have demonstrated a clinical benefit in reducing homocysteine levels through vitamin supplements (Hiatt and Nehler, 2001). PAD may progress if these atherosclerotic risk factors remain uncontrolled (Mohler III, 2004).

Current treatment strategies for patients with symptomatic PAD include aggressive modification of risk factors for cardiovascular disease, such as cessation of smoking, treatment of hypertension and diabetes, normalisation of low-density lipoprotein cholesterol (Regensteiner and Hiatt, 2002b) and exercise (Beebe, 2001). The focus on improving functional impairment as well as on aggressive risk factor modification is

important (Regensteiner *et al.* 1997a). In many patients, a significant reduction of symptoms and prevention of disease progression (Beebe, 2001) can be achieved by correction of associated risk factors and supervised exercise training (e.g. walking) (Duprez *et al.* 1999), which can also improve the functional status of patients (Beebe, 2001).

Although cardiovascular and cerebrovascular complications are more prevalent in patients with severe PAD, patients with asymptomatic disease are still at significant risk, therefore the focus on the management of PAD should be on early diagnosis and efforts to reduce the risk of adverse events including risk factor modification and anti-platelet therapy (Eberhardt and Coffman, 2004). Attempts to reduce atherosclerotic risk factors in patients with PAD are less common than in patients with coronary artery disease (CAD) (McDermott *et al.* 1997), and such 'under treatment' may contribute to the high rates of cardiovascular disease morbidity and mortality in PAD (McDermott *et al.* 2002c).

Even after adjustment for risk factors, PAD appears to increase the risk for ischaemic events in other vascular territories with an approximate two-fold increase in myocardial infarctions and perhaps stroke (Eberhardt and Coffman, 2004). The reasons for the under-treatment of atherosclerotic risk factors in PAD are unknown, however one possible explanation is that physicians are less aware of the high rate of cardiovascular morbidity and mortality or the importance of risk factor reduction in PAD (McDermott *et al.* 2002c).

1.3.6 Key modifiable risk factors in PAD

1.3.6.1 Smoking

Cigarette smoking has both long-term and short-term affects on arterial blood flow in the lower extremities in patients with PAD (Gardner *et al.* 2004a). Smoking is the single most important modifiable risk factor for patients with PAD and has a synergistic effect on other risk factors associated with intermittent claudication, including hypertension, hypercholesterolemia, and diabetes (Beebe, 2001). Cigarette smoking causes lingering impairments in peripheral blood flow and oxygen delivery to the lower-extremity musculature following acute exposure to smoking (Yataco and Gardner, 1999; Ricci *et al.* 1993).

Cigarette smokers with PAD have more severe claudication, reduced peripheral circulation, lower exercise capacity and poorer cardiopulmonary measurements at peak exercise than ex-smoking claudicants (Gardner, 1996), possibly because they are less physically active than non-smokers (Gardner *et al.* 1997). Evidence suggests that smokers engage in activities of similar intensity, but for a shorter duration of time than ex-smoking claudicants (Gardner *et al.* 1999b), resulting in reduced exercise capacity. This places patients who smoke at a greater risk of dependency than patients who do not smoke (Gardner, 1996).

Non-smokers can walk further than current or former smokers and they have a higher ABPI than patients who currently smoke (Cahan *et al.* 1999). The more rapid development of claudication pain in current smokers has been associated with lower peak $\dot{V}O_2$ compared to former smokers or patients with PAD who have never smoked (Gardner *et al.* 2004a; Gardner, 1996; Gardner *et al.* 1999a). In one study, smoking cessation alone was associated with a 40% improvement in MWD (Quick and Cotton 1982). Cigarette smoking has been suggested to result in peripheral vasoconstriction in the lower extremities (Ricci *et al.* 1993). The greater impairment in perfusion of the calf musculature in patients who smoke is a potential explanation for their lower CD and overall physical function than in the non-smoking patient with PAD (Gardner *et al.* 1997; Gardner *et al.* 1999b).

Consequently, patients with PAD who smoke are on the lower end of the physical function spectrum and may be prime candidates to regain lost functional independence through a program of exercise rehabilitation (Gardner *et al.* 2004a). Furthermore smoking may affect patient's health-related quality of life (Gardner *et al.* 2004a). Although a 6-month exercise rehabilitation programme has reported similar improvements in claudication pain distances, ambulatory function, physical activity, peripheral circulation and health-related quality of life in smoking and non-smoking patients with PAD (Gardner *et al.* 2004a), smoking cessation is important (Girolami *et al.* 1999) as it is associated with improved postoperative graft patency rates and a reduction in the complications of PAD (Radack and Wyderski, 1990). All available strategies to help patients stop smoking such as counselling and nicotine replacement should be used (Gey *et al.* 2004).

1.3.6.2 Diabetes

Type 2 diabetes is common in both men and women with PAD. Diabetic patients with PAD are younger, have a higher BMI, a poorer neuropathy score, a higher prevalence of hypertension and a greater number of cardiovascular co-morbidities (predominantly cardiovascular) compared with non-diabetic patients with PAD (Dolan *et al.* 2002). Differences in physical activity levels exist between PAD patients that have and do not have diabetes. Patients with diabetes have a shorter mean 6-minute walking distance and a slower fast-pace 4-metre walk velocity compared with those without diabetes. Patients with diet-controlled diabetes perform better than those on diabetes medication (Dolan *et al.* 2002). In diabetic patients with PAD, the disease tends to follow a more aggressive course, with early large vessel involvement coupled with microangiopathy (Aquino *et al.* 2001). Thus, aggressive lifestyle modification for diabetes prevention should be offered in patients with PAD at high risk of developing the disease (Dolan *et al.* 2002). Monitoring for diabetes generally occurs on a regular basis once a patient is diagnosed with PAD (Dolan *et al.* 2002). Diabetic patients with PAD should be evaluated for the presence of associated co-morbidities that could contribute to further disability (Dolan *et al.* 2002). Intensive blood glucose control and aggressive risk factor modification (Hiatt and Nehler, 2001) should be implemented. However, although intensive blood glucose control may have favourable effects on the risk of cardiovascular events, it does not improve the risks associated with PAD (Hiatt and Nehler, 2001).

Diabetic patients with PAD are less likely to report classical intermittent claudication (i.e. the onset of a cramp-like pain during walking) than those without diabetes, and more likely to report leg pain on both exertion and rest, which might be explained by the altered foot architecture in these patients (Dolan *et al.* 2002). Compared with non-diabetic patients, diabetic patients with claudication have a 2.9-fold increased risk for development of ischaemic ulceration and a 1.7-fold increased risk for development of ischaemic rest pain (Aquino *et al.* 2001). Death in patients suffering with PAD and diabetes has been reported to be 2.2 times that for PAD alone (Leibson *et al.* 2004). Diabetes is a risk factor for both PAD and PAD-associated mortality, emphasising the need to detect and monitor PAD in diabetic patients (Leibson *et al.* 2004).

1.3.6.3 Hypertension and hyperlipidaemia

Hypertensive patients with PAD should be aggressively managed (Hiatt and Nehler, 2001). Normalisation of blood pressure (less than 130/90 mm Hg) should be the goal to decrease the rates of cardiovascular ischaemic events in all patients with PAD, unless otherwise contraindicated (Hirsch and Reich, 2001). All classes of anti-hypertensive agents can safely be administered to patients with PAD (Hiatt and Nehler, 2001).

For primary prevention of CHD the British Heart Foundation recommends a total cholesterol level of less than 5.2 mM for normal adults (Tan *et al.* 2000a) and low-density lipoprotein (LDL) cholesterol should be less than 3.4 mM (American College of Sports Medicine, 2000; Hirsch and Reich, 2001). Niacin, is regarded as an important treatment agent in patients with PAD for lowering triglyceride levels and increasing high-density lipoprotein (HDL) cholesterol (Hiatt and Nehler, 2001).

1.3.7 Physical activity

1.3.7.1 Introduction

Over the past 15 years or so, the medical community has become increasingly aware of the important role which physical inactivity plays in the development of many chronic degenerative diseases (Fletcher *et al.* 1992; Pate *et al.* 1995; Bouchard, 2001). Physical inactivity itself is an independent risk factor for atherosclerosis (Stewart and Lamont, 2001). Patients with PAD who have impaired lower extremity performance are less physically active than non-PAD patients and this might contribute to subsequent disability (McDermott *et al.* 2002a; Regensteiner *et al.* 1994).

Low performance scores on a test battery, which combine walking velocity and time for five repeated chair rises and standing balance (which measures leg strength and balance), have been found in more sedentary patients, and it is possible that their lower level of physical activity could form part of the causal pathway linking reduced lower extremity performance to functional decline and mortality (McDermott *et al.* 2002a). These reductions in daily activity are similar to those of patients with severe heart failure and thus indicate a profound limitation in physical performance (Hiatt, 1999).

1.3.7.2 Exercise rehabilitation

A substantial number of patients referred to vascular clinics with intermittent claudication cannot be helped by conventional treatments, for example those with

lesions unsuitable for angioplasty, or those in whom angioplasties have failed, and those whose symptoms are not sufficiently disabling to justify the risks of reconstructive surgery (Binnie *et al.* 1999). For these patients conservative therapy programmes, such as exercise rehabilitation in conjunction with risk factor management are a possibility (Binnie *et al.* 1999). In the general elderly population regular exercise can often slow or reverse the decreased mobility that contributes to disease and disability (Buckwalter, 1997). However, it is important to note that individual responses to exercise might vary considerably (de Vries *et al.* 2002). Exercise is a good alternative to reconstructive surgery in patients with intermittent claudication (Ekroth *et al.* 1978), since it is non-invasive, effective (Treesak *et al.* 2004), inexpensive and deemed to be of low risk (Leng *et al.* 2000). Indeed, it has been suggested that for the treatment of intermittent claudication the success rate of exercise therapy compares favourably with percutaneous transluminal angioplasty and some infrainguinal bypass studies, with very low threat to limb viability and without the risk of surgical complications (Menard *et al.* 2004). By improving functional exercise capacity, physical abilities may also improve (Bauman and Arthur, 1997).

Formal exercise programmes to treat claudication have been evaluated for over 30 years and exercise has been shown to be efficacious in terms of improving walking performance, quality of life, functional capacity (Nehler and Hiatt, 1999b) and community-based functional status (Regensteiner *et al.* 1997a; Hiatt, 1991). Exercise is also generally well tolerated by patients (Regensteiner and Hiatt, 1995). Increases in walking ability following supervised exercise are independent of the location of the atherosclerotic lesion or the presence of diabetes (Ekroth *et al.* 1978). There is no age limit to the benefit of exercise (Buckwalter, 1997). In older individuals, leisure-time physical activity enhances health and function (Tager *et al.* 1998). This is increasingly important in intermittent claudication, since compared with aged-matched healthy individuals, claudicants exhibit lower levels of physical activity and the severity of PAD increases as patients become progressively more sedentary (Sieminski and Gardner, 1997).

All published studies of exercise conditioning in patients with PAD, whether randomised, controlled trials or not, have reported an increase in treadmill exercise performance and a lessening of claudication pain severity during exercise (Regensteiner and Hiatt, 1995). Exercise as a treatment for intermittent claudication is not new, with

improvements in walking having been described from as early as 1898 (Stewart and Lamont, 2001). It has become the mainstay of non-pharmacologic therapy (Beebe, 2001) and can also be used in conjunction with medications specifically indicated to improve symptoms (Treat-Jacobson and Walsh, 2003). Certainly, in the last 50 years, exercise training in some form has been recommended as a means to help patients with symptomatic PAD improve their walking ability (Regensteiner and Hiatt, 1995).

Exercise increases walking distances to the onset of pain and to MWD, and improves walking economy (i.e. efficiency) (Hiatt *et al.* 1995b; Wolmack *et al.* 1997), and function (Katzel *et al.* 2000), thereby conferring greater improvements than angioplasty (Perkins *et al.* 1996). Furthermore, exercise does not interfere with the option for surgery should this become necessary in the immediate or latter course of the disease (Ekroth *et al.* 1978). Exercise rehabilitation provides benefit, and in addition to the low associated morbidity, should be recommended as an important treatment option for patients with intermittent claudication (Regensteiner *et al.* 1997a; Regensteiner and Hiatt, 1995).

1.3.7.3 Possible contraindications to exercise in diabetic patients with PAD

Although physical activity is a major therapeutic modality for type 2 diabetes (Allbright *et al.* 2000), patients with PAD and diabetes have a poorer lower extremity function compared to patients with only PAD, which might be explained by diabetes-associated neuropathy, differences in exertional leg symptoms, and greater cardiovascular disease in patients with diabetes (Dolan *et al.* 2002). Both neuropathy and foot ulceration in these patients are associated with an increased risk of gangrene and lower extremity amputation (Nathan, 1993). Furthermore, the development of autonomic neuropathy in patients with diabetes affects the heart rate response to exercise, and as a result ratings of perceived exertion rather than heart rate may need to be used to moderate the intensity of physical activity in these patients (Allbright *et al.* 2000). Type 3 diabetic patients with PAD generally have a low level of fitness ($\dot{V}O_2$ max) compared to non-diabetic patients, and as a consequence, exercise intensity should be at a comfortable level (RPE 10-12) in the initial periods of training and should proceed cautiously as tolerance for physical activity improves (Allbright *et al.* 2000).

1.3.7.4 Mechanisms associated with improved walking ability

The mechanism by which exercise rehabilitation produces improved walking ability in intermittent claudication is not completely understood (McCombs and Subramanian, 2002). It is believed that exercise training improves walking distance via a combination of mechanisms, including an adaptation or redistribution of the peripheral blood flow (collateral development), metabolic adaptations within the exercise-trained skeletal muscle, an inhibition of atherosclerotic disease progression (Remijnse-Tamerius *et al.* 1999), improved circulatory dynamics (McCombs and Subramanian, 2002), improved cardiac status, reduced oxygen cost of exercise or reduction of lactate load (Tan *et al.* 2000a). Such physiological adaptations frequently improve both the patient's physical aspect and quality of life (Tan *et al.* 2000b).

1.3.7.5 Central and peripheral circulatory adaptations

Normal individuals can increase the quantity and velocity of blood flow to an exercising extremity via a combination of physiological responses, including an increase in cardiac output and reduction in the peripheral resistance of arterioles supplying the exercising muscles, thereby achieving a modest increase of lower extremity blood flow in response to physical training (McCombs and Subramanian, 2002). There is evidence that central cardiac pumping capacity can be improved with aerobic exercise training in patients with symptomatic PAD (Walker *et al.* 2000). With improved central cardiac pumping capacity, a decrease in resting and exercising heart rate is achieved (Tan *et al.* 2000a). Following a short period of structured upper-and lower-limb aerobic exercise training (Walker *et al.* 2000) and walking exercise rehabilitation (Tan *et al.* 2000a) in patients with symptomatic PAD, at equivalent submaximal intensities the heart rate response to exercise intensities has been shown to be reduced. These studies suggest that an improvement in central cardiac pumping capacity can have a significant impact on exercise tolerance (Tan *et al.* 2000a).

Vascular bypass grafts improve the exercise tolerance of patients with intermittent claudication by directly increasing blood flow to the lower-limbs (Tan *et al.* 2000a). This is an uncommon finding following exercise training (Tan *et al.* 2000b; Nehler and Hiatt, 1999b), which suggests the involvement of mechanisms other than an increase in absolute blood flow (Tan *et al.* 2000a). In previous studies, changes in flow have not been correlated with changes in exercise performance (Nehler and Hiatt, 1999b; Regensteiner and Hiatt, 1995). Indeed, improvements in walking occur largely

independently of ankle pressures, thereby suggesting that the adaptation is not purely a flow phenomenon (Johnson *et al.* 1989; Carter *et al.* 1989). However, it is possible that there might be a better redistribution of flow to exercising muscles (Nehler and Hiatt, 1999b; Regensteiner and Hiatt, 1995) without an increase in the absolute flow rate (Tan *et al.* 2000a). Collateral blood flow is believed to be the most important determinant of functional parameters, such as exercise tolerance and intensity of symptoms (McCombs and Subramanian, 2002). A decrease in blood viscosity (Ernst and Matrai, 1987) or an increase in capillary density and surface area, as well as haemorheological changes may also alter the exchange of oxygen and substrate at the capillary/muscle fiber interface (Regensteiner and Hiatt, 1995).

Patients with PAD exhibit a high incidence of abnormal blood rheology (Pararajasingam *et al.* 1998). In one study, almost half of the patients had a plasma viscosity in excess of the upper limit of normal (1.72 cP) (Tan *et al.* 2000a). In PAD, blood viscosity plays a major role in residual microvascular perfusion, indeed during acute leg ischaemia factors influencing microvascular blood viscosity include the plasma fibrinogen concentration, red and white blood cell rheology, as well as platelet aggregation and activation (Ciuffetti *et al.* 2003). In normal individuals, exercise training reduces plasma viscosity (Ernst, 1987; Chien *et al.* 1966) and decreases packed cell volume (PCV) (Fellmann, 1992). This decrease in PCV can consequently lead to improved blood flow (Tan *et al.* 2000a).

A significant improvement in blood rheology in patients with intermittent claudication has been found following a supervised training programme in some studies (Ernst and Matrai, 1987), but not in others (Tan *et al.* 2000a). Furthermore, endothelial function, which is a measure of vascular health, is also impaired in patients with PAD. Exercise rehabilitation which improves ambulatory function can also improve endothelial-dependent vasodilation in older patients with intermittent claudication (Brendle *et al.* 2001).

1.3.7.6 Local metabolic adaptations in skeletal muscle

An additional mechanism which has been proposed is an increase in muscle enzyme activity (Nehler and Hiatt, 1999b). Increases in the activity of cytochrome oxidase, citrate synthetase and 3-hydroxyacyl-CoA dehydrogenase, and changes in blood rheology and improved blood oxygen extraction have all been suggested (Whyman and

Ruckley, 1998). Metabolic adaptations may occur in the ischaemic muscle in response to exercise, via an up-regulation of glucose and fatty acid metabolism under reduced oxygen tensions (McCombs and Subramanian, 2002).

In normal individuals, exercise training leads to an improvement in the oxidative metabolism of skeletal muscle and these changes are associated with an improvement in the extraction of oxygen and substrate during exercise (Regensteiner and Hiatt, 1995). In patients with intermittent claudication, regular exercise is also believed to be effective in altering skeletal muscle metabolism (Sidoti, 1992), thereby preserving aerobic glycolysis and preventing the accumulation of lactate and pyruvate (McCombs and Subramanian, 2002). Skeletal muscle mitochondrial ATP production rate has been shown to be significantly higher in trained patients compared with controls (Hou *et al.* 2002). This, and citrate synthase activity have been shown to be highly correlated with walking performance in patients with PAD, suggesting that muscle mitochondrial capacity to oxidise carbohydrate is positively related to walking performance in patients with PAD (Hou *et al.* 2002).

The determination of peak $\dot{V}O_2$ is considered important for assessing functional capacity and exercise prescription (Womack *et al.* 1998). Associated metabolic dysfunction of the skeletal muscles is rectified by exercise, resulting in a change in oxidative capacity of the skeletal muscle and greater utilisation of oxygen (Tan *et al.* 2000b). A period of supervised treadmill walking (12 weeks) can increase peak $\dot{V}O_2$ by 30%, with no change in control patients (Hiatt *et al.* 1990). Part of the metabolic adaptation that occurs with training in normal individuals is an increase in the oxidative capacity, and a fall in the RER (Holloszy and Coyle, 1984). A fall in RER in claudicants has also been shown following supervised exercise training (Hiatt *et al.* 1990).

A further metabolic adaptation relates to changes in carnitine metabolism with exercise training (Regensteiner and Hiatt, 1995). Under normal metabolic conditions, carnitine is required for the transportation of long-chain fatty acyl groups into the mitochondria (Regensteiner and Hiatt, 1995). Under abnormal metabolic conditions, such as muscle ischaemia, carnitine interacts with the cellular acyl-CoA pool to form acylcarnitines thereby removing a variety of acyl groups from acyl-CoA intermediates (Bieber *et al.* 1982). Patients with claudication accumulate acylcarnitines in their skeletal muscle (Nehler and Hiatt, 1999b).

Elevated levels of plasma concentration of acylcarnitines are associated with functional impairment of PAD and reflect the metabolic state of ischaemic skeletal muscle (Hiatt *et al.* 1990). Exercise training clears these acylcarnitine compounds and the degree of removal from skeletal muscle is directly correlated with improved exercise performance, suggesting some metabolic improvement as a result of training (Nehler and Hiatt, 1999b; Hiatt *et al.* 1990). Indeed, a 12-week supervised treadmill walking programme has been shown to result in a 26% decrease in resting plasma short-chain acylcarnitine concentration, which was correlated with improved maximum walking time (Hiatt *et al.* 1990). Furthermore, a decrease in venous lactate levels after exercise has also been found through training, supporting the concept of the reduction in anaerobic metabolism (Tan *et al.* 2000a), which has been associated with increased MWD (Tan *et al.* 2000a).

It has been suggested that the presence of a chronic state of arterial insufficiency might lead to changes in the metabolic state of muscle (Jansson *et al.* 1988), and that the main mechanism of improvement in exercise performance appears to involve peripheral adaptations in skeletal muscle metabolism rather than increases in cardiac output or peripheral blood flow (Hiatt, 1991).

1.3.7.7 Other adaptations

A further possible mechanism for the improved walking ability following exercise training could be a change in gait (Regensteiner and Hiatt, 1995). Patients with claudication compared to aged matched controls demonstrate abnormal gait parameters, and it has been suggested that further studies should evaluate whether the abnormal gait significantly curtails walking ability (Scherer *et al.* 1998). It is likely that patients with intermittent claudication perform minimal exercise, and subsequently develop features of disuse atrophy. Exercise training might help to overcome some of the inefficiencies of walking associated with such gait disturbances (Tan *et al.* 2000a).

Improvements in the biomechanics of walking through exercise training in patients with PAD have also been associated with improved walking ability (Tan *et al.* 2000a), and hence an improved walking efficiency and decreased energy expenditure for a given work load (Regensteiner and Hiatt, 1995). In this respect, exercise training results in a decreased $\dot{V}O_2$ at sub-maximal workloads (Hiatt *et al.* 1990). This suggests an improvement in walking efficiency (Nehler and Hiatt, 1999b) and the biomechanics of

walking (Womack *et al.* 1997). If the onset of claudication is due to a mismatch of oxygen delivery to oxygen demand, then the lower $\dot{V}O_2$ per workload may be associated with the ability to walk longer after exercise training (Regensteiner and Hiatt, 1995).

Changes in the psychological approach to exercise (Whyman and Ruckley, 1998), adjustments in gait, pain threshold (Regensteiner and Hiatt, 1995) and pain perception (Remijnse-Tamerius *et al.* 1999) could all account for the improved walking efficiency (Nehler and Hiatt, 1999b), as well as a possible improved tolerance to exercise.

1.4 Exercise training

1.4.1 Supervised vs. non-supervised exercise training

Supervision is a well-documented key factor in the success of exercise programmes for intermittent claudication (Beebe, 2001). It is regarded as the preferred gold standard among conservative treatment options (Degischer *et al.* 2002) to improve walking capacity (Brevetti *et al.* 2002). Supervised exercise programmes are superior to unsupervised exercise (Gardner and Poehlman, 1995), for improving treadmill exercise performance (Whyman and Ruckley, 1998) and functional status (Regensteiner *et al.* 1997b), however they are still very rarely employed (Carlon *et al.* 2003). Perhaps due to elevated indirect costs (Brevetti *et al.* 2002).

Structured dynamic exercise programmes increase pain-free walking distance (Radack and Wyderski, 1990), relieve pain and promote optimal wellness (Ciaccia, 1993). Significant improvement in walking speed and distance with the WIQ and in the physical function and vitality domain of the SF-36 have also been reported following supervised training (Nehler and Hiatt, 1999b). There is overwhelming evidence that supervised exercise is of symptomatic benefit for intermittent claudication and little evidence that exercise advice alone is an effective treatment (Stewart and Lamont, 2001). Primarily this results from the fact that simple advice from a healthcare provider is insufficient to induce patients with PAD to exercise to maximum benefit (Beebe, 2001). Although a home-based exercise programme, incorporating weekly lectures relating to PAD and weekly exercise instruction can improve walking performance and health perception, this is attributable to the high degree of interaction between patients and healthcare providers (Patterson *et al.* 1997). Without such personalised and direct supervision, some individuals would lack sufficient motivation to continue on their own (Beebe, 2001).

A typical supervised exercise programme lasts approximately 60 minutes, and is conducted for a period of 3 to 6 months, and is monitored by a skilled nurse or technician (Nehler and Hiatt, 1999b). Patients should be reassessed clinically, on a regular basis, as they are able to walk further and further at their chosen workload, which necessitates an increase in speed or grade, or both, to allow patients to successfully work at harder and harder workloads, in order to induce a training benefit (Nehler and Hiatt, 1999b).

It is perceived that patient-specific exercise programmes and risk factor modification are standard interventions in patients with intermittent claudication (Beebe, 2001). A survey of consultant surgeons conducted in the UK and Ireland with an interest in vascular disease showed that supervised exercise programmes were only available to 27% of consultants (Stewart and Lamont, 2001). Most programmes consisted of only once weekly exercise classes (44.6%), 3.6% comprised of three or more sessions a week, and most (58.9%) lasting two or three months (Stewart and Lamont, 2001). In patients with PAD considerable effects on functional capacity and certain dimensions of quality of life can be achieved by a short exercise and education programme (Gartenmann *et al.* 2002). Weekly supervised exercise and motivation classes for a 6-month period provide a significant improvement in patients symptoms, quality of life and distance walked compared with advice alone and this improvement has been shown to continue after attendance at the classes has ceased (Cheetham *et al.* 2004).

Given the dramatic increase in walking distance produced by an effective, supervised exercise programme, and the poor results of simply giving advice, it remains surprising that supervised programmes are not more widely available (Stewart and Lamont, 2001), particularly in light of the Chief Medical Officers recommendation that for "people with peripheral vascular disease, exercise rehabilitation can improve walking ability and the ability to perform everyday tasks" (Chief Medical Officer, 2004). The costs of physiotherapy supervision are low, at less than £5,000 a year for two classes a week, and there may be further morbidity and health related cost benefit through encouraging a healthier and more active lifestyle in this high risk group (Stewart and Lamont, 2001). However, patient compliance to exercise programmes is often disappointing (Beebe, 2001). Compliance can be greatly improved through a good understanding of patients' limitations, and development of a so-called "rapport with the patient" at the initial consultation session, which should not be underestimated.

1.4.2 Importance of initial consultation sessions

At the initial appointment, patients often reveal quite negative attitudes, many are sceptical about the value of exercise, while others are disappointed or angry that they have not been offered a "high-tech" treatment to cure their problem (Binnie *et al.* 1999). There are drawbacks with undertaking an exercise training programme in that patients must spend a considerable amount of time participating in such a training programme to derive a benefit (Regensteiner and Hiatt, 1995). This is in contrast to an interventional procedure in which the patient, outside of consenting to a procedure is a more passive participant, and to pharmacological therapy, in which the patient's involvement is limited to taking a medication (Regensteiner and Hiatt, 1995). Acknowledging and accepting these attitudes is essential to providing an honest basis for beginning therapeutic work (Binnie *et al.* 1999).

Allowing a generous amount of time for consultations is crucial, usually an hour for the initial appointment and half an hour for follow-up sessions (Binnie *et al.* 1999). During this period, strategies for exercise or other behavioural change can be considered in the context of each patient's daily life, their other health problems and their particular perceptions and concerns. A great deal of patient listening and careful exploration of sensitive issues can be required to identify the right motivational triggers or to expose the real stumbling blocks (Binnie *et al.* 1999).

The continuity of patients seeing the same nurse in the hospital setting allows for the development of a relationship in which the personal dimension of each patient's disability can be explored and in which the details of their efforts to deal with it can be followed and supported (Binnie *et al.* 1999). Investing time, skill and energy in establishing a relationship which is comfortable and appropriate for each patient is seen as the central element of the conservative therapy programme, and it is the medium through which practical strategies for behavioural change are negotiated and supported (Binnie *et al.* 1999). Such a strategy can increase patient compliance and adherence to lengthy exercise programmes.

1.4.3 Time of day preferences to undertake exercise

The time of day when exercise is performed can influence performance. The optimal time of day for exercise is a complex issue and is determined not just by endogenous rhythms (rhythms, which are body clock driven), but by the nature and intensity of

exercise, the population concerned, environmental conditions and individual phase types (Reilly, 1990). Circadian phase types have been referred to as larks (morning types) and owls (evening types) indicating a preference for morning or evening activity. When considering exercise programmes, patient preferences should be considered, and this should remain consistent throughout a study to eliminate bias. Patients' rating of perceived exertion can also be affected by the time of day. The time of day when exercise is undertaken should be consistent throughout a study. The administration of a simple questionnaire (Horne and Ostberg, 1976) "lark/owl questionnaire" (Appendix 10) can classify individuals accordingly.

1.4.4 Limitations and long-term efficacy of structured exercise programmes

Though exercise rehabilitation (e.g. walking exercise) has been shown to improve walking performance, it is important to note that at the end of an intervention period, patients might still be impaired due to claudication (Izquierdo-Porrera *et al.* 2000). Furthermore, doubts exist regarding the long-term efficacy of exercise therapy and few trials report medium to long term effectiveness (Stewart and Lamont, 2001). Continued physical activity following a structured exercise programme is important to sustain improvements in walking performance. A 12-month period of less frequent exercise, preceded by a six-month exercise rehabilitation programme can sustain improvements in claudication distance, walking economy, 6-minute walk distance, peripheral circulation and increase daily physical activity levels by 31% in intermittent claudication (Gardner *et al.* 2002).

1.4.5 Adverse effects with exercise

The expectation is that improved walking confers cardiovascular benefits as well as giving a better quality of life (Whyman and Ruckley, 1998). However, evidence suggests that walking until the onset of calf pain (ischaemia) followed by rest (reperfusion) can result in the generation of oxygen-derived free radicals, neutrophil activation and a generalised increase in vascular permeability, and thus a low grade inflammatory response (Tisi and Shearman, 1998). Furthermore, baseline levels of chronic inflammatory markers such as acute-phase proteins are elevated in claudicants compared with controls, suggesting that the transient acute inflammatory response has longer-term consequences (Tisi and Shearman, 1998).

It has been hypothesised that this so called ischaemia/reperfusion injury may give rise to systemic vascular endothelial damage (Khaira *et al.* 1995a; Khaira *et al.* 1995b), and the cumulative effects of these individual events could have an adverse effect on the progression of atherosclerosis (Tisi and Shearman, 1998). In these patients the administration of vitamin C has been shown to prevent the acute systemic impairment in endothelial function induced by maximal exercise (Silvestro *et al.* 2002). Therapeutic exercise training appears to lead to an attenuation of these inflammatory markers (Tisi and Shearman, 1998), however researchers have concluded that the concerns about exercise training potentiating the vascular inflammatory response appear to be unjustified, and that exercise should be considered as an important treatment option for claudication (Tisi and Shearman, 1998).

1.4.6 Cardiovascular demand and safety during exercise

The potential for an adverse event exists in any exercise programme, especially in one in which an elderly group of patients with cardiovascular disease is involved in (Regensteiner and Hiatt, 1995). Patients with PAD frequently have concomitant-cardiovascular problems during exercise, such as hypertension (Gardner *et al.* 1995), due mainly to the high prevalence of systemic cardiovascular disease as well as PAD in these patients (Regensteiner and Hiatt, 1995). For testing and rehabilitation purposes, exercise which elicits a lower heart rate and blood pressure at a given metabolic intensity should be preferred over a more demanding task (Gardner *et al.* 1995).

The sudden release of catecholamines coupled with local ischaemia during exercise may accelerate the pre-existing pro-thrombotic potential of the atherosclerotic vessel wall (Mustonen *et al.* 1998). Indeed, sudden extreme physical stress has been associated with an increase in the risk of myocardial infarction especially in individuals with pre-existing atherosclerosis (Mustonen *et al.* 1998). Adverse effects with supervised exercise programmes have included angina and dyspnoea on a treadmill (Larsen and Lassen, 1966).

1.4.7 Effects of exercise rehabilitation on cardiovascular risk factors

Dynamic, relatively intense physical training, performed at least 3 times per week for 30 minutes for 1 to 8 months, has been shown to reduce blood pressure, particularly in hypertensive patients (Fagard, 1994). Exercise rehabilitation can also potentially improve glucose tolerance. Control of such factors is an integral part in the management

of PAD (Izquierdo-Porrera *et al.* 2000), since it can reduce cardiovascular risk (Stewart and Lamont, 2001). However, previous reports have been unable to find a correlation between changes in functional performance and changes in cardiovascular risk factors, suggesting that exercise acts through different mechanisms in order to achieve improvements in these parameters (Izquierdo-Porrera *et al.* 2000).

Exercise has a beneficial effect on the risk factors that contribute to the development of PAD and the rate of atherosclerosis progression, including lowering total cholesterol and low-density lipoprotein cholesterol (LDL-C) (Izquierdo-Porrera *et al.* 2000), which might reduce the risks of coronary events (Tan *et al.* 2000a). Although, it has been argued that despite the large functional gains following exercise rehabilitation, the absolute amount of exercise in this debilitated population might be insufficient to elicit favourable alterations in cardiovascular risk factors (Izquierdo-Porrera *et al.* 2000).

1.4.8 Optimum exercise programme and prescription

Exercise training programmes have a clinically important impact on functional capacity in patients in whom spontaneous recovery of symptomatic PAD does not occur (Regensteiner and Hiatt, 1995). Important details about aerobic exercise include the physiological responses to an acute bout of exercise, chronic adaptations to training, prescription of training programmes, and health benefits (Wilmore, 2003). The ability to improve the cardiovascular, musculoskeletal, and respiratory response to aerobic exercise is directly related to the frequency, intensity and duration of the programme (Evans *et al.* 1994) and mode of exercise (Wilmore, 2003).

Of the exercise prescription factors, the most important is intensity. With older and high risk individuals, intensity must be monitored carefully to ascertain that they are training at levels that will not only provide a training stimulus, but also be safe (Wilmore, 2003). The patients' initial fitness level, age, personal goals, and methods for monitoring the intensity of exercise are also important considerations (Wilmore, 2003). Activities commonly used by older adults to improve these responses include walking, jogging, cycling and swimming (Evans *et al.* 1994). The American College of Sports Medicine recommends that the mode of activity should use large muscle groups, maintain a continuous pace and be rhythmical and aerobic in nature (American College of Sports Medicine Position Stand: 1998). However, there is no consensus about the indication of exercises for patients with intermittent claudication of the lower extremity and the

characteristics of an exercise programme to improve waking distance (Brandsma *et al.* 1998). Many studies have shown that exercise training is beneficial for patients with PAD, however there is little research comparing various modes of training (Jones *et al.* 1996). Exercise principles that have been shown to be effective in increasing walking distance in claudicants include exercising to near maximal pain during training for more than 30 minutes, for at least three times per week, in a programme lasting at least six months in duration and which includes walking as the mode of exercise (Gardner and Poehlman, 1995). However, interventions designed to encourage adoption of an exercise regimen must be responsive to the individual's current stage of readiness and focus efforts on moving the individual through the various "stages of change" (Allbright *et al.* 2000). Differences in both CD and MWD observed between studies can be interpreted due to differences in exercise intensity and duration, which can have a bearing on improvement (Table 3).

Table 3. Improvement in CD and MWD in various studies (Gardner and Poehlman, 1995).

Study	Mode of Exercise	Duration of Class (min)	Program Length (wk)	Frequency (per week)	Patients (N=)	Claudication Pain Distance		Maximal Pain Distance	
						Pre-test, m	Post-test, m	Pre-test, m	Post-test, m
(Larsen and Lassen, 1966)	Walking	ND	26	ND	7	105.2 ± 33.4	268.3 ± 104.5	226.9 ± 112.8	626.5 ± 423.
(Skinner and Strandness, 1967)	Walking	60	24	1.5	5	97.1 ± 34.9	171.9 ± 88.9	288.4 ± 231.5	2495.3 ± 285
(Alpert *et al.* 1969)	Walking	ND	26	ND	19	111.9 ± 48.3	224.6 ± 164.1	209.3 ± 79.0	361.9 ± 187.
(Ericsson *et al.* 1970)	Combination	45	48	2	7	186.0 ± 163.0	380.0 ± 366.0	273.0 ± 196.0	537.0 ± 370.
(Zetterquist, 1970)	Combination	60	15	2	9	191.0 ± 18.0	331.0 ± 20.0	320.0 ± 21.0	> 400.0
(Holm *et al.* 1973)	Combination	30	17	3	6	100.0 ± 26.7	346.7 ± 193.3	320.0 ± 106.7	693.3 ± 200.
(Dahloff *et al.* 1974)	Combination	30	26	3	10	91.0 ± 34.8	265.0 ± 103.0	296.0 ± 167.6	650.0 ± 104.
(Dahloff *et al.* 1976)	Combination	30	26	3	23	127.0 ± 21.0	345.4	318.0 ± 37.0	725.0
(Ekroth *et al.* 1978)	Combination	30	22	3	129	108.0 ± 33.0	392.0 ± 75.0	283.0 ± 42.0	720.0 ± 67.(
(Clifford *et al.* 1980)	Combination	ND	4	ND	20	ND	ND	299.4 ± 30.0	535.1 ± 46.4
(Lepantalo *et al.* 1984)	Combination	ND	52	5	12	75.0 ± 34.6	173.0 ± 152.4	ND	ND
(Ruell *et al.* 1984)	Combination	30	9	3	14	67.0 ± 59.5	402.5 ± 267.2	283.0 ± 193.2	795.5 ± 149.
(Rosetzsky *et al.* 1985)	Combination	45	13	3	79	ND	ND	133.0 ± 190.5	401.0 ± 112.
(Ernst and Matrai, 1987)	Walking	5	9	10	22	59.0 ± 37.0	120.0 ± 52.0	127.0 ± 59.0	281.0 ± 91.(
(Jonason and Ringqvist, 1987)	Combination	45	13	2	63	114.0 ± 74.0	197.0 ± 125.0	430.0 ± 213.0	717.0 ± 304.
(Carter *et al.* 1989)	Walking	10	26	3	56	240.0 ± 200.0	430.0 ± 50.0	590.0 ± 30.0	1000.0 ± 70.
(Lundgren *et al.* 1989b)	Combination	30	48	3	21	67.0 ± 35.0	187.0	183.0 ± 110.0	459.0
(Mannarino *et al.* 1989)	Combination	NS	26	2	8	40.0 ± 17.0	75.0 ± 27.6	76.4 ± 18.7	127.4 ± 26.3
(Rosfors *et al.* 1989)	Combination	30	26	2	25	111.0 ± 105.0	270.0 ± 340.0	575.0 ± 345.0	924.0 ± 460.
(Mannarino *et al.* 1991)	Combination	ND	26	2	10	50.4 ± 22.5	95.3 ± 30.9	80.8 ± 33.6	150.3 ± 35.3
(Feinberg *et al.* 1992)	Walking	ND	12	3	19	96.5 ± 56.6	816.6 ± 894.2	205.1 ± 94.3	1351.6 ± 718

ND indicates no data provided in the source study

1.4.9 Cost implications

It emerges that PAD places a great burden on health systems and on society as a whole (Brevetti and Chiariello, 2004). Some of these costs, including indirect and intangible costs (i.e. those related to productivity, and reduced quality of life, respectively) could be reduced if the condition were to be recognised and correctly treated at an early stage (Brevetti and Chiariello, 2004). Furthermore complications associated with PAD, for instance during invasive therapy, can take a great toll in terms of treatment costs (Brevetti and Chiariello, 2004).

Physical inactivity is a major health concern today (Wilmore, 2003). Cost effectiveness and the economic implication of exercise needs careful consideration, since the national implication of physical inactivity might have immense future implications for PAD care. Maintaining an active lifestyle throughout life appears to be critical to maintaining independence and health (Wilmore, 2003). Low levels of physical activity have already become a major public health problem in most Western societies, with the cost of physical inactivity in England estimated to be at least £8.2 billion a year (Chief Medical Officer, 2004).

A test that is used in clinical trials should address patient-focused clinical outcomes, including functional status, walking ability and quality of life (Regensteiner and Hiatt, 1995). The potential benefits of sustained exercise programmes for intermittent claudication not only include improvements in effective exercise performance, walking distance and increases in levels of physical functioning, but also cost-effectiveness (Beebe, 2001). A 6-month programme of exercise rehabilitation has been found to be more effective and cost less than percutaneous transluminal angiolplasty, and has been suggested to be cost-saving (Treesak *et al.* 2004), even in the form of supervised classes, since many patients can be treated at the same time (Whyman and Ruckley, 1998). However it is important to take into consideration that patients must invest time before reaping any health reward, therefore exercise may not be as inexpensive as it seems when this perspective is considered, since the cost of the time spent exercising must be taken into account (de Vries *et al.* 2002). Furthermore non-medical costs including transportation costs should also be considered (de Vries *et al.* 2002).

1.5 Comparison of various modes of exercise training

1.5.1 Walking exercise

Walking is not only rhythmic and dynamic, but it is the most natural aerobic weight-bearing activity of large skeletal muscles, and in the general population it confers various benefits with minimal adverse effects (Morris and Hardman, 1997). It is associated with an increase in bone related strength in individuals of all ages (Morris and Hardman, 1997). In intermittent claudication, exercise in the form of walking is effective in reducing pain and improving walking distance (Bartelink *et al.* 2004). At the very least, walking prevents a deterioration in symptoms in the majority of patients, and the greatest effect is generally noted within the first three months of commencing a walking programme (Whyman and Ruckley, 1998).

Early descriptions of exercise therapy for patients with PAD consisted of general advice to take daily walks (Regensteiner and Hiatt, 1995). This was to be done at an intensity below the threshold of claudication pain, and exercise was to cease at the onset of pain (Foley and Wright, 1953). More recently, it has been suggested that patients should be encouraged to walk primarily on a treadmill, because this most closely reproduces walking in a community setting (Hiatt and Nehler, 2001). The benefits of a supervised walking exercise programme have been considered and therefore exercise rehabilitation constitutes an important form of therapy for these patients (Regensteiner, 2004), since walking distance (Brandsma *et al.* 1998) and exercise performance are improved (Regensteiner *et al.* 1996).

It has been suggested that the initial workload should be set to a speed that brings on claudication pain within three to five minutes, and that patients should walk at this intensity until they achieve claudication of moderate severity (Nehler and Hiatt, 1999b). Patients should then rest until the claudication abates, and then resume further exercise (Nehler and Hiatt, 1999b). Supervised physical training beyond the claudication threshold significantly improves both walking time and the quality of life of patients with intermittent claudication (Carlon *et al.* 2003).

To date, the most utilised and effective mode of exercise therapy for PAD has been treadmill walking exercise in a hospital-based setting (Regensteiner and Hiatt, 1995). Supervised treadmill training programmes can improve functional status during daily activities, with 24-weeks of training being more effective than 12-weeks (Regensteiner

et al. 1996). Treadmill training alone has been demonstrated to be more effective in improving functional status in patients with intermittent claudication than strength training or combinations of the training modalities (Regensteiner *et al.* 1996). As such, a 24-week treadmill training programme for patients with disabling claudication has been recommended (Regensteiner *et al.* 1996). Such programmes are associated with well-established changes in treadmill exercise performance and community-based walking ability in patients with intermittent claudication (Hiatt *et al.* 1990; Regensteiner and Hiatt, 2002a). Improvements in walking distance have been reported to be in the region of 44 - 300 % and 25 - 442 %, for pain-free and MWD, respectively (Regensteiner *et al.* 1997a).

1.5.2 Potential problems with walking exercise rehabilitation programmes

Incentives associated with starting and continuing walking have included advice from a doctor, relief of complaints and achievement of a better general condition (Bartelink *et al.* 2004). However, walking exercise programmes do have several disadvantages. Firstly, patients with intermittent claudication are limited in their ability to walk (Hiatt *et al.* 1988) and the physical discomfort encountered by performing lower-limb weight-bearing exercise is undoubtedly a major reason why this strategy has failed to achieve widespread popularity (Walker *et al.* 2000).

Walking exercise requires patients to be well motivated and not to have severe co-morbid conditions such as disabling angina, dyspnoea or arthritis, which might render exercise to be impossible (Whyman and Ruckley, 1998). Exercising patients over the pain threshold might also be dangerous (Carlon *et al.* 2003). Further disadvantages with community-based walking programmes include the deterrents of road traffic accidents, heavily polluted air and the smell of traffic (Morris and Hardman, 1997). Cracked or uneven pavements may present additional hazards.

Patients frequently complain that the prospect of walking up a hill terrifies them and generally they plan their route to minimise any hill walking, due to the excruciating pain that they experience as a consequence of their intermittent claudication. Resistance and anxieties, may have to be overcome before patients adopt walking exercise (Table 4) (Binnie *et al.* 1999). In addition, a lack of specific advice and supervision, and the presence of co-morbidity have all been found to be important barriers to taking up walking exercise (Bartelink *et al.* 2004).

Table 4. Patients anxieties associated with walking exercise (Binnie *et al.* 1999).

1. Fear of the pain (i.e. that walking with pain will do some damage)
2. A perception that going for a walk is not possible because of the pain
3. A fear of not being able to get home, or of legs 'giving way'
4. Feeling foolish when having to stop ('people wonder what you are doing, just standing there')
5. A perception of not having time to go for regular walks
6. A dislike of walking without a purpose
7. Fear or dislike of going out alone
8. Confusing 'stop-start' activities (e.g. 'pottering about'; 'I'm on my feet all day'; wandering around the shops') with the sustained effort of a purposeful walk

Walking may also be regarded as a convenient low-impact mode for diabetics, but some patients, because of peripheral neuropathy and/ or foot problems, may need to do non-weight-bearing activities (Allbright *et al.* 2000).

1.5.3 Alternative training modalities

The effects of other modes of exercise training on functional status in the PAD patient population have not been fully assessed (Regensteiner *et al.* 1996). Although many studies have shown that exercise training is beneficial for patients with PAD, there is little research comparing various modes of training. In previous studies, $\dot{V}O_2$ during walking and stair climbing has been found to be similar (Gardner *et al.* 1995). Indeed, one study involving exercise tests performed on a StairMaster apparatus has produced improvements in exercise capacity that are similar to those elicited by treadmill tests, and it has been suggested that this type of apparatus should be incorporated as part of the exercise prescription for the treatment of patients with PAD (Jones *et al.* 1996).

Other studies have utilised pneumatic foot compressions to improve walking distance in these patients. Intermittent pneumatic foot compression augments arterial leg inflow, and following 4.5 months of prolonged use of impulse leg compressions at home, CD and resting ABPI and post ABPI after exercise and arterial calf inflow have been shown to improve, suggesting an improved collateral circulation (Konstantinos *et al.* 2000). A 24-week programme of progressive resistance training can also improve pain-free walking distance in these patients (McGuigan *et al.* 2001). A 12-week programme of

strength training with treadmill training has also been compared (Regensteiner *et al.* 1996). Strength training of the lower leg muscles was evaluated because of the observation that patients with PAD have leg muscle weakness (Regensteiner *et al.* 1993b). In addition, it has previously been observed that strength training may augment the response to an aerobic training programme in normal subjects (Hickson *et al.* 1988). However, the study found that strength training does not improve peak exercise performance or peak $\dot{V}O_2$, whereas treadmill training does (Hiatt *et al.* 1996). Treadmill training alone is thus more effective in improving functional status, when compared with strength training or a combination of treadmill and strength training modalities (Regensteiner *et al.* 1996).

Cycling as a testing modality in the treatment of intermittent claudication has also been compared with graded walking (Askew *et al.* 2002). Maximal exercise times in the two modalities, although different, were highly correlated, suggesting that the level of exercise intolerance established using a cycle test is similar to that determined from a treadmill test (Askew *et al.* 2002). Peak $\dot{V}O_2$ measured during the cycle test was similar to that observed during treadmill walking, and the two sets of peak $\dot{V}O_2$ were highly correlated with each other (Askew *et al.* 2002), suggesting that cycle testing elicits a peak $\dot{V}O_2$ comparable with that observed during a treadmill test. It has thus been suggested that tests that reduce the risk of falling and are not weight bearing (i.e. cycle test) may be of considerable benefit in the assessment of frail and very de-conditioned individuals (Askew *et al.* 2002). In many clinical settings a Monark leg ergomater is used (Kang *et al.* 1999). However, the need for an optimal rehabilitation programme has been stressed (Robeer *et al.* 1998), since exercising the lower-limbs can be painful, and this can limit the training intensity. During walking, calf pain is the primary limiting symptom, whereas the symptoms during cycling are more varied and include thigh pain, calf pain and dyspnoea (Askew *et al.* 2002).

The efficacy of walking using modified ski poles (pole striding exercise), which uses the muscles of the upper and lower body in a continuous movement similar to cross-country skiing, has shown to improve exercise tolerance of patients with intermittent claudication (Collins *et al.* 2003) following a 24-week training period (Langbein *et al.* 2002).

A further alternative training modality is upper-limb exercise training. Such exercise is often performed on a mechanically braked ergometer, which permits accurate measurement of power output (Astrand, 1977). The Monark (Varberg, Sweden) arm ergometer is one such device that is widely used (Kang *et al.* 1999). Stationary arm-cranking is a mode of exercise commonly used for fitness testing and aerobic conditioning in individuals with lower extremity and spinal cord injuries (Balady, 1993; Graves and Pollock, 1993).

The potential advantages of such an exercise regimen in patients with intermittent claudication are two-fold. Firstly, patients do not experience the ischaemic pain which is associated with leg exercise, Secondly, upper-limb exercise might not induce the systemic inflammatory response associated with relative ischaemia-reperfusion and neutrophil activation that is associated with lower-limb exercise, thereby allowing patients to exercise to a greater intensity (Nawaz *et al.* 1999). Thus, preliminary evidence suggests that carefully prescribed upper-limb exercise training can be used as an alternative exercise strategy for evoking symptomatic improvement in patients with intermittent claudication (Walker *et al.* 2000). This type of exercise strategy might therefore have a role to play in exercise rehabilitation, as it might be a more acceptable mode of training by these patients, whilst simultaneously evoking positive cardiovascular adaptations.

A 6-week programme of upper-limb cardiovascular training has reported to produce an improvement in pain-free walking distance, which was comparable to that achieved using lower-limb training in a parallel group of patients (Walker *et al.* 2000). This suggests that exercise-induced central adaptations influence improvements in walking distance after training as well as local adaptations in leg skeletal muscle (Walker *et al.* 2000).

1.5.4 Physiology of upper- and lower-limb exercise

Questions arise as to whether upper-body exercise on an arm ergometer and leg ergometer will elicit different physiological and perceptual responses even though the exercise is performed at a similar power output (Kang *et al.* 1999). Upper-body exercise on an arm ergometer has been shown to elicit greater cardiorespiratory, metabolic and perceptual responses compared with a modified leg ergometer at the same sub-maximal power outputs, as manifested by higher $\dot{V}O_2$, heart rate, respiratory

exchange ratio, pulmonary ventilation and perceived exertion (Kang *et al.* 1999). Such cardiorespiratory differences between upper- and lower-limb exercise have previously been reported in healthy (Aminoff *et al.* 1998; Kang *et al.* 1999), and ischaemic heart disease patients (Lazarus *et al.* 1981), but not in patients with intermittent claudication.

Peak aerobic exercise capacity for arm-crank exercise in healthy individuals is in the region of 60 - 80% of comparable lower-limb exercise capacity (Cummins and Gladden, 1983; Reybrouck *et al.* 1975; Vokac *et al.* 1975; Astrand *et al.* 1961). Suspected physiological mechanisms to account for these differences in $\dot{V}O_2$ are outlined in Table 5.

Table 5. Physiological mechanism(s) suspected to be responsible for the lower peak $\dot{V}O_2$ values during arm-exercise compared to leg-exercise (Sawka, 1986).

Reduced potential to generate muscular tension
smaller total skeletal muscle mass
smaller cross-sectional area of muscle
Reduced oxidative capacity
smaller skeletal muscle mass
differences in muscle fibre composition
differences in motor unit recruitment patterns
Reduced blood perfusion of skeletal muscle
smaller total capillary cross-sectional area (maximal vasodilation)
vascular capillary bed differences (fibre type)
intramuscular pressures exceeding perfusion pressure

During arm-crank exercise, the smaller amount of active skeletal muscle might account for the lower peak aerobic exercise capacity in healthy individuals, however this does not appear to be the case for patients with symptomatic PAD. Fardy *et al* (1977) reported the case of a patient with PAD whose maximum physical work capacity for arm-cranking exercise was equivalent to that for treadmill walking exercise (6 METs) due to the ischaemic pain encountered during walking (Fardy *et al.* 1977). This case suggests that arm-cranking could be an equivalent exercise stimulus to weight-bearing walking exercise for evoking positive cardiovascular adaptations in this patient group.

Thus, an improved insight into the factors that influence exercise tolerance with alternative muscle groups could lead to better exercise prescriptions for these patients with intermittent claudication.

1.6 Study aims

The aim of this study was to determine the relative efficacy of a 24-week programme of twice weekly upper-limb and lower-limb exercise training on both pain-free and MWD in patients with stable intermittent claudication and its impact on community-based walking ability and quality of life, by assessing patients at 6-weekly intervals throughout the intervention period.

This study was also designed to provide an insight into the possible mechanism(s) underlying the exercise-induced symptomatic improvements in these patients, such as central cardiovascular, localised metabolic adaptations or psychological factors, such as improved confidence in walking or pain tolerance. The relative importance of these factors and possible cross-over effects were determined over the duration of the 24-week training programme. Patients' actual and perceived walking ability, functional capacity, physical activity and quality of life were also observed at 6-, 12-, 24- and 48-weeks following the end of the intervention period. These time-points were selected, in order to consider both the short to medium, and longer-term effects following a programme of exercise rehabilitation in patients with intermittent claudication.

Chapter 2 - Methodology

2.1 Research design

This was a randomised controlled trial (RCT), with patients randomised into one of three groups: - upper-limb exercise training, lower-limb exercise training or to a non-exercise training control group. The study was designed to include an intervention period of 24-weeks in duration, followed by a 48-week follow-up period.

2.2 Patient selection and accustomisation to test procedures

2.2.1 Selection and recruitment

Ethical approval was obtained from the North Sheffield Local Research Ethics Committee. Clinically diagnosed patients with stable intermittent claudication were selected and recruited from clinical notes, from the Sheffield Vascular Institute, at the Northern General Hospital, Sheffield, U.K. Selection was based on patient's medical history, previous physical examination and on the inclusion and exclusion criteria dictated by this study (Appendix 1). In accordance with previous suggestions, nursing home residents, wheelchair bound patients, and patients with foot or leg amputations were excluded, because their function was uniquely impaired (McDermott *et al.* 2002a). Vascular consultants also referred suitable patients onto this study.

Patients satisfying the study criteria were sent a letter (Appendix 2), with an attached patient information sheet (Appendix 3) and a leaflet describing the facilities and directions to the *Centre for Sport and Exercise Science.* The letter clearly stated that there was no obligation or pressure to participate in this study. If patients did not wish to participate, their future medical care would not be jeopardised. Patients declining to be contacted were requested to leave an answer-phone message by a specified date.

Patients, who had not left an answer-phone message declining to take part, were presumed to have a possible interest in study participation. These patients were contacted via telephone, and vetted to ascertain that they still fulfilled the study criteria. All initial patients' questions were answered. Patients satisfying the study criteria were invited to the *Centre for Sport and Exercise Science* for an initial consultation session to view the facilities and to thoroughly discuss all aspects of the study.

The composition of the three study groups, the randomisation procedure, potential benefits of both training programmes, the required commitment to the training sessions and the measurements that were to be taken during the assessment sessions were all discussed, as were the requirements from patients if randomised to the control group. Suitability was re-assessed on the basis of previous history, in accordance with the study inclusion and exclusion criteria.

Based on the guidelines of the American College of Sports Medicine (American College of Sports Medicine., 1991) and Regensteiner *et al* (Regensteiner *et al.* 1996) patients with any of the following criteria were excluded from the study: Fontaine stage I PAD (ambulation not limited by claudication); Fontaine stage III PAD (pain at rest); exercise tolerance limited by factors other than claudication (e.g. severe CAD, poorly controlled hypertension, pulmonary disease, severe arthritis or orthopaedic conditions); poorly controlled diabetes mellitus; or other active major medical problems including cancer, renal or liver disease, anaemia, substance abuse or dementia (Gardner *et al.* 2001).

Patients with unstable hypertension were excluded as blood pressure rises considerably when hypertensive patients perform dynamic exercise (Fagard, 1994). Patients with diabetes were included in this study. Previous studies have excluded these patients on the grounds that authors wished to avoid the confounding effects possibly resulting from complications common to diabetes (i.e. neuropathy, autonomic dysfunction) that can interfere with the ability to benefit from a training programme (Regensteiner *et al.* 1996).

2.2.2 Inclusion criteria

Patients were included in the study on the basis of:-

- Clinical symptoms and signs of PAD supported by the presence of usual risk factors
- Symptoms of stable intermittent claudication of 12 months or more duration
- An ABPI of less than 0.9
- No interventional procedures within the last 12 months (i.e. angioplasty etc)
- Ability to undertake exercise
- No exercise-limiting angina
- No shortness of breath
- No severe arthritis

2.2.3 Exclusion criteria

Patients were excluded on the basis of:-

- Symptoms of intermittent claudication present for less than 12 months
- Significant change in walking ability within the last 12 months (denoting unstable claudication)
- Exhibiting features of critical limb ischaemia
- A re-vascularisation procedure, or other surgical intervention to the lower-limbs within the last 12 months
- If initial assessment established that the patient suffered from
  - severe arthritis
  - or unstable cardio-respiratory conditions, such as
    - shortness of breath
    - or exercise-limiting angina

Upon providing verbal agreement to study participation, informed consent (Appendix 4) was obtained and a Physical Activity Readiness Questionnaire (PAR-Q; Appendix 5) form was completed. Patients fulfilling the study criteria were thoroughly familiarised with all test protocols and equipment. Smoking status was confirmed by a smokerlyzer test (Bedfont, UK), which measured and verified carbon monoxide (CO) levels.

2.2.4 Power calculations for determination of sample size

The primary outcome variable for the calculation of sample size was MWD due to intolerable claudication pain, since CD is recognised as a less reliable walking performance measure compared to MWD in incremental walking assessments (Gardner et al., 1991; Hiatt et al., 1988; Hiatt et al., 1995; Labs et al., 1999). In a preliminary study, MWD increased from a baseline level (± SD) of 289 ± 127 to 427 ± 219 m following a 6-week period of upper-limb aerobic exercise (Walker *et al.* 2000). A similar improvement in MWD was observed following lower-limb aerobic exercise training. An improvement in MWD of this magnitude is considered to be clinically important in patients with PAD. On the basis of these data, and taking into account an expected patient drop-out of 30% over a 6-month intervention period, recruitment of 35 patients for each group yielded an 80% power to detect an increase in MWD of this magnitude at the alpha level of 0.05.

2.2.5 Accustomisation of patients to the test procedures

2.2.5.1 Accustomisation to Borg (RPE and CR-10) scales

All patients received instructions regarding the definition of perceived exertion and the use of the exertion (Borg 15-graded RPE) and pain (Borg CR-10) rating scales (Appendix 6, 7, 8 and 9; (Borg, 1998)). Six points were followed in accordance with these instructions set out by *Noble and Robertson (1996)* (Noble and Robertson, 1996), regarding their administration namely:-

1. Defining perceived exertion and perceived pain
2. Anchoring the perceptual range
3. Explaining the nature and use of the scales
4. Explaining differentiated ratings
5. Correctness of perceptual responses
6. Answering participant's questions

Both the Borg 15-graded RPE scale (Appendix 6) and Borg CR-10 pain scale (Appendix 7) were shown and remained on view whilst the scale instructions were subsequently read out to the patient (Appendix 8 and 9, for RPE and pain scale instructions, respectively). The instructions emphasised that the perceptual ratings of perceived exertion should reflect sensations of exertion, stress, and/or discomfort in the limbs and respiratory system (Kang *et al.* 1999). Any questions were answered.

2.2.5.2 Leg and arm-cranking accustomisation

The first step in the pre-participation evaluation was to assess for contraindications to exercise testing and training and to identify any risks or limitations relevant to the exercise prescription (Kligman *et al.* 1999). Prior to undertaking any exercise, systolic (SBP) and diastolic blood pressure (DBP) was measured (manual sphygmomanometer). Heart rate (HR) was continuously monitored using a short-range radio-telemetry monitor (Polar Sport Tester, Kempele, Finland), which was slightly moistened and applied to the lower thorax. Patients were asked to exercise on a standard friction braked arm ergometer (Monark 881E, Varberg, Sweden).

In accordance with previous suggestions, prior to undertaking exercise the height of the ergometer crank sprocket was adjusted so that the crank axle was at shoulder level and the elbow was extended, but not locked when the handgrip was farthest from the body (Kang *et al.* 1999). Patients exercised at 50 revs.min^{-1}, for 2 min at 7.5 W. A metronome was used to keep pace when required. HR was ascertained during the last 15 seconds of the 2-min exercise bout. Patients were asked to evaluate without overestimating or underestimating both their feelings of exertion and perceived pain using the Borg 15-graded RPE and pain scales (Borg CR-10), respectively.

Following a 2-min rest interval, patients continued to exercise in bouts of 2 min of exercise, followed by 2 min of rest. Each time the exercise intensity was increased by 7.5 W until exertion was perceived to be 13 (*somewhat hard*) on the Borg RPE scale, or pain was of a moderate intensity (number 3 on the Borg CR-10 scale), whichever was experienced first. This cycle of events incorporated both the lower and higher anchors of the scale, thereby acquainting patients with the feelings of exertion that they should experience at each of those anchors. Following an adequate rest interval, patients repeated the procedure on a standard stationary cycle ergometer (Monark 824E, Varberg, Sweden) with the exercise intensity increased by 15 W each increment due to the larger skeletal muscle mass involved.

Patients were shown the gas analysis equipment used to measure and record breath-by-breath data. The correct use of the mouth piece and nose-clip was demonstrated to the patient, after which the patient was asked to insert a suitably sized mouth piece into their own mouth and instructed to breathe as normally as possible. The nose clip was applied in order to prevent inhalation and exhalation through the nasal passage. Patients

were asked to breathe only through the mouth piece and were instructed that this process would be required during the assessment visits.

2.2.5.3 Incremental shuttle-walk accumstomisation

Walking ability was assessed using an incremental shuttle-walk test (Zwierska *et al.* 2004). The protocol was initially demonstrated to the patient. All patients were accustomised with the protocol, during which their CD and MWD were assessed.

2.2.6 Time of day preferences to undertake exercise

Patients were asked to consider their time of day preferences to perform exercise. Patients completed *Horne and Ostberg's (1976)* Lark-Owl questionnaire (Appendix 10) which relates to individuals time of day preferences to perform physical activity (Horne and Ostberg, 1976).

The questionnaire was scored accordingly:-

Table 6. Scoring of lark/owl questionnaire.

Score	Type of Individual (i.e. morning (lark) or evening (owl) type)
70 - 86	Definitely a ***morning*** person
59 - 69	A ***moderate morning*** person
42 - 58	Neither a ***morning*** nor an ***evening*** person
31 - 41	A ***moderate evening*** person
16 - 30	Definitely an ***evening*** person

Scores were evaluated against a patient's self perception of time of day preferences. Patients were advised that all training and assessment sessions would be conducted at similar times of the day, at their perceived optimum time of day to perform exercise in accordance with their expressed preference, as confirmed via the questionnaire.

2.2.7 Medical examination

Prior to entering the study, all patients on a separate occasion underwent a thorough medical examination performed by Mr. Sohail Choksy, FRCS (Vascular Surgeon, Northern General Hospital, Sheffield, U.K.). During the peripheral vascular examination the diagnosis of intermittent claudication was further confirmed by the Doppler assessment of ABPI, in accordance with current U.K. medical practice. Some patients had previously undergone duplex ultrasonography and/or intra-vascular peripheral angiography assessments, and these results were made available during the examination. In two-thirds of the patients, claudication was due to superficial femoral artery disease as determined by angiogram, duplex scanning or examination of pulses. The remainder of patients had tibial vessel disease.

During the medical examination, details of surgical history, co-morbid conditions and risk factors such as smoking status were assessed (Appendix 11). Efficient screening highlights previous exercise programmes, present activity and existing chronic or acute disease (Kligman *et al.* 1999). The physical examination also includes vital signs and cardiorespiratory and musculoskeletal evaluation (Kligman *et al.* 1999). Current medication was also confirmed. Medical history needs to be taken and medication reviewed in order to determine any potential interaction with exercise testing or training (Kligman *et al.* 1999). Smoking status was assessed on the basis of history and further confirmed by CO analysis using a smoke meter (Bedfont, U.K.). Patients on long-term medication continued on their treatment. Blood pressure was taken (manual sphygmomanometer) and a resting 12-lead ECG (Seca, CT3000B, Switzerland) was performed with the patient in the supine position, in order to identify evidence of arrhythmias (the commonest being atrial fibrillation), previous myocardial infarction (Q waves) or ischaemia (ST segment depression).

Absolute contraindications to formal exercise testing include recent electrocardiographic changes or acute myocardial infarction, unstable angina, third-degree heart block, and acute congestive heart failure (Mahler and American College of Sports Medicine, 1995). Patients with abnormal resting ECG readings were excluded from participation in the study. Relative contraindications to exercise testing include elevated blood pressure, cardiomyopathies, valvular heart disease, complex ventricular ectopy and uncontrolled metabolic diseases (Kligman *et al.* 1999). The initial arm-cranking assessment to maximum exercise tolerance was undertaken in the presence of

Mr. Sohail Choksy, FRCS. All other sessions were undertaken in the presence of personnel that had received training in advanced life support procedures. All patients GP's were notified in writing of study participation (Appendix 12).

2.2.8 Randomisation and frequency of attendance

2.2.8.1 Patient randomisation

Upon completing all baseline assessments, patients were randomised (random selection without replacement) into either the lower-limb exercise training, upper-limb exercise training or control group, using the fishbowl technique (Baumgartner and Strong, 1998). The fishbowl technique involved writing the names of recruited patients on a piece of paper. The pieces of paper were placed in a box and drawn. This approach ensures randomisation and an equal distribution of patients into each of the three study groups.

The randomisation procedure was conducted by a member of the research team not involved in the recruitment, familiarisation or assessment process. Patients were randomised into the groups regardless of gender, age, severity of symptoms, current medication or smoking status.

2.2.8.2 Frequency of assessment sessions

The initial leg-crank test (LCT), arm-crank test (ACT) and walking assessments were repeated every 6-weeks during the 24-week intervention period. During each assessment week, patients randomised to the training study did not perform any training sessions. During the intervention period patients performed five assessments in total. All patients were also assessed 6-, 12-, 24- and 48-weeks after the end of the intervention period.

2.3 Assessment sessions

One hundred and four patients (median age 69 yr, range 50-85 yr) with stable intermittent claudication were recruited from the Sheffield Vascular Institute at the Northern General Hospital, Sheffield, U.K. Demographic data (sex, age, weight, height, body mass index, diabetic and smoking status) are shown in Table 8. In accordance with previous suggestions (Tan *et al.* 2000a), patients were instructed not to perform any exercise for 24 hr prior to each assessment session. Patients were also advised to abstain from caffeinated beverages and nicotine intake for at least 2 hr prior to each test.

2.3.1 Assessment of walking performance using the incremental shuttle-walk test

Intermittent claudication was defined as exertional calf pain which never begins at rest and resolves within 10 min of rest. Walking performance was assessed using an incremental shuttle-walk test. This ascertained that the severity of claudication pain was the limiting symptom during daily activities and during walking assessment in the laboratory.

The shuttle-walk test was a modified version of the protocol developed by Singh *et al* (Singh *et al.* 1992) for use in patients with chronic airways obstruction. This test has recently been evaluated against an internationally accepted, standardised treadmill protocol (walking speed 3.2 $km.h^{-1}$ at 12% gradient) (Labs *et al.* 1999a) in patients with intermittent claudication, with respect to test-retest reliability, cardiovascular responses and patient preferences (Zwierska *et al.* 2004).

All patients were confirmed to be pain-free (using the Borg CR-10 scale) prior to commencing the shuttle-walk test. HR at rest was recorded using a short-range radio-telemetry monitor (Polar Sport Tester, Kempele, Finland) and a small resting blood sample for lactate analysis (25 µl) was taken. The incremental shuttle-walk test required patients to walk back and forth between two cones placed 10 metres apart on a flat floor. Walking speed was controlled by bleeps recorded onto an audio-tape and the accuracy of the timed signal was ensured by the inclusion on the tape of a calibration period of 1 minute. Patients began walking on hearing the first bleep and aimed to reach the opposite cone by the next. If patients arrived before the bleep, they were required to wait for it before walking back. Patients arriving after the bleep were given verbal instructions to increase their walking speed so as to make it to the opposite cone before the next bleep. Patients achieved the correct walking pace within two or three repetitions (20-30 metres).

The initial walking speed was 3 $km.h^{-1}$. At the end of each minute, the time interval between audible bleeps decreased, and this resulted in a step-increase in walking speed of 0.5 $km.h^{-1}$. This incremental increase in walking speed gradually stresses the cardio-respiratory system to a symptom-limited maximum, potentially making it safer for patients with cardiac and respiratory conditions (Singh *et al.* 1992).

For each patient the time taken to reach the onset of claudication pain (claudication distance, CD) was recorded, at which point patients were encouraged to continue walking until they could no longer tolerate the claudication pain (maximum walking distance, MWD). The time taken to reach this point was noted, and the test was concluded. The time measurements were converted into distances walked (metres) using a macro-program, developed by Dr. Richard D. Walker. HR at CD and MWD was recorded using a short-range radio-telemetry monitor (Polar Sport Tester, Kempele, Finland). At CD patients were asked to consider their degree of claudication pain (Borg CR-10 scale) and at MWD their degree of claudication pain and RPE, using the Borg CR-10 and Borg RPE scales, respectively. A post-walking and a 5-min post-walking blood sample for lactate analysis (25 μl) was taken. After the walking assessment, patients were allowed to rest whilst being continuously monitored in order to ensure that BP and HR returned to resting levels.

The initial assessment of walking performance using the incremental shuttle-walk test was performed on a separate occasion, usually a few days after undertaking the ACT and following prior familiarisation with the shuttle-walk protocol. To minimise inconvenience to patients, all other 6-weekly re-assessments of walking performance were undertaken prior to, but on the same day as the ACT. A time period of at least 15 min was allowed before undertaking the ACT and patients were asked to confirm that they were pain-free (Borg CR-10 scale) prior to undertaking the ACT.

2.3.2 Precautions during the shuttle-walk assessment

Previous reports have suggested that walking surface, incline walking, the type of footwear worn and environmental conditions can all influence walking ability. In order to prevent bias, all shuttle-walk tests were undertaken in the same laboratory under consistent and controlled environmental conditions. All walking was undertaken on the flat. Ladies in the past have stipulated that walking undertaken with footwear having a heel can alter their walking ability. For each assessment all patients were instructed to wear the same type of footwear.

2.4 Outcome measures during walking performance

2.4.1 Heart rate, perceived pain and perceived exertion

HR and perceived pain responses (Borg CR-10 scale) at CD and perceived exertion (Borg RPE scale) at MWD were assessed during the shuttle-walk test to assess the consistency of effort and the degree of pain experienced during each walking assessment at the different time points throughout the intervention period.

2.4.2 Ankle-Brachial Pressure Index (ABPI)

ABPI was determined prior to, and immediately following the incremental shuttle-walk test, at each assessment time-point. For the baseline ABPI measurement, patients rested in a recumbent position for at least 5 min. SBP and DBP (manual sphygmomanometer) were measured using an appropriately sized blood pressure cuff in the left and right brachial artery above each malleolus (McDermott *et al.* 2002b). If one brachial arterial pressure was greater than the opposite brachial arterial pressure and the difference was at least 10 mm Hg, subclavian stenosis was suspected, and the pressure measurement from the arm with the highest SBP was used to calculate ABPI (McDermott *et al.* 2002b).

SBP was then measured in the posterior tibial and dorsalis pedis artery at the ankle in both the symptomatic and non-symptomatic leg using a Doppler ultrasound probe (Huntleigh Diagnostics, U.K.) and a standard-sized ankle BP cuff (10-cm width). Both arterial pressures were recorded. Resting ankle to brachial pressure index (ABPI), recommended for evaluating treatment outcome in claudicants (Hiatt *et al.* 1995b), was determined by averaging the values from the dorsalis pedis and posterior tibial arteries (McDermott *et al.* 2000) and dividing this ankle SBP by the brachial SBP. Patients with an ABPI of 0.9 or less were classified as having PAD (McDermott *et al.* 2002b). For each patient, the measurement from the leg with the lower ABPI, denoted their symptomatic limb.

ABPI was re-assessed immediately following the walking test. The couch was positioned centrally at the side of the 10 m walk-way, so that the time taken to reach the couch for measurements was similar for all patients. To reduce variability a single investigator performed all shuttle-walk tests and ABPI measures.

2.4.3 Blood lactate

The pain experienced during claudication is caused in part by elevated levels of lactate resulting from anaerobic metabolism. A small (25 µl) blood sample for lactate analysis (YSI 1500 Sport, Ohio, U.S.A) was taken from the finger tip immediately and 5-min after the cessation of walking. A change in end-exercise blood lactate levels could indicate a potential mechanism by which exercise training increases walking performance, since in young, healthy subjects training can increase tolerance to these lactate levels.

2.5 Assessment of functional capacity

2.5.1 Incremental arm- and leg-cranking assessments

Patients were weighed and had their height measured during each assessment visit, and prior to undertaking exercise. A calibrated electronically-braked cycle ergometer (Gould, Bilthoven, Holland) was used for the incremental LCT and was modified for the incremental ACT (Figure 2). Both the LCT and the ACT were performed on separate occasions, at similar times of the day, in accordance with patients previously expressed preferences (Horne and Ostberg 1976, Appendix 10). There was typically a two day interval between the LCT and ACT, in order to eliminate fatigue. The LCT and ACT were performed in random order throughout the study period to prevent any learning, bias or order effect, since this could limit the ability of assessing the intervention (Regensteiner and Hiatt, 1995).

Prior to each assessment, resting blood pressure was measured using a manual sphygmomanometer. An appropriately sized arm cuff was chosen for each patient, and each time that blood pressure was measured the cuff was wrapped as carefully and as snugly as possible. Patients were subsequently connected to a 6-lead ECG (Marquette CaSE 15, Winconsin, U.S.A.), allowing the continuous monitoring of ECG traces and HR, which was recorded at rest. A small (25 µl) blood sample was taken from a finger-tip for blood lactate (YSI 1500 Sport, Ohio, U.S.A) and haematocrit analysis (Microhematocrit Centrifuge, Hawksley & Sons Ltd, Sussex, England) using appropriate capillary tubes. Patients were confirmed to be leg or arm pain-free (Borg CR-10 scale), as appropriate. During each exercise increment, pulmonary gas exchange variables were measured directly, breath-by-breath, using on-line expired gas analysis system (CaSE EX670 PulmoLab, Kent, U.K.).

For the LCT, the seat height was adjusted to allow slight knee flexion at bottom dead centre, and for the ACT, the mid-point of the sprocket was set at shoulder height. Both the LCT and ACT were discontinuous in nature, comprising 3-min bouts of constant exercise at a cranking rate of 50 revs.min^{-1} interpolated with 2-min rest intervals, to maximum exercise tolerance. During exercise, patients HR and ECG were continuously monitored to detect any exercise-induced dysrhythmias (Tsai *et al.* 2002). The initial intensity was 9 W for both tests. On the basis of previous pilot work (Walker *et al.* 2000), power output was increased by 7 W and 14 W per increment in the LCT and ACT, respectively, due to the differences in muscle mass involved.

In the last 30 seconds of every 3-min bout of exercise, patients were asked to consider their RPE and degree of pain experienced as a result of the exercise, using the Borg 15-graded RPE scale and Borg CR-10 scale, respectively. These were on view at all times. In the last 10-15 seconds of every 3-min bout of exercise HR was recorded, in accordance with previous procedures (Kang *et al.* 1999). RPE and degree of pain were ascertained. SBP and DBP readings were measured (manual sphygmomanometer) immediately after each exercise increment and a finger tip blood sample for blood lactate analysis was collected. Following the 2-min rest interval, patients repeated the cycle of 3-min bouts of exercise followed by 2-min rest intervals until maximum exercise tolerance was reached. Each patient was verbally encouraged to continue exercising until maximum exercise tolerance.

If maximum exercise tolerance was reached during an incomplete 3-min bout of exercise, HR, blood pressure, blood lactate, RPE and pain were determined immediately upon cessation of exercise. After reaching maximum exercise tolerance, patients rested on a chair and were monitored at 5-min intervals until complete recovery. Cardio-respiratory recovery following exercise is more rapid in trained individuals than in untrained subjects (McArdle *et al.* 1991), for this reason as well as the issue of safety, patients were monitored until complete recovery.

Exercise sessions were terminated if HR considered to be maximal for a patients age was reached or patients exhibited ST depression (1.0 mm or more correctly identifies a patient with CAD) (American College of Sports Medicine, 2000), abnormal ECG readings (as specified prior) or symptoms of exercise-induced angina during exercise. For safety reasons, these patients were excluded from study participation. In our study,

no patient suffered any cardiovascular complication. Some patients reported an exacerbation of existing musculoskeletal problems (i.e. knee stiffness), however in the majority of cases, patients tolerated the assessment sessions well.

2.5.2 Standardisation of assessment sessions

The same members of the research team performed all of the upper- and lower-limb peak aerobic power assessments and shuttle-walk assessments. Prior to every assessment, all patients were informed of the necessity to walk to intolerable claudication pain (MWD) and to exercise on the arm- and leg-crank ergometers to maximum exercise tolerance. Breath by breath data were collected using the same equipment (CaSE EX670 PulmoLab, Kent, U.K.) throughout the study period, and this was appropriately calibrated prior to every assessment session.

For the upper- and lower-limb peak aerobic power assessments, RPE and CR-10 scales were on view at all times while the patients were exercising. All assessments were performed at a similar time of the day, in accordance with patients' time of day preferences.

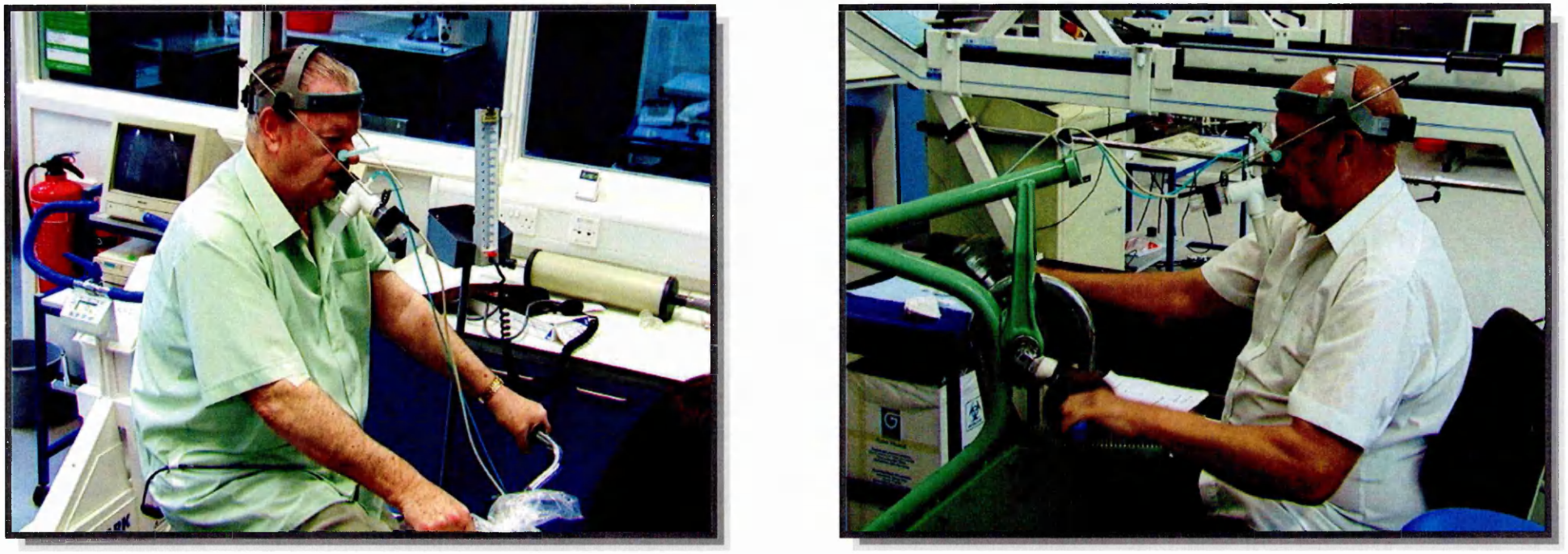


Figure 2. Patient undertaking a LCT (left) and an ACT (right)

2.6 Outcome measures during incremental exercise

2.6.1 Maximum achieved power

This was recorded as the maximum power output achieved during the incremental LCT and ACT. The maximum achieved power (MAP) in an incremental exercise test has previously been shown to increase after a 6-week training programme (Walker *et al.* 2000) and is a useful indicator of individual exercise capacity. The training intensity prescribed for those patients randomised to the lower- and upper-limb training groups was based on their individual performance during the assessment sessions.

2.6.2 Pulmonary variables

Pulmonary variables included $\dot{V}O_2$, which provides an indication of aerobic capacity, carbon dioxide production ($\dot{V}CO_2$), respiratory exchange ratio (RER defined as $\dot{V}CO_2 / \dot{V}O_2$), pulmonary ventilation ($\dot{V}E$), ventilatory equivalent for oxygen ($\dot{V}E / \dot{V}O_2$), tidal volume (Vt) and breath frequency (Bf). All variables were averaged from the last 30 seconds of breath-by-breath data from each exercise increment.

The RER is used as an indicator of the general progress of an exercise test, with starting levels of around 0.8 expected, rising to greater than 1 under stress. Increases in maximal $\dot{V}O_2$ as a consequence of exercise training are indicative of improved cardio-respiratory fitness (Hiatt *et al.* 1994). At low to moderate exercise intensities the rate of tissue $\dot{V}O_2$ is linearly related to work rate. However, at high work rates, further increases in exercise intensity produce no further increase in $\dot{V}O_2$ and the plateau is defined as the peak $\dot{V}O_2$. At this point, high intensity exercise can only be accomplished by supplemental anaerobic metabolism, resulting in the accumulation of lactic acid.

The ratio between the amount of oxygen consumed by the tissues ($\dot{V}O_2$) and the volume of air ventilated ($\dot{V}E$) in a given amount of time indicates breathing economy, and is referred to as the *ventilatory equivalent for oxygen,* or $\dot{V}E / \dot{V}O_2$. It is typically measured in litres of air breathed per litre of oxygen consumed per minute. $\dot{V}E / \dot{V}O_2$ at rest can range from 23-28 L of air per litre of oxygen consumed, which can increase above 30 L of air per litre of oxygen consumed as work increases to near maximum.

2.6.3 Cardiovascular variables

SBP and DBP were measured using a manual sphygmomanometer at rest and at the end of each 3-min bout of exercise, which were determined for both the LCT and ACT. The cuff was rapidly inflated to 20 mm Hg above the audible systolic pressure in each arm and deflated at a rate of 2 $mm.s^{-1}$, and recorded as the pressure at which the first sustained systolic pressure was audible (McDermott *et al.* 2002b). Hypertension was defined as SBP higher than 140 mm Hg and/ or a DBP higher than 90 mm Hg, on two or more visits and/or with the use of blood pressure medication.

HR alone, or better still HR blood pressure products (rate pressure product, RPP) are satisfactory predictors of coronary blood flow and myocardial oxygen consumption in normal, young subjects over a wide range of upright exercise (Kitamura *et al.* 1972). HR was continuously monitored using a 6-Lead ECG (Marquette CaSE 15, Winconsin, U.S.A.). The RPP, an index of myocardial workload (Kitamura *et al.* 1972; Nelson *et al.* 1974), was calculated for each work increment as the product of peak SBP and HR. From a diagnostic perspective, information on peak HR and RPP is also useful in assessing the likelihood that a test can detect coexisting cardiac disease (Askew *et al.* 2002).

2.6.4 Blood lactate

Examination of the blood lactate profile during incremental exercise has previously been a useful tool for studying the relationship between aerobic and anaerobic metabolism. Assessment of the blood lactate profile in response to incremental exercise following upper- and lower-limb training can provide an insight as to whether training induced adaptations are primarily occurring at the local or the central level.

2.6.5 Perceived exertion and pain

Patients rating of perceived exertion (RPE) and perceived pain were obtained using the Borg 15-graded RPE scale and the Borg CR-10 scale, respectively (Borg, 1998). The 15-graded RPE scale (Appendix 6), is a universally accepted perceptual scale (Noble and Robertson, 1996), commonly used in exercise testing, training and rehabilitation (Borg, 1998), in both research and clinical settings for its ease of use (Noble and Robertson, 1996). The Borg CR-10 scale (Appendix 7) is similar to the RPE scale. Although it has a wider applicability and can be used for most perceptual intensities, it is most commonly used to estimate pain (Borg, 1998).

2.6.6 Other variables of interest

2.6.6.1 Haematocrit

The haematocrit is the ratio of the formed elements in the blood (red and white cells, and platelets) to the total blood volume. The percentage of the total blood volume composed of cells or formed elements is referred to as haematocrit. Normally haematocrit constitutes about 40-50% of total blood volume. Training reduces the haematocrit (total blood volume and plasma volume increase, although slight increases in erythrocyte numbers are noted). The change in the ratio of plasma to cells, resulting from an increase in the fluid portion reduces blood viscosity. Reduced viscosity may facilitate blood movement through the blood vessels, particularly through the smallest vessels, such as the capillaries, and a lowering of blood viscosity enhances oxygen delivery to the active muscle mass (Wilmore and Costill, 1994).

2.6.6.2 Venepuncture

Venepuncture was performed at each assessment time point. With the patient semi-recumbent, the venepuncture procedure was explained, thus allaying any fears or anxieties. Subsequently, a tourniquet was applied to the upper arm at a pressure high enough to impede venous distension, without restricting arterial flow (Mallet & Dougherty 2000). A sterile alcohol swab (Isopropyl Alcohol 70% v/v, Seton Healthcare Group plc, Oldham, U.K.) was used to clean the puncture site and the area was allowed to dry. Blood sampling was facilitated by the insertion of either a 0.7 (x 38 mm) or 0.8 (x 38 mm) Precision Glide needle (Becton Dickinson, Plymouth, U.K.) at an angle of approximately 30 degrees into the basilica vein at the elbow. Once the needle was in the correct position, blood was collected (one of serum (9.5 ml SST) and two of plasma (4.5 ml K3E 15% 0.054 ml)). Blood was allowed to clot for 30 min, after which samples were centrifuged (Labofuge 400 R, Kendro Laboratory products, Germany) for 10 min at 1000-1300 *g* at 25°C and aliquots stored at -80°C until analysis.

2.6.6.3 Body Mass Index (BMI)

The Body Mass Index (BMI) is a measure of the relationship of weight relative to height, defined in $kg.m^{-2}$ (Kligman *et al.* 1999) and is regarded as a reliable indicator of total body fat and is related to the risk of premature death, cardiovascular disease, high blood pressure, osteoarthritis, diabetes and some cancers. Although generally useful, this index is of questionable value in older subjects, especially those who have

decreased bone mineralization (Kligman *et al.* 1999). BMI was determined at all assessments (Table 7).

2.6.6.4 BMI score interpretation

Table 7. BMI score interpretation.

BMI	*Weight Status*
Below 18.5	Underweight
18.5 - 24.9	Normal
25.0 - 29.9	Overweight
30.0 and above	Obese

2.7 Calibration of equipment

2.7.1 Expired gas analysis (Mass Spectrometer)

Pulmonary gas exchange variables were directly measured, breath-by-breath, using an on-line expired gas analysis, mass spectrometer system (CaSE EX670 PulmoLab, Kent, U.K.). Prior to each test the system was calibrated by inputting the patient's weight and height details, barometric pressure (Holtain, Crymych, U.K.), temperature and humidity (Oregon Scientific, U.S.). The turbine was calibrated based on a fixed volume, using a large (3L) syringe. The acceptable range was 2.97 to 3.03 L, thereby allowing an error of 0.1%. Calibration was achieved using known gases; nitrogen, oxygen, carbon dioxide and argon.

By the nature of the mass spectrometer, the measured gas concentrations are all fast-response and synchronous, however the output on screen occurs some hundreds of milliseconds after the event. The turbine produces a single signal for volume, which occurs within 10 ms of the event. A realignment of these two signals is achieved with a 'delay' value. This 'delays' the volume by the intrinsic delay value of the gases. A breath is defined as a period containing an inspirate phase, followed by an expirate phase. The expirate is compared to the inspirate to determine gas exchange. During expirate the volume is measured and the expirate will contain rising CO_2 and falling O_2 concentrations.

2.7.2 Calibration of YSI sport

The YSI Sport (YSI 1500 Sport, Ohio, U.S.A) is a portable, battery powered blood lactate analyser. It is designed to provide a quick measurement of lactate in whole blood. The buffer reagent, reference and waste bottles hold the solutions needed for sample analysis.

The reagent solutions for the Sport were prepared manually (YSI Model 1504 Starter Kit). The buffer solution was prepared by filling a 500mL mixing bottle with reagent water. High quality deionised water was used, since the reagent water must be very pure. One package of buffer concentrate (YSI 2357) was added to the water and stirred, ensuring that the buffer chemicals had completely dissolved. Prior to every assessment the YSI SPORT was calibrated with a 5 mM standard (YSI 2327), using a capillary tube injector (YSI 1502 (25 µl)). The face of the probe, covered by a membrane, is situated in a buffer-filled sample chamber into which the sample was injected. The probe is fitted with a three-layer membrane containing immobilised lactate oxidase in the middle layer. The Sport automatically senses the injection device.

For initial calibration the 25 µl of calibration standard was dispensed into the chamber, which already contains approximately 500 µl of buffer. Some of the substrate diffuses through the membrane. The sensor response increases, until it reaches a plateau, this taking approximately 30 seconds. When it contacts the immobilised enzyme (lactate oxidase), it is rapidly oxidised producing hydrogen peroxide (H_2O_2). The H_2O_2 is in turn oxidised at the platinum anode, producing electrons. A dynamic equilibrium is achieved when the rate of H_2O_2 production and the rate at which H_2O_2 leaves the immobilised enzyme layer become constant. Equilibrium is indicated by a steady state response. The electron flow is linearly proportional to the steady state H_2O_2 concentration and therefore to the concentration of lactate.

The reference pump then flushes the chamber for approximately 33 seconds and the sensor response changes to a different value. At this point the instrument calculates the relationship of the known standard to the reference solution and stores this information until another calibration injection is performed. The buffer pump then flushes the chamber for approximately 33 seconds and the sensor response decreases to the normal baseline value. Once the analysis is complete, the result is displayed on screen. Each sample is stored in memory, identified by date and time.

The calibration procedure is necessary to compare the relative concentration of the standard with the relative concentration of the unknown sample. During each subsequent sample cycle, the reference solution is again measured and then internally compared to the reference solution concentration measured during the initial calibration. If a variation exists, the calculation of the sample concentration will be compensated accordingly.

2.7.3 Calibration of cycle ergometers and arm-crankers

Both the arm ergometer (Monark 881E, Varberg, Sweden) and standard stationary cycle ergometer (Monark 824E, Varberg, Sweden) used in the exercise training sessions were calibrated at the Monark (Varberg, Sweden) works. Calibration of both pieces of equipment was routinely verified as per the manufacturer's instructions. The electronically-braked cycle ergometer (Gould, Bilthoven, Holland) utilised during both the upper- and lower-limb assessment sessions was calibrated using an external calibrator (Lode Portable Calibratior 2000, Lode BV, Groningen, Netherlands). An actual value was compared against a display value, from which a calibration curve was drawn.

2.8 Questionnaires

In agreement with previous studies, the potential for bias in the self-evaluation of walking ability and functional status was minimised by administering the questionnaires before the walking test (Regensteiner *et al.* 1996). Thus questionnaire responses were not influenced by a patient's shuttle-walk performance. In addition, the interviewer and patient were blinded to previous questionnaire scores. Functional status was assessed by questionnaires characterising walking ability (WIQ), habitual physical activity levels (PAD-PAR), and physical, social, and role functioning, well-being, and overall health (SF-36) (Regensteiner *et al.* 1996).

2.8.1 Quality of Life. Medical Outcomes Study SF-36 v2 and the EuroQol EQ-5D

Quality of life assessments were made using the SF-36 *v2* (Appendix 13) and the EuroQol EQ-5D (Appendix 14) questionnaires. Both questionnaires were administered to all patients at the start of the study, at 6-weeks into, and at the end of the intervention period, in order to assess both the short- and longer-term benefits of exercise training on quality of life, respectively. The questionnaires were also administered at all four time points of the follow-up period, namely 6-, 12-, 24- and 48-weeks to assess changes in

perception of quality of life following the period of supervised exercise training. The questionnaires were administered to the control patients at identical time points. Questionnaire completeness was checked in the presence of the patient.

The SF-36 *v2* questionnaire evaluates physical function and general health perceptions as well as limitations due to mental, social function and vitality (Regensteiner *et al.* 1997a; Regensteiner, 1997). The questionnaire encompasses eight quality of life domains, four specifically relating to physical health namely;- general health, physical functioning, role limitation physical, bodily pain, and four relating to mental status, namely, mental health, energy and vitality, role limitation emotional and social functioning. With the SF-36 *v2* each of the domains was scored separately on a scale of 0 to 100% (Regensteiner *et al.* 1996). A typical range of responses for many diseases, although not PAD has been established for this questionnaire (Stewart *et al.* 1989).The SF-36 *v2* is a self-administered questionnaire which is easy to score (Regensteiner and Hiatt, 1995).

The EuroQol EQ-5D questionnaire is a non-disease specific instrument, developed within the framework of a joint European project. The visual analogue scale is similar to that of a thermometer (Health Policy, 1990). It measures health and health-related quality of life in patients, and is designed for self-completion. It comprises five dimensions of health: mobility, self-care, degree of difficulty in performing usual activities, pain and discomfort, and anxiety and depression. The EuroQol instrument is specifically designed to complement other quality of life measures (Health Policy, 1990), such as the SF-36 *v2*. It has been utilised in previous studies comparing symptom severity and health values (De Vries *et al.* 1998).

2.8.2 Walking Impairment Questionnaire (WIQ)

The Walking Impairment Questionnaire (WIQ; Appendix 15) was investigator administered at every assessment session, prior to the assessment of walking ability (incremental shuttle-walk test). It is simple to administer (Hiatt, 1999) and is valid for characterising walking ability and detecting changes in walking impairment due to interventions in patients with intermittent claudication (Regensteiner *et al.* 1990).

The WIQ is a disease-specific questionnaire that asks a series of questions regarding patients self-reported claudication severity and ability to walk defined distances and

speeds, and stair climbing ability (Hiatt *et al.* 1995a). Patients rank their ability to walk specific distances on a 0-4 Likert scale. The WIQ distance score is calculated by multiplying the Likert scale score with the corresponding distance, summing these products, and then dividing by the maximum score possible to get a percentage score (Regensteiner *et al.* 1996). Thereby, allowing outcome to be expressed as a percentage of full function (Menard *et al.* 2004). The distance summary score ranged from 0% (patient unable to walk 50 feet without claudication pain) to 100% (patient able to walk 1,500 feet without claudication pain) (Regensteiner *et al.* 1996).

Walking speed is assessed by asking patients to rank their degree of difficulty in walking a block (300 feet) slowly, at average speed, quickly, and running or jogging on a 0-4 Likert scale (4=best). Patients' responses on the Likert scale are multiplied by the approximate miles per hour represented by each walking speed. The resultant score is then divided by the maximum possible score to achieve a percentage score. The summary score for walking speed ranged from 0% (patient unable to walk 300 feet slowly without claudication pain) to 100% (patient able to jog 300 feet without difficulty) (Regensteiner *et al.* 1996).

Similarly, stair climbing ability and claudication severity are calculated for each patient. The stair climbing score was rated so that 0% indicated a patient could not climb one flight of stairs without claudication, while 100% indicated no difficulty in climbing three flights of stairs (Regensteiner *et al.* 1996). The claudication severity score was scaled so that 0% indicated that the patient had much claudication pain when walking, while 100% indicated no claudication with walking difficulty (Regensteiner *et al.* 1996). The feasibility is good for this questionnaire, which can be administered and scored in 6-8 min (Regensteiner and Hiatt, 1995).

2.8.3 Self perceived walking ability

At the end of the intervention period patients were asked regarding their self perceived walking ability (Appendix 16). Patients were asked whether they felt that their walking ability had improved, remained unchanged or deteriorated over the 24-week intervention period. Patients were asked to give one response only, by circling the appropriate response. Data were presented as the percentage of patients in each of the study groups giving each response.

2.8.4 *Confidence in walking*

At the beginning and end of the intervention period, and at each follow-up time point, patients were asked regarding their general confidence in walking (Appendix 17). Patients were asked to circle the number on the scale (0-10 scale, 0 denoting no confidence and 10 denoting total confidence in walking). The median (range) value for each study group was calculated.

2.8.5 *Physical activity recall*

The PAD-Physical Activity Recall (PAD-PAR) questionnaire (Appendix 18) is specific for PAD patients, and provides a global measure of habitual physical activity levels by estimating the total energy expenditure of the patient at work, in the home, and during leisure/recreational time (Sallis *et al.* 1985; Hiatt *et al.* 1995a). The amount of energy expenditure for each activity is expressed as metabolic equivalent hours per week (METs). One MET equals 3.5 mL/kg per minute of oxygen consumption (Hiatt *et al.* 1995a). The PAD-PAR has been modified from the original version (Sallis *et al.* 1985) to be more appropriate for patients with claudication who can perform only low levels of physical activity (Hiatt *et al.* 1995a).

The PAD-PAR was administered every week throughout the intervention period to all patients regardless of group. For each category (work, household and leisure or recreational activities) the patient was asked to estimate the number of hours per week spent within the category during the preceding week. A card with a range of physical activities (Appendix 19) was used as a prompt for the patients, who were asked about specific activities within each intensity of exercise (heavy to very light). For each activity (heavy to very light), the number of hours spent in that activity was calculated (days per week times hours per week). Activities are classed according to the following scale: very light (0.9 to 2.0 METs), light (2.1 to 3.0 METs), moderate (3.1 to 5.0 METs), and heavy (5.1 to 7.0 METs). For each category the hours per week were summed to determine the total hours per week.

Data are reported in MET hours per week (hours per week times the MET value of the activity) (Hiatt *et al.* 1995a). The PAD-PAR must be administered by an interviewer, but it was usually administered and scored in less than 12 min in accordance with previous studies (Regensteiner and Hiatt, 1995). It was also administered at all four time

points of the follow-up period to assess patients' physical activity levels, following the end of structured, supervised exercise training.

2.8.6 Self perception of physical activity status

At the beginning and end of the intervention period and at each of the follow-up assessment time-points, patients were asked to rate their physical activity status using the physical activity ladder (0-10 scale; Appendix 20) (Biener and Abrams, 1991). The median (range) value for each study group was calculated.

2.8.7 Incentive to perform physical activity

At the end of the 24-week intervention period patients were asked whether they felt that the study had provided them with an incentive to perform physical activity (Appendix 21). Patients were asked to circle the appropriate response, that being, incentive to perform physical activity or no incentive to perform physical activity. For each response the percentage of patients in each group was calculated.

2.9 Supervised Exercise Sessions

2.9.1 Structure of training sessions

Patients randomised to the lower-limb exercise training or upper-limb exercise training groups undertook a 24-week period of twice weekly supervised exercise sessions, organised into blocks of five weeks of training and exercise assessments in every sixth week. Patients thus performed 20-weeks worth of training, interpolated with 5-weeks of assessment sessions, during the intervention period.

Training was undertaken on a group basis (maximum of 8 patients), with the sessions equally balanced during the week. Classes were consistently organised on Mondays and Thursdays. This provided a structure and allowed patients to rest between sessions, thereby allowing recovery and the possible influence of fatigue to be minimised. Training sessions were organised in both the mornings and afternoons on both days, namely at 10am, 11am and 2.30pm, taking into account and excluding the lunch-time dip, which could possibly affect exercise performance. Patients attended the session in which they felt at their optimum time of day to perform exercise, as described earlier.

Those patients randomised to the upper-limb exercise training group performed exercise on a standard friction braked arm ergometer (Monark 881E, Varberg, Sweden) and

those to the lower-limb exercise training group on a standard stationary cycle ergometer (Monark 824E, Varberg, Sweden; Figure 3). A 2-min warm-up period preceded the exercise training session, designed to slowly increase HR. Patients were instructed to maintain the speed of 50 ± 2 revs.min^{-1}, at all times. During each session, training was undertaken at the required intensity in cycles of 2-min of exercise, followed by 2-min rest intervals, for a total exercise time of 20-min in a 40-min session (Walker *et al.* 2000). These parameters were strictly adhered to.

This strategy enables a greater volume of higher intensity work to be performed in a given amount of time than can be achieved using continuous exercise of a similar nature, and therefore optimises the stimulus for cardiovascular adaptations (Astrand and Rodhal, 1986). All patients wore a short-range radio-telemetry monitor (Polar Sport Tester, Kempele, Finland), for continual HR monitoring. The RPE and CR-10 scales were on view at all times. HR, RPE and CR-10 were recorded for the first and last 2-min exercise bouts. A 2-min cool-down period followed the last 2-min bout of exercise, in order to return the HR to baseline and thus minimise risk of injury.

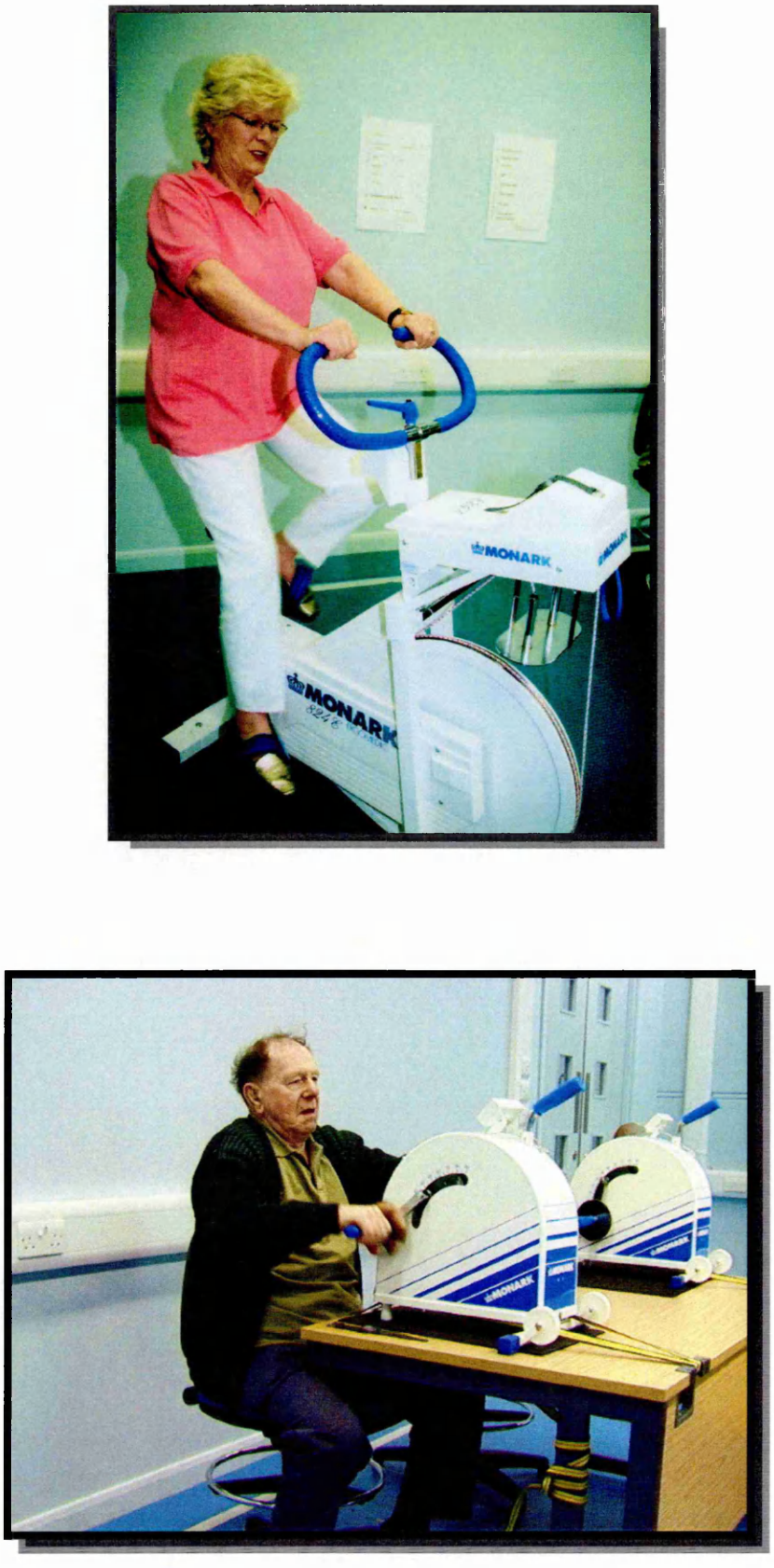


Figure 3. Patient undertaking lower-limb exercise training (above) and upper-limb exercise (below)

2.9.2 *Exercise intensity during training sessions*

Supervised exercise training was undertaken at equivalent limb-specific relative exercise intensities. For each patient, training intensity was individualised using the penultimate power output achieved in the respective LCT and ACT assessment. Use of penultimate power output enabled training intensity to be balanced at 85-90% of the limb-specific peak $\dot{V}O_2$ between the upper- and lower-limb exercise training groups, thus ensuring a similar cardiovascular stimulus. In addition to power output, training intensity was also balanced on the basis of HR, RPE and pain data from the penultimate power output achieved during the respective assessment session. This ensured that the correct training intensities were used in the supervised exercise sessions, with most patients exercising between the Borg RPE scale ratings of 13 ("somewhat hard") to 16 ("hard to very hard). In certain patients, the training intensity was increased to the maximal work rate achieved during the assessment session after 3-weeks of training in order to ensure that a sufficient training stimulus was maintained as fitness levels improved (Walker *et al.* 2000). For all patients, exercise training intensity was adjusted following each 6-week incremental assessment, as appropriate.

2.9.3 *Precautions during the training sessions*

Patients with PAD often have co-morbid medical problems that may interfere with their ability to safely participate in exercise rehabilitation programs (Katzel *et al.* 2000). To promote safety, all patients during the training sessions were monitored using telemetry devices regardless of whether they had clinical evidence of co-morbid coronary disease. During the exercise sessions, HR and cardiac rhythm were continuously evaluated. Blood pressure was measured before and after the training sessions in those patients with a history of coronary problems. Some patients from the lower-limb training group in the initial stages of the exercise programme reported an exacerbation of existing musculoskeletal problems (i.e. knee stiffness). These were in the main relieved following the 2 day rest interval between training sessions. A similar long-term programme has also previously recommended that training sessions be separated by 48 hr (McGuigan *et al.* 2001). In the majority of patients the exercise training sessions were well tolerated.

2.9.4 *Monitoring of attendance*

Attendance at the twice weekly training sessions was monitored. Any patient providing prior notice of their inability to attend their specified exercise session were allocated an

equivalent time of day session on another day, usually conducted on an individual basis, to maintain twice-weekly adherence and compliance. Patients who were absent from their specified session without prior notice (usually due to ill health or an unexpected commitment) were contacted by telephone, and a suitable arrangement was made, in order to maintain twice-weekly compliance.

2.9.5 Monitoring of control patients

Patients randomised to the control group were provided with an in-depth lifestyle advice consultation session. In accordance with current U.K. medical practice, all patients were advised to "stop smoking and keep walking "(Housley, 1988). This message was reinforced by telephone every week during the intervention period.

Patients were informed that their level of physical activity in accordance with the PAD-PAR questionnaire (Appendix 18) would be monitored on a weekly basis, stressing the importance that patients should be as honest as possible. Patients were thus contacted weekly by telephone, during which their level of physical activity was assessed via completion of a PAD-PAR questionnaire. Emotional support identical to that received by the patients randomised to the supervised exercise programme was provided when appropriate. Control patients undertook all re-assessments at identical time points as the training cohorts.

2.9.6 Medication

During the intervention period, patients on long-term medication continued with their treatment. These were stable and no major changes were introduced into the medication profile. Slight adjustments to drug dosages in some patients were made. Patients prescribed GTN did not need to use the medication during the assessment sessions, since it has been shown that walking distance can improve following GTN administration in patients with intermittent claudication (Heer *et al.* 2001).

2.10 Statistical analysis

Trials of healthcare interventions fall into two categories: explanatory and pragmatic. Explanatory trials usually measure treatment efficacy on the basis of intermediate outcomes, as a means to elucidating the time-course and biological bases of a positive response. It is felt that this study was an explanatory trial, investigating the efficacy of upper-limb exercise in relation to that of comparable lower-limb exercise, with the aim

of attempting to identify possible underlying mechanisms. The efficacy of upper-limb exercise training for patients with PAD is still in the early stages of being examined, and following our earlier preliminary study (Walker *et al.* 2000), a larger-scale RCT was needed to prove that upper-limb exercise training can evoke positive health outcomes and to further understand the mechanisms of action. Such a robustly designed trial has never been performed previously.

Given these considerations, it was felt more appropriate to restrict analysis to those patients who completed the course of treatment at the intended intensity for the intended time interval. Missing data points were not therefore considered on an intention to treat basis. The rationale to this approach is that this was a scientific study aimed at evaluating the influence of upper- and lower-limb aerobic exercise training on the clinical status of these patients. This was not a pragmatic trial, designed to evaluate the effectiveness of a physical activity intervention programme. During the intervention and follow-up period, data analysis was performed on 94 and 76 patients, respectively (32, 30 and 32; and 25, 25 and 26 patients from the lower- and upper-limb exercise training and control groups, respectively). Haematocrit and walking confidence data analysis were performed on fewer patients (n=65), since the decision to include these variables was made once the study had commenced, and this accounts for the difference in patient numbers.

Descriptive statistics were obtained for all baseline variables during the intervention and follow-up period. Dependent variables were first tested for normal distribution using the Shapiro-Wilkes and Kolmogorov-Smirnov goodness of fit tests. Histograms of all data parameters, at all time-points were obtained to confirm normality of distribution. Levens test of equality of variance checks were also carried out on all data. Where applicable, data transformations (for example log transformations) were performed to obliterate skewness. In instances where skewed interval or ratio level data could not be normalised using logarithmic or other transformation techniques, non-parametric tests were used. With the exceptions of peak power output, CD, RPE, CR-10, ABPI, patients self-reported walking ability, walking confidence, physical activity status, WIQ and EQ-5D questionnaire responses, all other variables were normally distributed. Peak power output and CD were normalised using logarithmic transformation before analysis. Parametric results are expressed as means ± SEM unless otherwise stated and non-parametric results are expressed as the median value, with ranges.

A mixed design factorial ANOVA was used to test for changes in normally distributed variables over time within groups and for differences between groups at the same time-points. If sphericity could not be assumed the Greenhouse Geisser and Huyndt-Feldt assumptions were observed to check for time and time x group interactions. The ANOVA is a robust procedure, which can withstand minor violations. Where significance was indicated, the mixed factorial ANOVA analysis was followed up with one way ANOVA's within and between groups and *post hoc* comparisons to determine where group and time-point differences occurred. Data, which could not be normalised using data transformation techniques were analysed using the Kruskall Wallace test, with group differences at each time-point being identified using the Mann-Whitney U test and changes over time within groups analysed using the Friedman and Wilcoxon signed ranks test.

The magnitude of the changes in walking performance (CD and MWD) between baseline and the 24-week intervention and the 48-week follow-up period were calculated using the mean percentage difference score. The percentage difference from baseline for each patient was obtained. The group mean of the individual percentage difference scores were calculated for each of the three study groups. Between group analysis was compared using one-way ANOVA.

The relationship between walking performance (MWD) as assessed using the incremental shuttle-walk test, and patients' perceived walking ability as identified using the WIQ, was assessed using Pearson's correlation coefficient. All statistical analyses were performed using SPSS for Windows (SPSS U.K. Ltd, Woking, U.K.), with significance indicated at the 0.05 level.

Chapter 3 – Intervention Study Results

3.1 Demographics, patient attendance and compliance

3.1.1 Demographics

A total of 104 patients (81 males, 23 females) were recruited for this study. The median age was 69 years (range 50 - 85 years) and their mean BMI was 27.6. Thirty seven, 34 and 33 patients were randomised to the lower- and upper-limb training and control groups, respectively. Demographic data (age, sex, resting ABPI, weight, height, current angina, previous MI and stroke, sleep duration, diabetic and smoking status) are shown in Table 8. The majority of patients (89%) claimed to eat a well-balanced diet, including fruit and vegetables, and to adhere to previous advice regarding the reduction of fat in their diet. Seventy-seven percent of patients reported a disturbed sleep pattern, awakening several times during the night, requiring the toilet.

Table 8. Demographics of the entire patient group and those of the three study groups.

Variable	**All Patients** *N=104*	**Lower-limb Training** *N=37*	**Upper-limb Training** *N=34*	**Control Group** *N=33*	**Sig**
Median age, years (range)	69 (50 to 85)	69 (50 to 85)	66 (54 to 84)	72 (56 to 84)	*NS*[a]
Sex					
Male, %	78 %	81 %	79 %	73 %	*NS*[a]
Female, %	22 %	19 %	21 %	27 %	
Duration of claudication, months	55	59	50	55	*NS*[a]
Resting ABPI	0.66 ± 0.02	0.64 ± 0.03	0.65 ± 0.03	0.69 ± 0.03	*NS*[b]
Weight, kg	78.4 ± 1.4	76.3 ± 2.2	80.8 ± 1.9	78.3 ± 3.2	*NS*[a]
Height, m	1.68 ± 0.01	1.69 ± 0.01	1.68 ± 0.01	1.67 ± 0.01	*NS*[a]
Previous MI, %	8 %	3 %	9 %	12 %	*NS*[b]
Previous stroke, %	17 %	19 %	18 %	15 %	*NS*[b]
Current angina, %	18 %	14 %	18 %	24 %	*NS*[b]
Diabetes mellitus, %	17 %	8 %	18 %	27 %	$P < 0.05$ [b]
Duration of sleep, hr	7.3	7.3	7.1	7.4	*NS*[a]
Smoking status					
Current, %	32 %	38 %	24 %	33 %	*NS*[b]
Previous, %	62 %	54 %	73 %	61 %	
Never smoked, %	6 %	8 %	3 %	6 %	

ABPI data are presented for the most symptomatic limb. Patients with diabetes mellitus were taking oral hypoglycaemics or insulin. Unless otherwise stated, values are means ± S.E.M. *NS* indicates no significance between the three study groups: [a]ANOVA, [b]Chi Square test.

3.1.2 Medication history

Some patients in this study were taking prescribed cardiac medication, including β-blockers, ACE-inhibitors, Ca^{2+} channel blockers, nitrates, diuretics, statins and aspirin

(Table 9). Patients were advised to continue on their drug regimen throughout the study period. Any changes to medication, including drug dosage, were recorded.

Table 9. Medication details of the entire patient group and of the three study groups.

	All Patients *N=104*	**Lower-limb Training** *N=37*	**Upper-limb Training** *N=34*	**Control Group** *N=33*
β-Blockers, %	26	19	24	36
ACE Inhibitors, %	15	14	18	15
Ca^{2+} Blockers, %	30	22	35	33
Nitrates, %	10	11	6	12
Diuretics, %	32	35	29	30
Digoxin, %	6	8	3	6
Warfarin, %	5	8	3	3
Statins, %	68	73	68	61
Aspirin, %	83	81	82	85

Data are represented as the percentage of patients in each group on the specific cardiac medication.

3.1.3 Patients time of day preferences to undertake exercise

The majority of patients in this study (N=62, 60%) did not have a preference for the time of day in which to perform exercise, and indeed according to Horne & Ostberg's lark/owl questionnaire the majority of patients were classed as neither morning nor evening types of individuals (Figure 4). Seven (7%), 34 (32%) and one (1%) patient were classed as definite morning, moderate morning and moderate evening types of individual. All patients undertook all training and assessment sessions according to their individual classification and personal time of day preference.

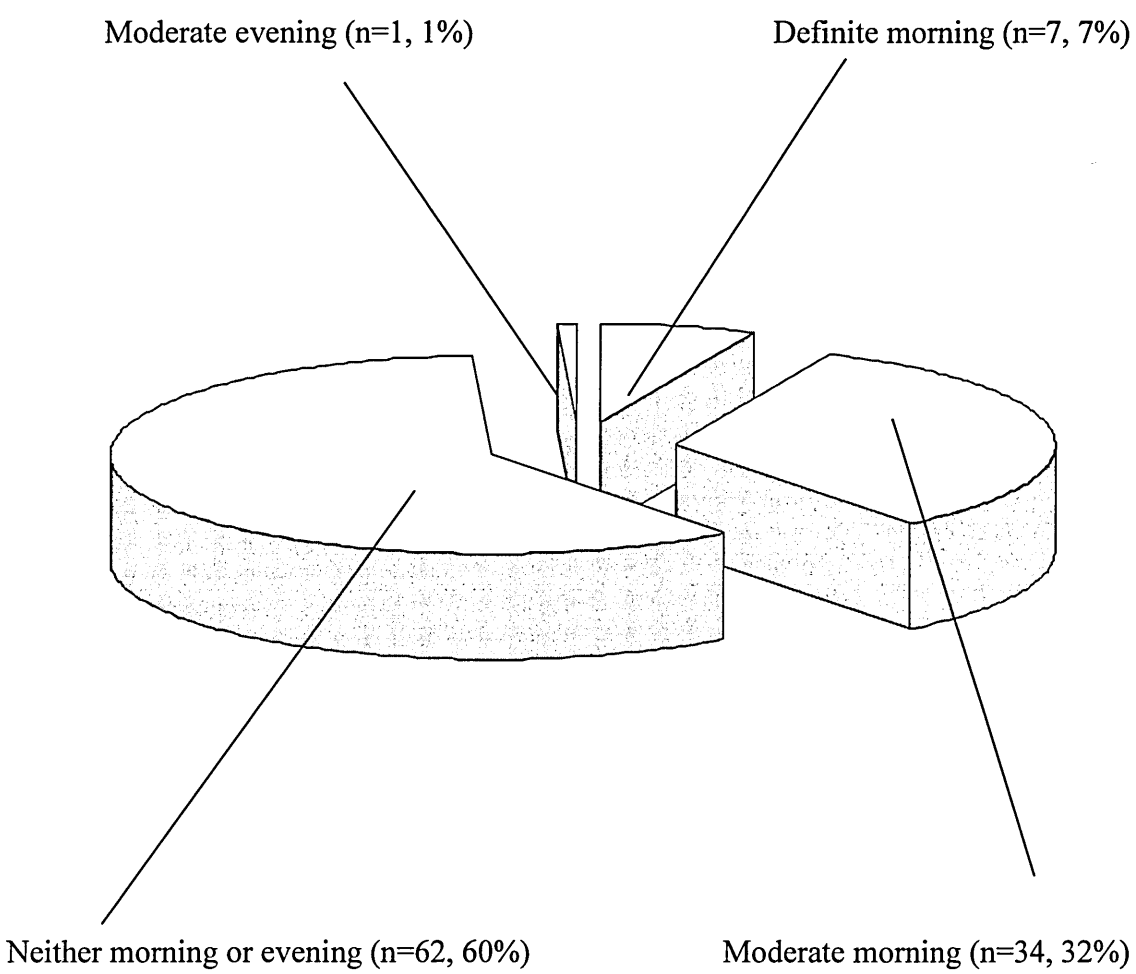


Figure 4. Patients time of day preferences to undertake exercise. Proportion of patients classed as definite morning, moderate morning, moderate evening, or neither morning or evening types of individuals.

3.1.4 Patient attendance and compliance

Of the 104 patients recruited, 94 patients completed the 24-week intervention period, with five, four and one patient withdrawing from the leg, arm and control groups, respectively. Patient drop-out rate during the intervention period was 9.6%.

Three patients withdrew between their initial assessment and their first 6-week re-assessment. One was diagnosed with bowel cancer, another became a full-time carer for his wife who had sustained a stroke; both patients were from the leg-training group. A third, from the control group found the assessments too stressful.

Five patients withdrew between the 6^{th} and 12^{th} week of the intervention period. One was diagnosed with gout, one sustained a heart attack following a fishing expedition, another fell ill with pneumonia which resulted in death, and one withdrew without providing an explanation. All were in the arm-training group. One patient from the leg-

training group was known to suffer with manic depression and found the training sessions too stressful.

Two patients, both from the leg-training group, withdrew in between the 12th and 18th week of the intervention period due to medical reasons. One developed ulcers on his leg, another broke his foot. Both were unable to continue with the training sessions.

Of the 94 patients who completed the 24-week intervention study, compliance to the arm-cranking, leg-cranking, and walking assessments at the five time-points (94 x 5 x 3 = 1,410 assessments in total) was 99.9%. Two of these 94 patients each failed to attend one assessment session (assessment 5). One because his daughter was killed in a hit and run accident, and another was diagnosed with bowel cancer prior to his last assessment. Compliance to the twice-weekly training sessions run over the 24-week intervention period was 99%.

3.2 Intervention study walking performance

3.2.1 Claudication distance

Claudication distance increased over time ($P < 0.01$) in both training groups, but was unchanged from baseline in the control group over the 24-weeks of the study period (Table 10). The magnitude of improvement in CD, in both training groups, over the intervention period was comparable. There was no difference between groups in the pre-intervention CD. Data were not normally distributed and are presented as median, with range in parentheses.

Table 10. CD at each assessment stage of the intervention period.

	Intervention Period (weeks)	Lower-limb Training	Upper-limb Training	Control Group
Claudication Distance (m)	**Baseline**	73 (20 - 568)	101 (25 - 430)	94 (28 - 408)
	6	113* (23 - 394)	120 (38 - 480)	101 (24 - 480)
	12	113** (20 - 692)	115** (39 - 430)	99 (30 - 463)
	18	134** (26 - 465)	142** (29 - 438)	103 (22 - 397)
	24	143** (34 - 579)	152** (42 - 508)	113 (25 - 333)

Data are presented as median value (with ranges). Statistical significance: * $P < 0.05$; ** $P < 0.01$ indicate significantly higher than baseline.

Following the 24-week intervention period, CD improved in the lower- and upper-limb training groups by 65% and 56 %, respectively, compared with the control group of patients ($P < 0.01$; Figure 5). There were no differences between the two training groups.

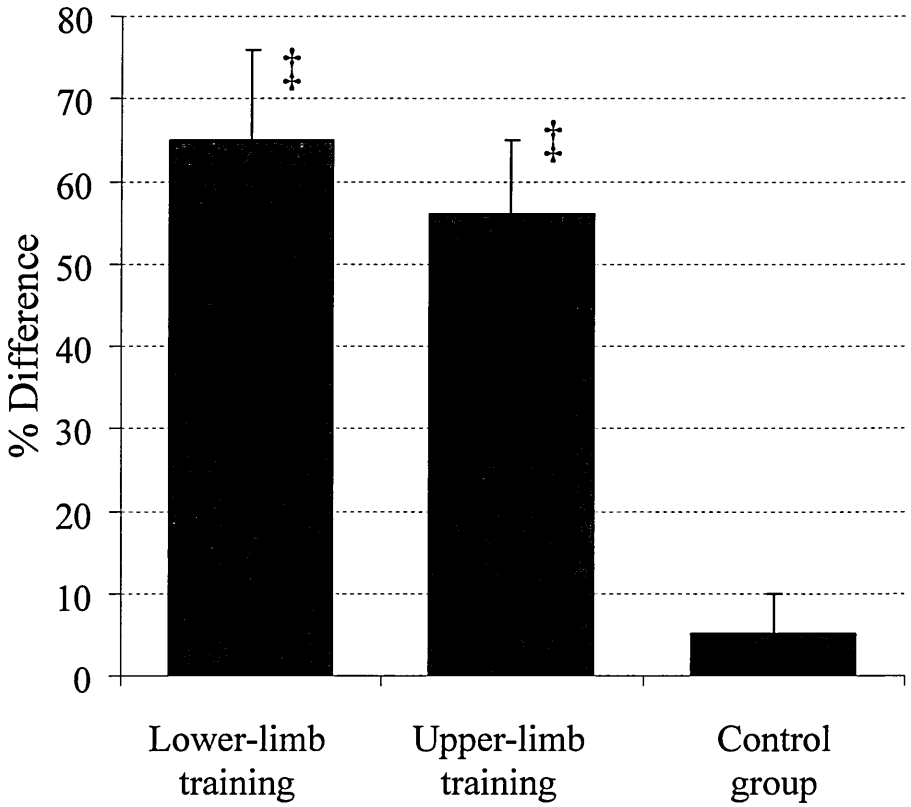


Figure 5. Changes in claudication distance upon completing the intervention period. Data are presented as means in relation to baseline measures, with error bars representing SEM. ‡ $P <$ 0.01 indicates significance between the lower- or upper-limb training groups and the control group of patients.

In the upper-limb training group a sharp improvement in CD was observed up to the 12th week of training (i.e. assessment 3), the rate of improvement thereafter being progressively slower, possibly indicating a plateau effect. In the lower-limb training group, CD continued to progressively improve at each assessment stage (Table 11).

Table 11. Mean percentage change in CD from baseline at each assessment stage of the intervention period.

	Intervention Period (weeks)	Lower-limb training	Upper-limb training	Control group
% Difference in CD from Baseline	**6**	+ 28 †	+ 24	+ 3
	12	+ 37 ‡	+ 41 ‡	- 2
	18	+ 54 ‡	+ 47 ‡	+ 3
	24	+ 65 ‡	+ 56 ‡	+ 5

Data are presented as the mean % difference from baseline. † $P < 0.05$; ‡ $P < 0.01$ indicates significance between the leg or arm-training group and the control group of patients.

Heart rate, blood lactate, perceived exertion and perceived pain responses were assessed during the incremental walking test to assess the consistency of effort and level of pain experienced between walking assessments at the different time-points.

3.2.1.2 Heart rate at claudication distance

Despite increases in CD in both training groups, the heart rate at CD was unchanged in all groups throughout the intervention period. The only significant difference between groups was observed between the arm-training and control group following 12-weeks of the intervention period (Figure 6).

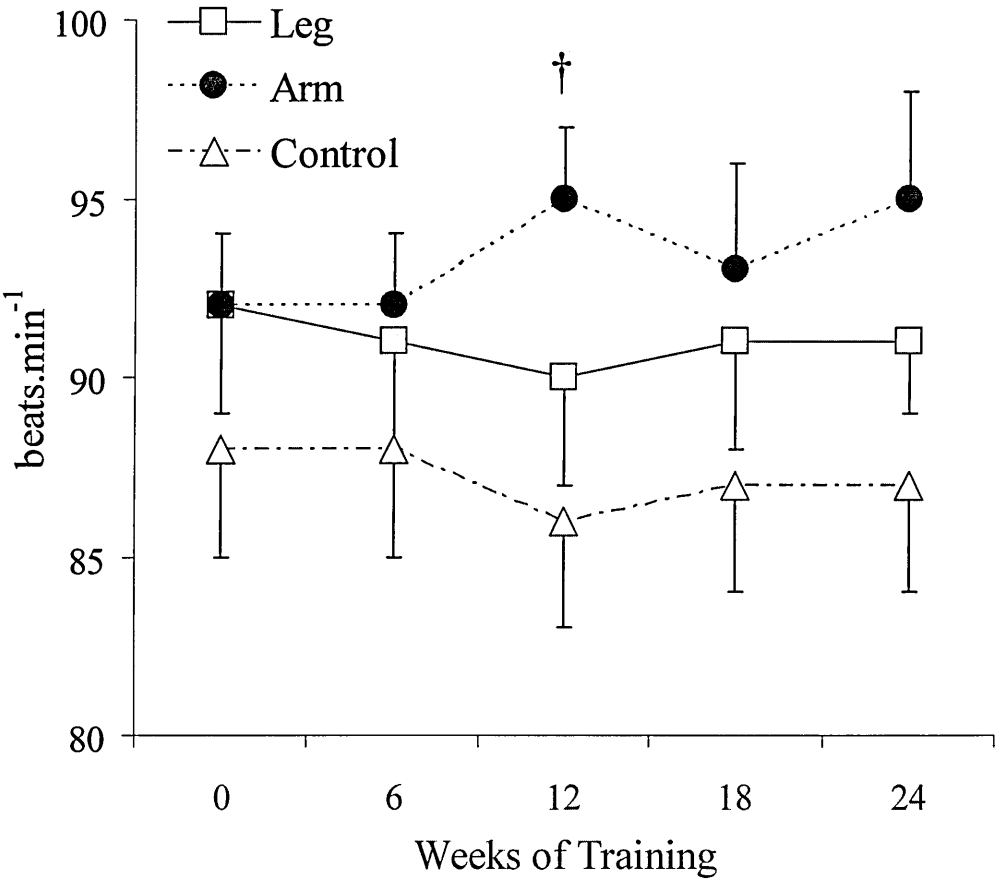


Figure 6. Changes in heart rate at claudication distance. Data are presented as mean ± SEM at each assessment stage of the intervention period. † $P < 0.05$ indicates significance between the arm-training and control group of patients.

3.2.1.3 Perceived pain at claudication distance

The degree of pain experienced at CD in the main was "very weak" (i.e. 1 on the Borg CR-10 scale) and was consistent between groups throughout the intervention period. Interestingly, despite being able to walk further prior to the onset of pain, patients in the lower-limb training group also reported the pain to be less intense at CD following the 24-week intervention period. These patients perceived their pain to be "extremely weak" (i.e. 0.5 on the Borg CR-10 scale) compared to "very weak" at baseline ($P < 0.01$). This difference in pain perception was significant compared with both the arm-training and control group of patients ($P < 0.05$; Table 12).

Table 12. Perceived pain (Borg CR-10 scale) at CD at each stage of the intervention period.

	Intervention Period (weeks)	Lower-limb training	Upper-limb training	Control group
Perceived Pain (Borg CR-10 Scale) at CD	**Baseline**	1.0 (0.3 - 3.0)	1.0 (0.3 - 3.0)	1.8 (0.5 - 3.0)
	6	1.0 (0.3 - 2.5)	1.0 (0.3 - 3.0)	1.0 (0.3 - 3.0)
	12	0.5 (0.3 - 5.0)	1.0 (0.3 - 3.0)	1.0 (0.3 - 7.0)
	18	1.0 (0.3 - 3.0)	1.0 (0.3 - 3.0)	1.0 (0.3 - 7.0)
	24	0.5**† (0.3 - 2.0)	1.0 (0.3 - 3.0)	1.0 (0.3 - 5.0)

Data are presented as median (range). ** $P < 0.01$ indicates significance from baseline. † $P < 0.05$ indicates significance between the leg-training group, compared with both the arm-training and control group of patients.

3.2.2 Maximum walking distance

The pattern of improvement in MWD (Figure 7) was similar to that observed for CD. Maximum walking distance increased by 35% and 30% in the lower- and upper-limb training groups respectively, compared with baseline measures ($P < 0.01$; Table 13). The differences in improvement between the two training groups were not significant. A trend indicating deterioration in MWD was observed in the control group of patients.

Table 13. Mean percentage change in maximum walking distance (MWD) from baseline at each assessment stage of the intervention period.

	Intervention Period (weeks)	Lower-limb training	Upper-limb training	Control group
% Difference in MWD from Baseline	**6**	+ 16 ‡	+ 15 ‡	- 2
	12	+ 23 ‡	+ 22 ‡	- 4
	18	+ 28 ‡	+ 27 ‡	- 5
	24	+ 35 ‡	+ 30 ‡	- 3

Data are presented as mean % difference from baseline. ‡ $P < 0.01$ indicates significance between the leg or arm-training group and the control group of patients.

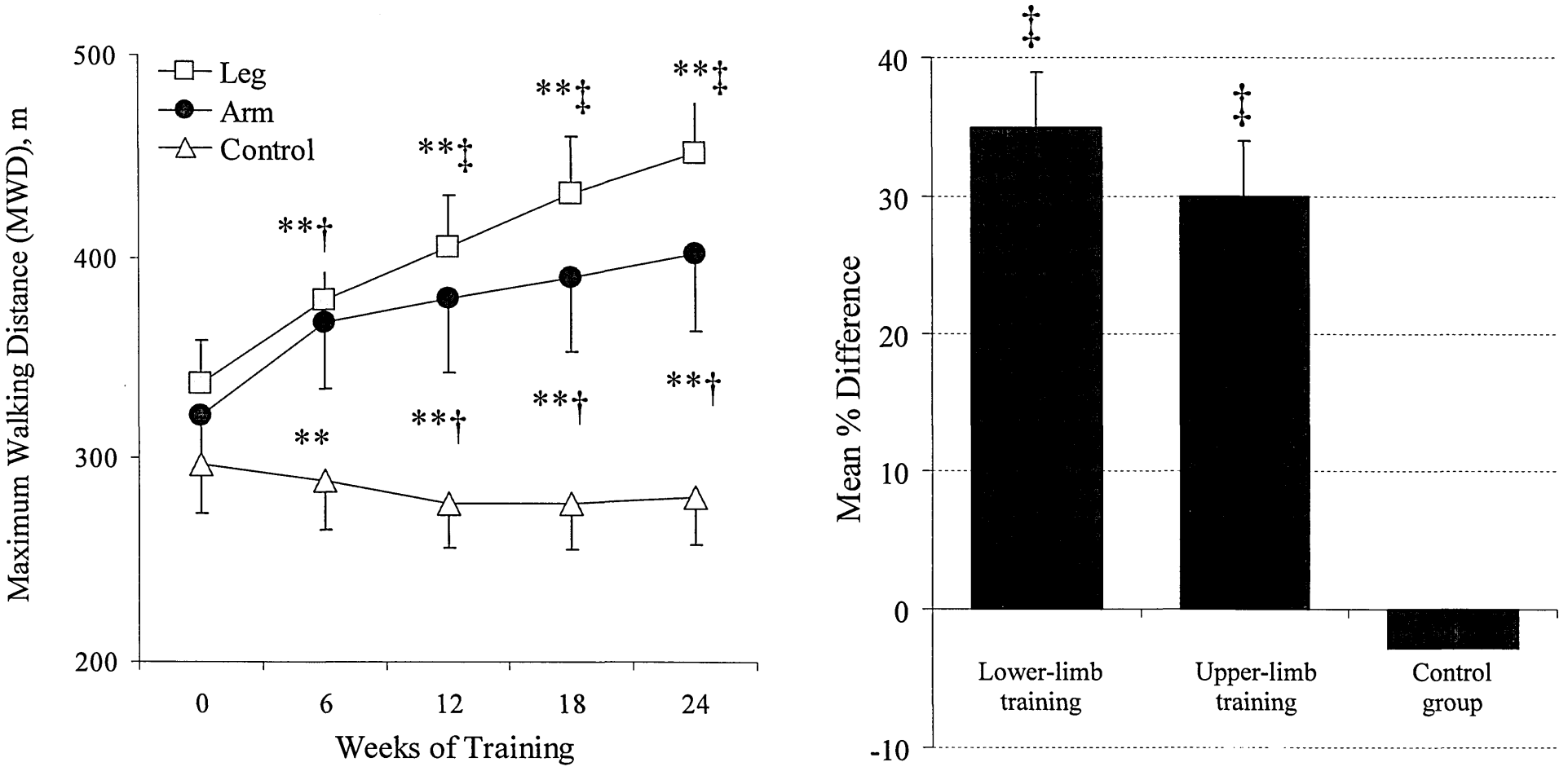


Figure 7. Changes in maximum walking distance throughout the intervention period. Changes in MWD (left) at 6-weekly intervals and mean % difference in MWD (right) after the intervention period. Changes in MWD are presented as mean ± S.E.M. ** $P < 0.01$ indicates significance from baseline. † $P < 0.05$; ‡ $P < 0.01$ between leg- or arm exercise training and the control group of patients.

3.2.2.1 Peak heart rate at MWD

Improvements in MWD in both exercise training groups were accompanied by progressive increases in peak HR at MWD compared to baseline (106 ± 3 *versus* 120 ± 4 and 110 ± 4 *versus* 116 ± 4 beats.min^{-1}, following lower- and upper-limb exercise training, respectively; $P < 0.05$). HR at MWD in both training groups was higher than that observed for the control group at the 24-week time-point ($P < 0.01$; Figure 8), indicating that both exercise groups attained a higher level of cardiovascular stress at MWD following the intervention period. The differences in HR between the two training groups were not significant.

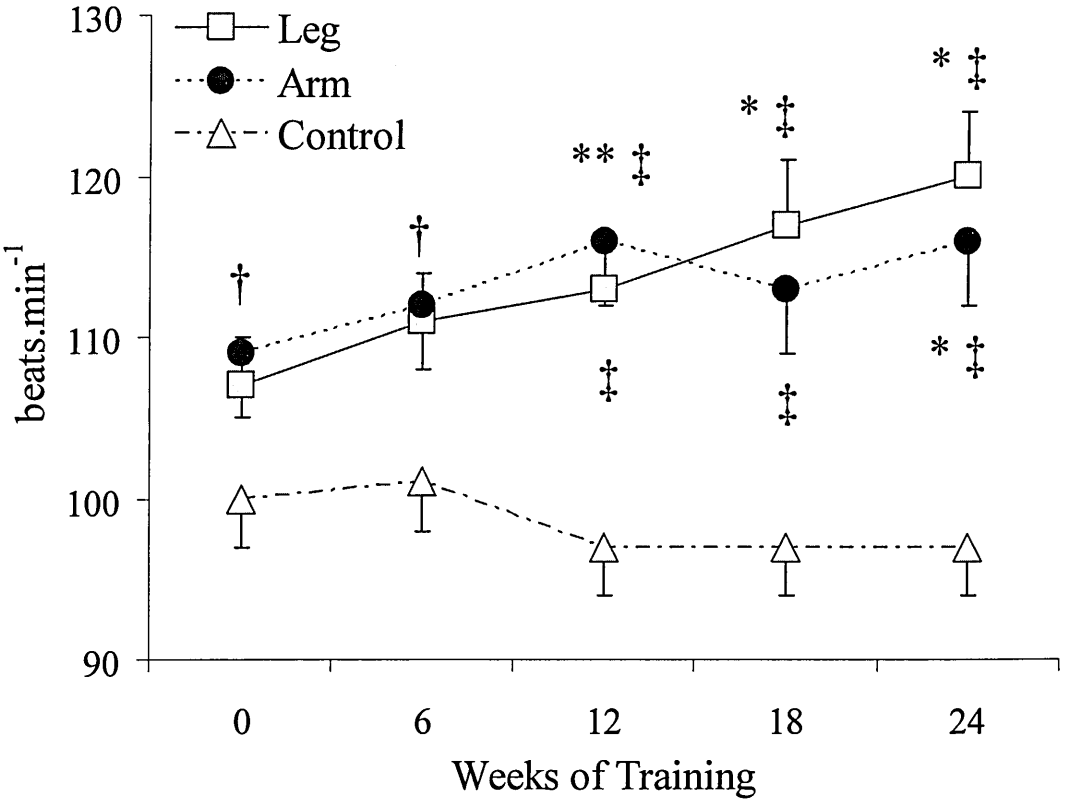


Figure 8. Changes in heart rate at MWD during the intervention period. Data are presented as mean ± SEM at each assessment stage, during the intervention period. * $P < 0.05$; ** $P < 0.01$ indicates significance compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ indicates significance between the leg- or arm-training group and the control group of patients.

3.2.2.2 Peak blood lactate at MWD

At the 12-, 18- and 24-week time-points, the concentration of blood lactate at MWD was higher in both exercise training groups compared to that observed in the control group of patients (P at least < 0.05). Following 6-, 12-, 18- and 24-weeks of the intervention period blood lactate concentration at MWD was increased from baseline in

the upper-limb exercise training group only (1.95 ± 0.14 vs. 2.40 ± 0.17 mM, pre- and post-intervention; $P < 0.05$; Figure 9). No changes in these parameters were observed in the control group of patients.

3.2.2.3 Peak blood lactate 5 min post MWD

Similarly, at the 6-, 12-, 18- and 24-week time-points, the concentration of lactate in blood taken 5-min post MWD was higher in both exercise training groups compared to that observed in the control group (P at least < 0.05). Following 12-, 18- and 24-weeks of the intervention period peak blood lactate concentration 5-min post MWD was increased from baseline in the upper-limb exercise training group only (2.00 ± 0.13 vs. 2.59 ± 0.19 mM, pre- and post-intervention; P at least < 0.05; Figure 9). No changes in these parameters were observed in the control group of patients.

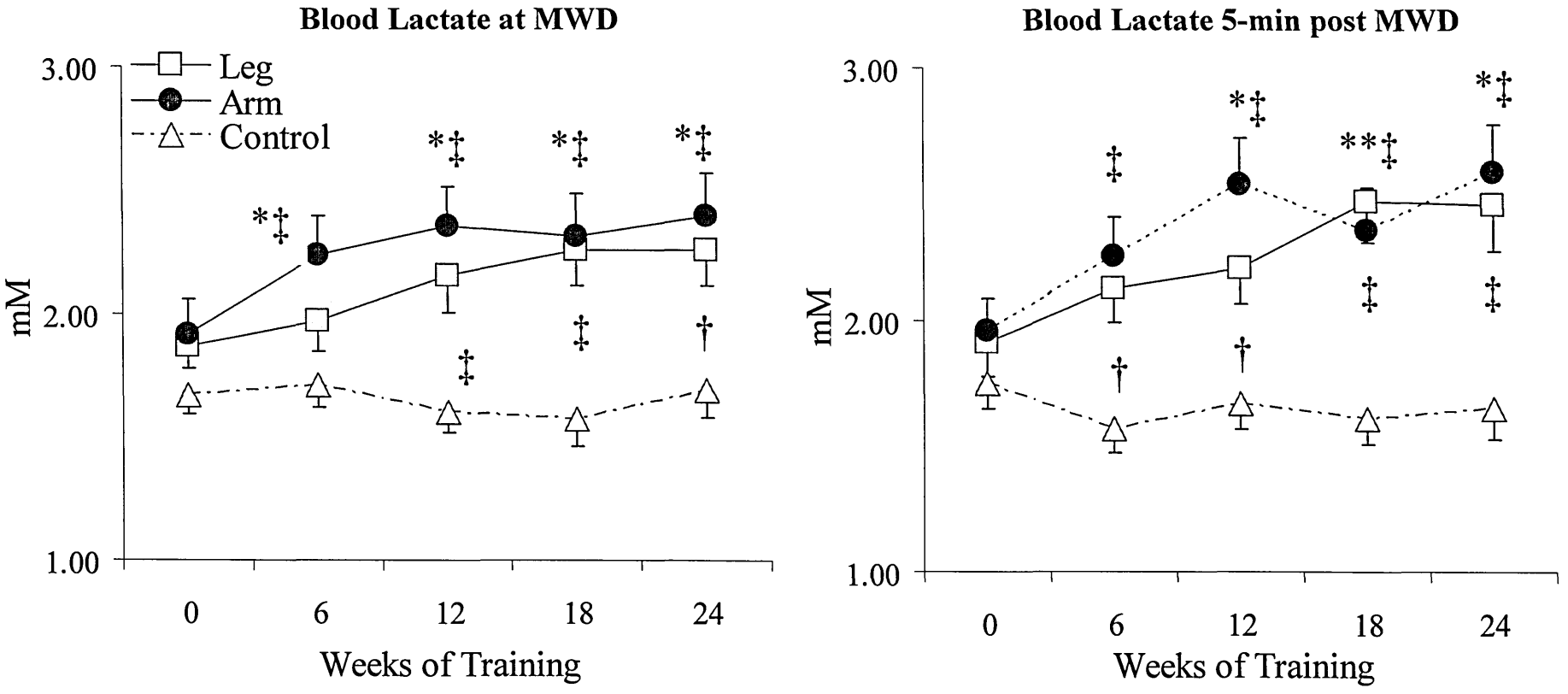


Figure 9. Changes in blood lactate concentration at MWD and 5-min post MWD during the intervention period. Data are presented as mean ± SEM, at each assessment stage of the intervention period. * $P < 0.05$; ** $P < 0.01$ indicates significance from baseline. † $P < 0.05$; ‡ $P < 0.01$ indicates significance between the leg or arm-training group and the control group of patients.

3.2.2.4 Perceived exertion and perceived pain at MWD

The level of pain experienced in the baseline assessment of MWD was fairly consistent between groups, although an increase in the amount of pain experienced at MWD at the 18- and 24-week time-points was observed in the upper-limb training group only ($P < 0.05$; Table 14). This increase in perceived pain at these time-points was also associated with a higher level of perceived exertion (RPE) at MWD in the upper-limb exercise training group, compared to baseline (P at least < 0.05).

Table 14. Perceived pain (Borg CR-10 scale) and perceived exertion (Borg RPE scale) at MWD at each assessment stage of the intervention period.

	Intervention Period (weeks)	Lower-limb training	Upper-limb training	Control group
Perceived Pain (Borg CR-10 Scale) at MWD	**Baseline**	6.0 (3.0 - 11.0)	5.0 (2.5 - 11.0)	5.5 (2.5 – 11.0)
	6	7.0 (2.5 - 10.0)	7.0 (1.5 - 11.0)	6.0 (2.5 – 10.0)
	12	7.0 (2.0 - 11.0)	7.0 (1.0 - 11.0)	6.0 (3.0 – 10.0)
	18	7.0 (3.0 - 11.0)	7.0* (2.5 - 11.0)	6.5 (2.0 – 11.0)
	24	7.0 (2.0 - 11.0)	7.0* (2.5 - 11.0)	5.0 (1.0 – 10.0)
Perceived Exertion (Borg RPE Scale) at MWD	**Baseline**	13.0 (9.0 - 20.0)	13.5 (7.0 - 20.0)	15.0 (7.0 – 19.0)
	6	15.0 (8.0 - 20.0)	13.5 (6.0 - 20.0)	14.5 (7.0 – 20.0)
	12	15.0 (9.0 - 20.0)	15.0* (6.0 - 19.0)	15.0 (11.0 – 19.0)
	18	15.0 (11.0 - 20.0)	15.0* (7.0 - 20.0)	13.0 (7.0 – 19.0)
	24	15.0 (7.0 - 19.0)	16.0** (6.0 - 20.0)	14.0 (6.0 - 20.0)

Data are presented as median (range). * $P < 0.05$; ** $P < 0.01$ indicate significance compared to baseline.

3.2.3 Patients self perceived walking ability

The majority of patients in both training groups stated that they had observed a noticeable improvement in their walking ability, both when walking up a hill, but particularly when walking on the flat (Table 15). This is in agreement with the improvement in walking ability observed in both the training groups.

Interestingly, almost half of the patients in the control group also perceived an improvement in walking ability, yet no actual improvement in walking ability was recorded in this group.

Table 15. Patients self perceived walking ability following the intervention period.

%	Lower-limb training	Upper-limb training	Control group
Improvement	84	90	44
No Change	16	-	47
Deterioration	-	10	9

Data are presented as the percentage of patients in each study group.

3.2.4 Confidence in walking

The improvement in walking ability observed in both training groups, was also associated with an improved confidence in walking upon completing the intervention period, compared to baseline measures ($P < 0.01$; Table 16). The increased confidence in walking, however, was not significant when compared with the control group.

Table 16. Patients perceived confidence in walking.

	Confidence in Walking	
	Pre-Intervention	**Post-Intervention**
Lower-limb Training	5 (2 - 10)	8** (3 - 10)
Upper-limb Training	5 (1 - 10)	9** (1 - 10)
Control Group	7 (1 - 10)	7.5 (3 - 10)

Data are presented as the median (range). ** $P < 0.01$ indicates significance from baseline. Data are presented from 23, 20 and 22 patients from the lower-, upper-limb training and control groups, respectively, due to some patients withdrawing throughout the study period.

3.2.5 Changes in ABPI

Despite the improvements in walking ability, no changes in resting ABPI were observed at any assessment time-point during the intervention period, either between or within groups. A significant decrease in post shuttle-walk ABPI was observed at 24-weeks in both training groups compared to baseline ($P < 0.01$). This decrease was significantly different to the control group in the upper-limb training group only ($P < 0.05$; Table 17).

Table 17. Resting, post shuttle-walk and mean individual difference in ABPI at each assessment stage of the intervention period.

	Intervention Period (weeks)	Lower-limb Training	Upper-limb Training	Control Group
Resting ABPI	**Baseline**	0.65 (± 0.03)	0.66 (± 0.03)	0.69 (± 0.03)
	6	0.63 (± 0.03)	0.67 (± 0.04)	0.68 (± 0.03)
	12	0.64 (± 0.02)	0.65 (± 0.03)	0.66 (± 0.03)
	18	0.67 (± 0.03)	0.65 (± 0.04)	0.68 (± 0.04)
	24	0.65 (± 0.02)	0.66 (± 0.04)	0.68 (± 0.03)
Post Shuttle-Walk ABPI	**Baseline**	0.46 (± 0.04)	0.43 (± 0.03)	0.48 (± 0.04)
	6	0.40 (± 0.04)	0.40 (± 0.03)	0.46 (± 0.03)
	12	0.40 (± 0.04)	0.36 (± 0.03)	0.47 (± 0.04)
	18	0.39 (± 0.03)	0.38 (± 0.04)	0.45 (± 0.04)
	24	0.37 (± 0.03)**	0.31 (± 0.02)**†	0.42 (± 0.04)
Mean Difference in ABPI (Post - Resting)	**Baseline**	- 0.20	- 0.24	- 0.22
	6	- 0.24	- 0.28	- 0.22
	12	- 0.24	- 0.30 †	- 0.19
	18	- 0.28	- 0.27	- 0.23
	24	- 0.28 *	- 0.35**†	- 0.26

Data are presented as mean ± SEM, at each assessment stage of the intervention period. * $P < 0.05$; ** $P < 0.01$ indicate significance from baseline. † $P < 0.05$ indicates significance between the arm-training group and the control group of patients.

3.3 Walking Impairment Questionnaire Domains

3.3.1 Claudication pain severity, walking distance, walking speed and stair climbing ability

Further to the changes in walking ability, patients' walking impairment, as defined using the walking impairment questionnaire (WIQ) was also altered during the course of the intervention period.

Following the 24-week intervention period an increase from baseline in walking distance, walking speed and stair climbing ability was observed in both exercise training groups ($P < 0.01$; Table 18). An improvement in claudication pain severity was also

observed in the upper-limb training group at the 24-week time-point ($P < 0.05$; Table 18) compared to the control group of patients.

Table 18. Changes in WIQ domains throughout the intervention period.

	Intervention Period (weeks)	Lower-limb training	Upper-limb training	Control group
Claudication Pain Severity	**Baseline**	50 (0-75)	50 (0-75)	50 (25-75)
	6	50 (0-75)	50 (25-75) †	50 (0-75)
	12	50 (0-75)	50 (0-75) †	50 (25-75)
	18	50 (25-75)	50 (0-100)	50 (0-75)
	24	50 (25-100)	63 (0-100) †	50 (0-75)
Walking Distance	**Baseline**	27 (4-89)	23 (0-100)	22 (2-100)
	6	28 (4-89)	36 (1-100)	24 (1-89)
	12	32 (7-83)	38 (1-100)*	22 (2-89)
	18	33 (7-83)	45 (1-100)*	26 (1-100)
	24	45 (7-100)**	49 (1-100)**	28 (4-100)
Walking Speed	**Baseline**	28 (0-89)	27 (0-93)	31 (3-89)
	6	37 (3-89)	39 (0-93)	38 (0-100)
	12	35 (10-72)	45 (0-93)**	32 (0-89)
	18	39 (11-89)	50 (0-100)**	39 (10-100)
	24	43 (18-100)**	46 (7-93)**	38 (0-72)
Stair Climbing Ability	**Baseline**	42 (0-100)	40 (4-100)	42 (0-100)
	6	52 (0-100)	54 (4-100)*	42 (4-100)
	12	67 (0-100)*	59 (0-100)	40 (0-100)
	18	67 (0-100)**	67 (4-100)*	42 (0-100)
	24	67 (0-100)**	71 (0-100)**	42 (0-100)

Data are presented as median (range), at each assessment stage of the intervention period. * $P < 0.05$; ** $P < 0.01$ indicates significance from baseline. † $P < 0.05$ indicates significance between the leg- or arm-training group and the control group.

3.3.2 Correlation of WIQ indices with walking performance

All WIQ indices were positively correlated with MWD prior to the intervention (Table 19). In particular, correlation coefficients for walking distance and walking speed were highly correlated with MWD. Weaker relationships existed between patients' perceived stair climbing ability and perceived pain severity due to walking.

Table 19. Relationship between walking performance (MWD) and WIQ scores for the entire patient group pre-intervention.

	MWD Correlated with WIQ Indices of			
	Pain Severity	**Walking Distance**	**Walking Speed**	**Stair Climbing Ability**
Baseline	0.37**	0.71**	0.67**	0.56**

Data are presented as the Pearson Correlation Coefficient. * $P < 0.05$; ** $P < 0.01$ indicating a positive correlation with MWD.

Similar relationships were found for walking distance and walking speed throughout the course of the intervention period, in all three study groups, again with weaker relationships for stair climbing ability and perceived pain severity, particularly in the lower-limb training group of patients (Table 20).

Table 20. Relationship between walking performance (MWD) and WIQ scores for the three study groups at each assessment stage during the intervention period.

	Intervention Period (weeks)	MWD Correlated with WIQ Indices of			
		Pain Severity	Walking Distance	Walking Speed	Stair Climbing Ability
Lower-limb Training	Baseline	0.32	0.70**	0.66**	0.50**
	6	0.27	0.62**	0.66**	0.55**
	12	0.20	0.52**	0.48**	0.48**
	18	0.21	0.60**	0.34	0.50**
	24	0.07	0.45*	0.45**	0.33
Upper-limb Training	Baseline	0.34*	0.63**	0.62**	0.52**
	6	0.28	0.68**	0.66**	0.43*
	12	0.39*	0.77**	0.72**	0.38*
	18	0.38*	0.66**	0.67**	0.54**
	24	0.57**	0.80**	0.62**	0.47**
Control Group	Baseline	0.52**	0.82**	0.75**	0.68**
	6	0.43*	0.70**	0.61**	0.57**
	12	0.44*	0.76**	0.64**	0.64**
	18	0.52**	0.73**	0.72**	0.64**
	24	0.46**	0.73**	0.62**	0.66**

Data are presented as the Pearson Correlation Coefficient. * $P < 0.05$; ** $P < 0.01$ indicating a positive correlation with MWD.

3.4 Physical activity

3.4.1 Incentive to perform physical activity

Ninety-one, and 93 % of patients in the lower- and upper-limb training groups, respectively, stated that the study had provided them with an incentive to increase their level of physical activity. Interestingly, 75% of patients in the control group also stated that the study had provided them with an incentive to exercise (Table 21).

Table 21. Patients self-assessed perception to perform physical activity.

%	Lower-limb Training	Upper-limb Training	Control Group
Incentive	91	93	75
No Incentive	9	7	25

Data are presented as the percentage value within each group

3.4.2 Self perception of physical activity status

An increase in physical activity status from baseline was observed in all three study groups upon completing the 24-week intervention period ($P < 0.01$). The physical activity status of the exercise training groups was rated higher than that of the control group following the intervention period ($P < 0.01$; Table 22).

Table 22. Patients self-assessed physical activity status.

	Physical Activity Status	
	Pre-Intervention	**Post-Intervention**
Lower-limb Training	2 (0 – 10)	10 **‡ (10 – 10)
Upper-limb Training	6 (0 – 10)	10 **‡ (8 – 10)
Control Group	6 (0 – 10)	6 (0 – 10)

Data are presented as the median (range). ** $P < 0.01$ from baseline. ‡ $P < 0.01$ between the leg or arm-training group and the control group of patients.

3.4.3 Global PAD-PAR physical activity

The observed increases in walking ability in both exercise training groups were associated with an increase in global physical activity of approximately 11 MET-h.wk^{-1} from baseline to the end of the 24-week intervention period (151 ± 8 vs. 162 ± 8 and 158 ± 7 vs. 169 ± 7 MET-h.wk^{-1} for the lower and upper-limb exercise training groups, respectively, $P < 0.01$). There was no change in global physical activity status in the control group at any time-point (Figure 10).

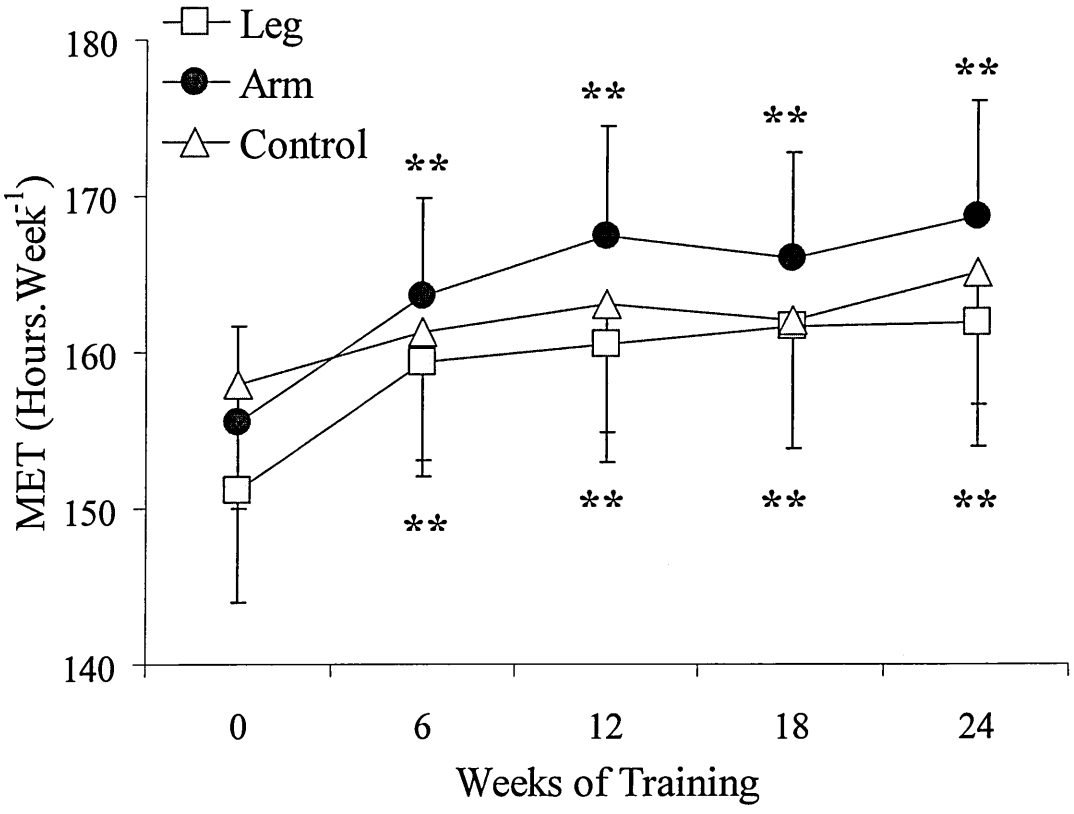


Figure10. Changes in global physical activity during the intervention period. Changes in global PAD-PAR scores. Data are presented as mean ± SEM. ** $P < 0.01$ indicates significance from baseline.

3.4.3.1 PAD-PAR work, household and leisure-time physical activity

The increases in global physical activity in the PAD-PAR in both training groups was attributed to an observed increase from baseline in the leisure-time physical activity domain of the questionnaire throughout the course of the intervention period in these patients ($P < 0.01$). This in the main was attributed to the twice weekly attendance to the supervised exercise classes. In the control patients, an increase ($P < 0.05$) in leisure time physical activity was also observed, but only for the first 12-weeks of the intervention period (Figure 11).

Despite the advancing years, some patients continued to undertake part or full-time employment (n=4, 5 and 7, for the lower-limb, upper-limb and control group, respectively). There was no difference between or within study groups in the level of work activities undertaken throughout the intervention period (Figure 11). Similarly, there was no significant difference between or within groups in the household activity domain of the PAD-PAR questionnaire throughout the study intervention period (Figure 11). This is a typical observation of elderly patients in the main, who routinely perform household chores with little change in pattern observed over time.

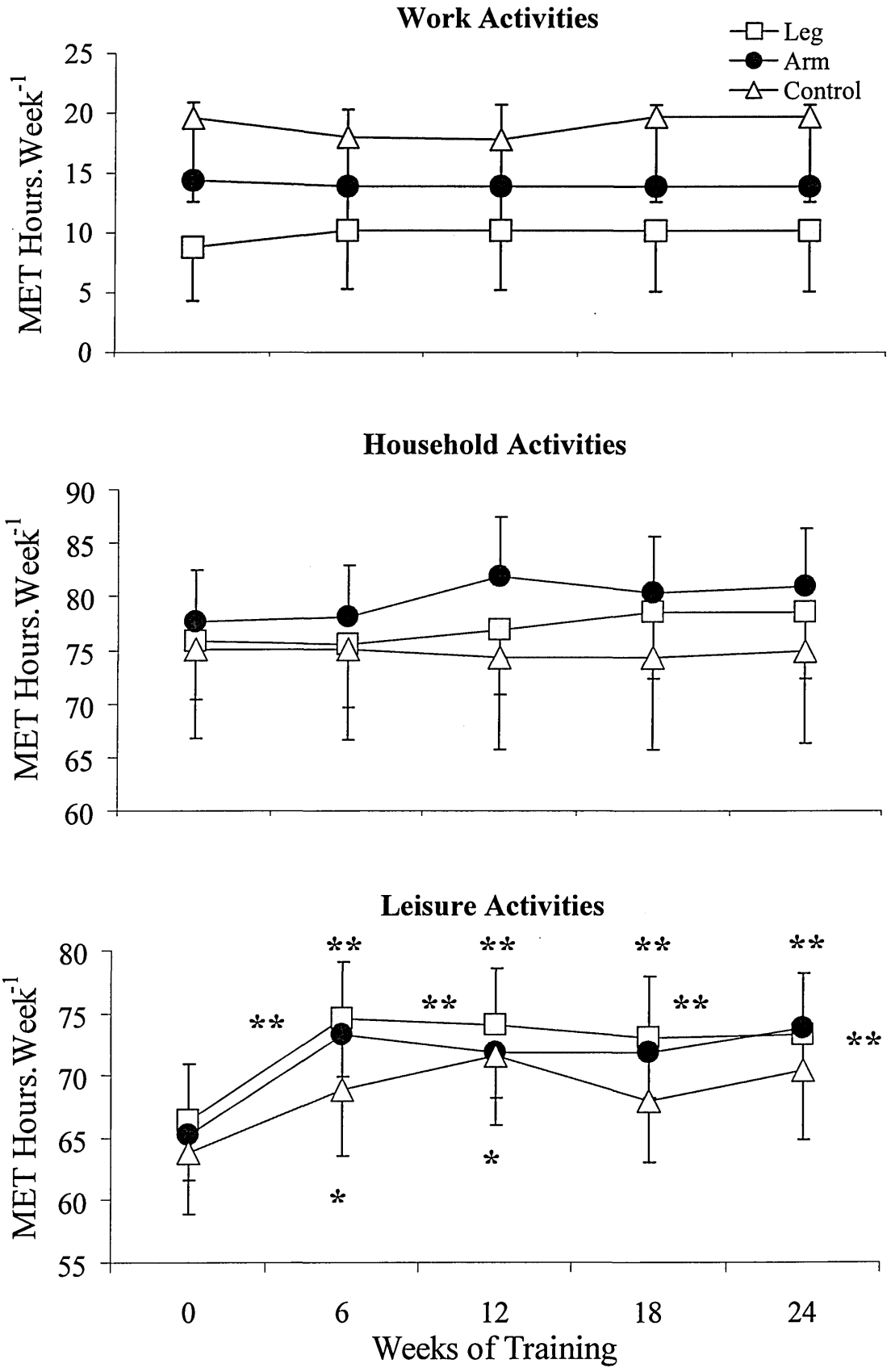


Figure 11. PAD-PAR questionnaire physical activity levels. Changes in PAD-PAR scores relating to work, household and leisure activities. Data are presented as mean ± SEM * $P < 0.05$; ** $P < 0.01$ indicate significance from baseline.

3.5 Quality of life – SF-36 *v2* questionnaire

3.5.1 The short-term influence of exercise on the dimensions of physical function

There were no differences in the pre-intervention responses of the three study groups. A significant mean improvement of 6 percentage points in the general health domain of the SF-36 *v2* following 6-weeks of exercise training was only observed in the lower-limb training group of patients compared to baseline (53.7 ± 3.4 vs. 59.7 ± 3.7; $P < 0.01$; Figure 10). No significant differences in this domain were observed between study groups. Although trends were observed, no significance differences in the bodily pain, physical functioning or role limitation physical domains were found, either within or between the study groups (Figure 12).

3.5.2 The longer-term influence of exercise on the dimensions of physical function

The general health of patients who had undertaken exercise training was significantly improved upon completing the 24-week intervention period, compared to the control group of patients (53.7 ± 3.4 vs. 57.6 ± 3.5; $P < 0.05$ and 59.5 ± 3.4 vs. 60.5 ± 3.7; $P < 0.01$, for lower- and upper-limb training, respectively). However, the improvements from baseline in these patients were not significant (Figure 12). A decline in general health over the course of the intervention period was observed in the control group of patients (49.9 ± 3.2 vs. 45.0 ± 3.5; $P < 0.05$).

In addition to the improvement in general health, an improvement in the physical functioning domain was observed in the upper-limb training group only, compared to baseline (47.5 ± 3.9 vs. 58.7 ± 3.9; $P < 0.01$), which was also improved compared to the control group of patients ($P < 0.05$; Figure 12). Bodily pain was also improved from baseline in this patient group (51.5 ± 3.7 vs. 62.8 ± 4.0; $P < 0.01$). No significant changes in the role limitation physical domain were observed either between or within study groups (Figure 12).

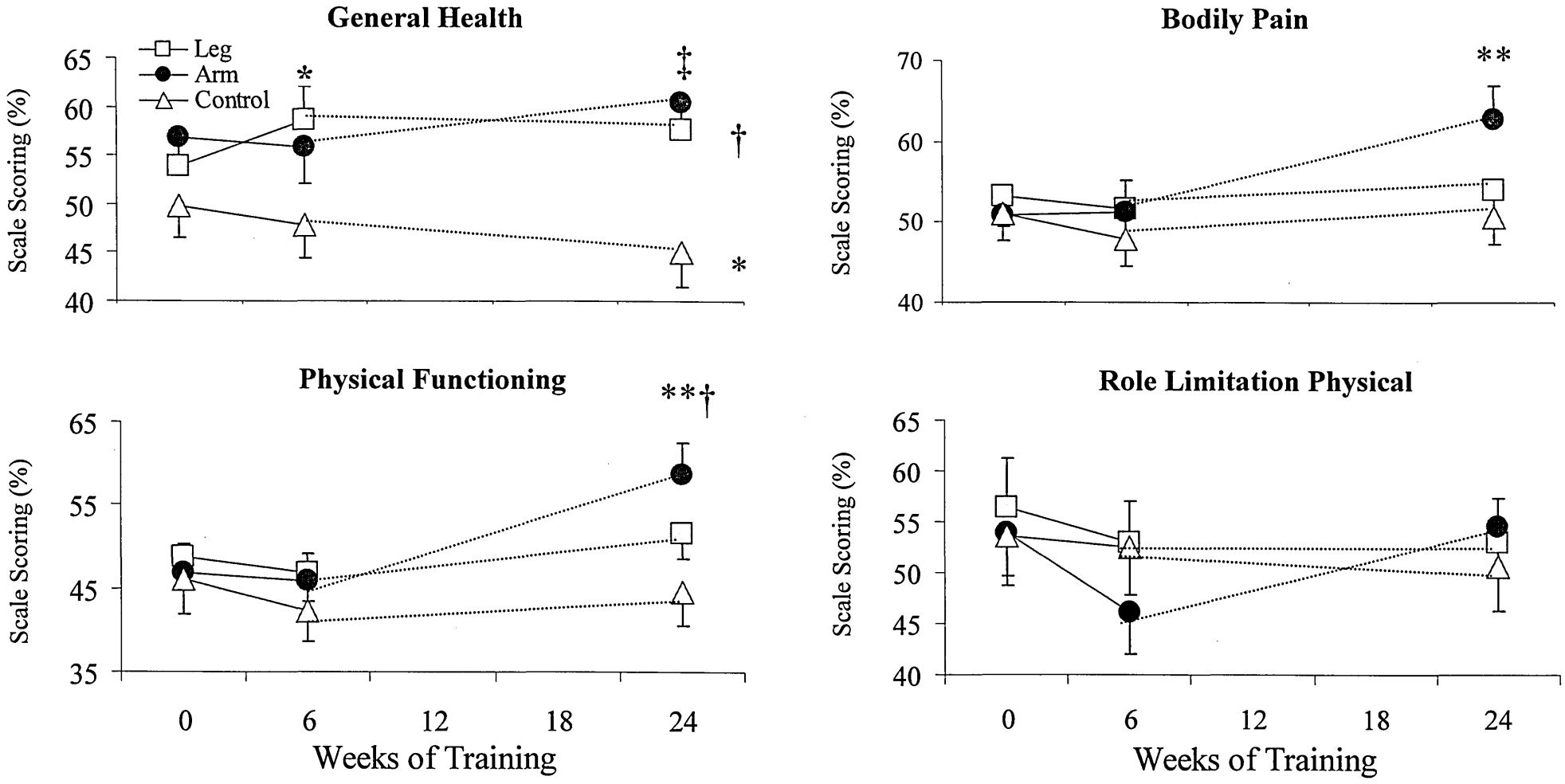


Figure 12. Changes in the Physical Function domains of the SF-36 *v2* Quality of Life Questionnaire. Data are presented as mean ± SEM, at baseline and following 6 and 24-weeks of the intervention period. * $P < 0.05$; ** $P < 0.01$ indicate significance compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ indicate significance between th leg- or arm-training group and the controls.

3.5.3 The short-term influence of exercise on the domains of mental health

The pre-intervention responses of the three study groups were not different. Although trends were observed, there were no significant differences within or between the study groups, in the mental health, energy and vitality, social functioning or role limitation emotional domains following 6-weeks of exercise training (Figure 13).

3.5.4 The longer-term influence of exercise on the domains of mental health

Deterioration in the role limitation emotional domain was observed in the control group of patients upon competing the 24-week intervention period (77.0 ± 4.2 vs. 69.0 ± 4.5; $P < 0.05$; Figure 13). In contrast, in the upper-limb training group an improvement in energy and vitality (53.5 ± 2.9 vs. 57.1 ± 3.2) was observed compared with the control group of patients ($P < 0.05$; Figure 13). However, this improvement in these patients was not significant from baseline. There were no significant changes in the mental health or social functioning domains of the SF-36 *v2*, either within or between study groups.

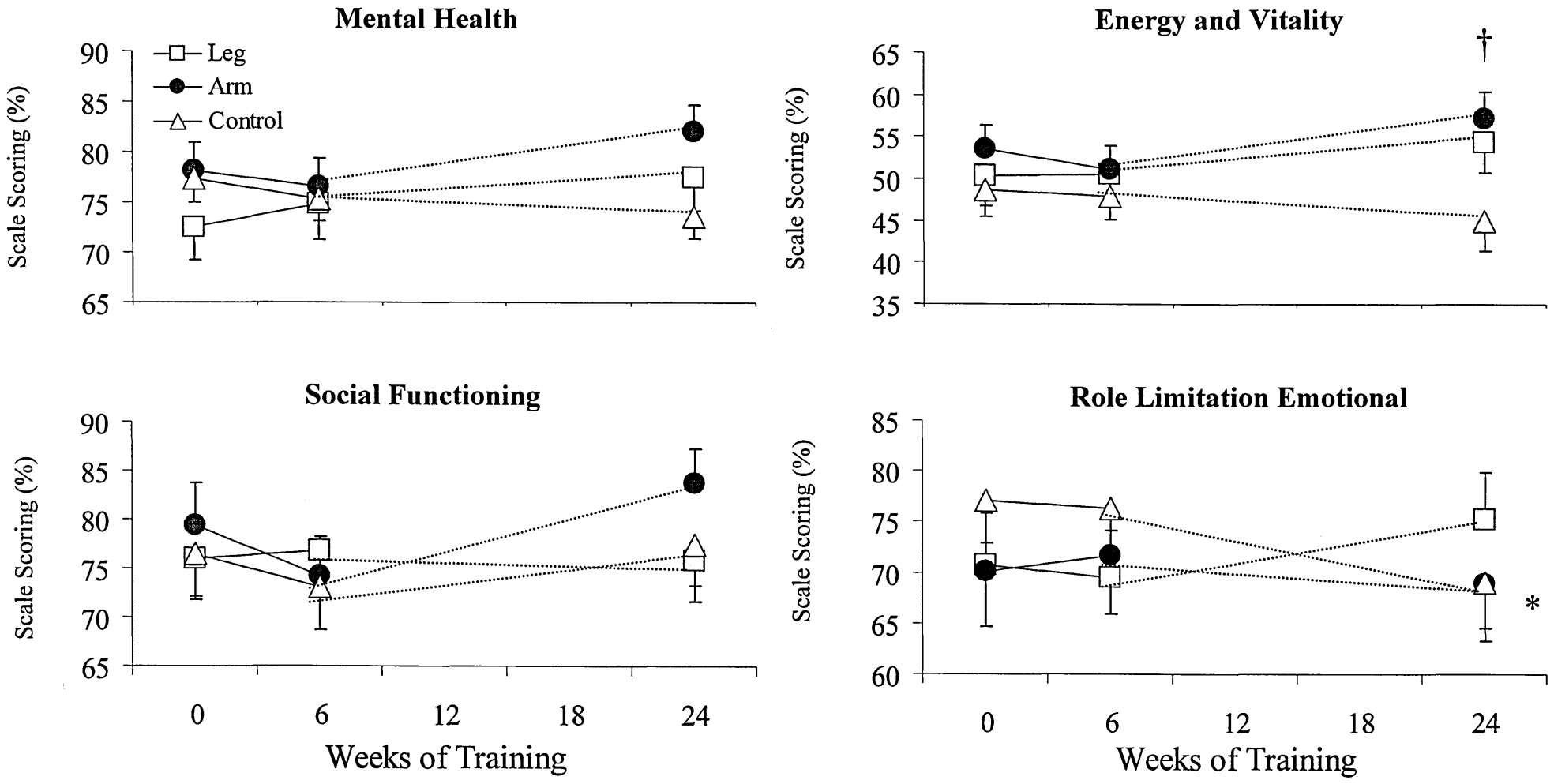


Figure 13. Changes in the Mental Health domains of the SF-36 *v2* Quality of Life Questionnaire. Data are presented as mean ± SEM at baseline and following 6- a 24-weeks of the intervention period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg or arm-training group and the controls.

3.6 General health status identified using the EuroQol (EQ-5D) questionnaire

3.6.1 The short-term influence of exercise on EuroQol questionnaire domains

General health was perceived to be better following 6-weeks of exercise training in the upper-limb training group compared to the control group ($P < 0.05$; Table 23). No changes in mobility, self care, patients' ability to perform usual activities, general bodily pain and discomfort and anxiety were observed following 6-weeks of the intervention period either between or within study groups (Table 23).

3.6.2 The longer-term influence of exercise on EuroQol questionnaire domains

General health was also improved following the 24-week intervention period in the upper-limb training group compared to the control group ($P < 0.05$; Table 23). In addition, an improvement from baseline in the degree of general bodily pain and discomfort in this patient group was observed following the intervention period ($P < 0.01$). A decline in mobility status was observed in the control group of patients ($P < 0.05$) following the 24-week study period. There were no significant differences between or within groups in perceived self care, ability to perform usual activities or anxiety status following the intervention period.

Table 23. EuroQol (EQ-5D) questionnaire domains throughout the intervention period.

	Intervention Period (weeks)	Lower-limb training	Upper-limb training	Control group
Health Status	**Baseline**	70 (40 - 95)	73 (35 - 90)	60 (40 - 95)
	6	70 (30 - 95)	70 † (45 - 90)	60 (30 - 95)
	24	70 (40 - 100)	70 † (50 - 100)	60 (30 - 90)
Mobility	**Baseline**	70 (25 - 100)	75 (30 - 100)	73 (35 - 100)
	6	62.5 (40 - 100)	75 (25 - 100)	70 (45 - 100)
	24	60 (40 - 100)	75 (25 - 100)	60* (40 - 100)
Self Care	**Baseline**	100 (50 - 100)	100 (75 - 100)	100 (30 - 100)
	6	100 (50 - 100)	100 (60 - 100)	100 (35 - 100)
	24	100 (50 - 100)	100 (70 - 100)	100 (40 - 100)
Usual Activities	**Baseline**	65 (20 - 100)	70 (25 - 95)	50 (25 - 100)
	6	62.5 (30 - 100)	67.5 (30 - 100)	60 (25 - 100)
	24	72.5 (25 - 100)	77.5 (30 - 100)	55 (35 - 90)
Bodily Pain and Discomfort	**Baseline**	65 (25 – 95)	70 (5 - 95)	65 (25 - 100)
	6	60 (25 - 85)	70 (5 – 100)	70 (20 - 90)
	24	72.5 (25 - 90)	75** (20 - 90)	73 (25 - 90)
Anxiety and Depression	**Baseline**	90 (50 - 100)	100 (30 - 100)	90 (50 - 100)
	6	85 (25 - 100)	90 (35 - 100)	90 (35 - 100)
	24	85 (40 - 100)	100 (50 - 100)	88 (50 - 100)

Data are presented as median (range), at each assessment stage of the intervention period, where 0% and 100% indicate severe difficulty and no difficulty, respectively. * $P < 0.05$; ** $P < 0.01$ indicate significance from baseline. † $P < 0.05$ indicates significance between the leg- or arm-training group and the control group of patients.

3.7 Physical function as assessed during the incremental leg and arm-cranking assessments

3.7.1 Pre-intervention cardiorespiratory performance

The pre-intervention peak $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, $\dot{V}E/\dot{V}O_2$, Bf, V_t, RPP and blood lactate responses of the three study groups were not different, for either the leg-cranking (LCT) or arm-cranking assessment (ACT).

When the entire cohort of patients (N=104) were compared, peak $\dot{V}O_2$ for the ACT was 92% of that measured for the LCT (1.01 ± 0.03 vs. 1.10 ± 0.03 $l.min^{-1}$, respectively; $P < 0.001$), representing an absolute difference of less than 0.10 $l.min^{-1}$ between upper- and lower-limb aerobic exercise capacity (Table 24). The initial maximum leg power (MLP) for the entire cohort of patients was 67 ± 2 W and maximum arm power (MAP) was 44 ± 1 W. Peak power output for the ACT was 66% of that achieved in the LCT ($P < 0.001$).

Peak values for $\dot{V}CO_2$ ($P < 0.01$), V_t ($P < 0.01$) were also lower for upper-limb exercise, but with no differences in the peak measures of RER, $\dot{V}E$, Bf, HR, SBP, RPP or RPE between the ACT and LCT were observed. Patients experienced a higher level of leg pain during the LCT than arm pain during the ACT at maximum exercise tolerance ("very strong" versus "moderate to strong"; $P < 0.01$), despite similar RPE and higher blood lactate levels during arm-cranking ($P < 0.05$; Table 24).

In a significant sub-group of patients (n=36; 35%; Table 24), peak $\dot{V}O_2$ for the ACT was equal to or exceeded that for the LCT, with mean values of 1.09 ± 0.04 and 0.95 ± 0.05 $l.min^{-1}$, respectively ($P < 0.001$). In this sub-group, peak power output for the ACT was 74% of that achieved in the LCT ($P < 0.001$). Other peak cardiorespiratory responses were also higher for the ACT in this patient sub-group, including HR ($P < 0.001$), RPP ($P < 0.01$), $\dot{V}E$ ($P < 0.001$) and Bf ($P < 0.001$). The discrepancy between arm and leg pain (7 vs. 4, respectively; $P < 0.001$) at maximum exercise tolerance was greater in this patient sub-group than in the remaining patients with higher leg aerobic exercise capacity (6 vs. 5, respectively; $P < 0.001$).

Table 24. Cardiorespiratory, metabolic and perceptual responses at maximum exercise tolerance during the ACT and LCT for all patients and for the sub-group with higher arm aerobic exercise capacity.

	All Patients (*N*=104)		Sub-group with higher arm aerobic capacity (*N*=36)	
Variable	ACT	LCT	ACT	LCT
Power Output. W	47 ± 1***	73 ± 2	50 ± 2***	68 ± 4
$\dot{V}O_2$, l.min^{-1}	1.01 ± 0.03***	1.10 ± 0.03	1.09 ± 0.04***	0.95 ± 0.05
$\dot{V}CO_2$, l.min^{-1}	0.99 ± 0.03***	1.07 ± 0.03	1.02 ± 0.04**	0.93 ± 0.05
RER, $\dot{V}CO_2/\dot{V}O_2$	0.99 ± 0.01	0.99 ± 0.01	0.96 ± 0.02	0.99 ± 0.02
$\dot{V}E$, l.min^{-1}	36.0 ± 1.1	37.5 ± 1.1	39.4 ± 1.8***	34.8 ± 1.8
Vt, l	1.26 ± 0.03***	1.36 ± 0.04	1.35 ± 0.05	1.30 ± 0.06
Bf, Br.min^{-1}	30.2 ± 0.6	29.6 ± 0.6	30.8 ± 1.1***	28.8 ± 1.0
SBP, mmHg	195 ± 3*	199 ± 3	195 ± 4	197 ± 4
DBP, mmHg	92 ± 1*	90 ± 1	89 ± 2	89 ± 2
HR, beats.min^{-1}	114 ± 2	113 ± 2	116 ± 4***	106 ± 4
RPP	22471 ± 593	22623 ± 608	22682 ± 983**	20888 ± 851
Blood lactate, mM	3.30 ± 0.11*	3.07 ± 0.10	3.48 ± 0.21***	2.83 ± 0.15
Perceived Exertion	17 (10-20)	17 (12-20)	17 (12-20)	17 (12-20)
Perceived Pain	4 (0-11) ***	7 (0-11)	4 (0-11) ***	7 (3-11)

Values are means ± SEM. Perceived exertion and perceived pain responses were not normally distributed, and are presented as medians with range in parentheses. * $P < 0.05$; ** $P < 0.01$, *** $P < 0.001$ between the ACT and LCT.

3.7.2 Physical function throughout the intervention period.

3.7.2.1 Peak power output

The improved walking performance in both exercise training groups following the intervention period was accompanied by an increase in peak power output at maximum exercise tolerance from baseline in the lower-limb training group during the LCT (67 (38 – 126) to 96 (53 – 169 W); $P < 0.01$) and in the upper-limb training group during the ACT (38 (17 – 82) to 53 (24 – 118 W); $P < 0.01$), which were also higher than those of the control group of patients ($P < 0.01$). The differences between the two training groups were not significant at any assessment time-point. When compared, the training effect was most apparent for the specific training apparatus, with some cross-

over improvement for the other exercise modality. Maximum power output during the LCT and ACT improved by 43% and 24%, and by 19% and 39% in the lower- and upper-limb training groups, respectively, indicating an improvement in peak power output for both trained and untrained skeletal muscle groups in exercising individuals (Table 25).

Table 25. Peak power output at maximum exercise tolerance during the LCT and ACT at each assessment stage of the intervention period.

	Intervention Period (weeks)	Power Output (W)	
		LCT	ACT
Lower-limb training	Baseline	67 (38 - 126)	46 † (24 - 82)
	6	82**‡ (53 - 155)	53**‡ (24 - 82)
	12	96**‡ (53 - 155)	53**‡ (24 - 82)
	18	96**‡ (53 - 155)	53**‡ (24 - 82)
	24	96**‡ (53 - 169)	57**‡ (24 - 89)
Upper-limb training	Baseline	75 (9 - 140)	38 (17 - 82)
	6	82**† (24 - 155)	53**‡ (24 - 111)
	12	82**† (38 - 155)	57**‡ (24 - 111)
	18	82**‡ (38 - 155)	57**‡ (24 - 111)
	24	89**‡ (24 - 155)	53**‡ (24 - 118)
Control group	Baseline	67 (24 - 105)	38 (17 - 60)
	6	67 (24 - 96)	38 (17 - 67)
	12	67 (24 - 96)	38 (17 - 67)
	18	53 (9 - 96)	38 (9 - 67)
	24	60 (9 - 96)	38 (9 - 67)

Data are presented as median (range), at each assessment stage of the intervention period. ** $P < 0.01$ indicates significance from baseline. † $P < 0.05$; ‡ $P < 0.01$ indicate significance between the leg- or arm-training group and the control group of patients.

3.7.2.2 Peak $\dot{V}O_2$

The observed improvement in walking performance in both training groups during the intervention period was associated with an improvement in peak $\dot{V}O_2$ at maximum exercise tolerance during both assessments. Patients assigned to exercise training showed an increase in peak $\dot{V}O_2$ of 17% and 19% during the LCT (1.12 ± 0.04 vs. 1.31 ± 0.06 and 1.12 ± 0.06 vs. 1.33 ± 0.09 $l.min^{-1}$ following lower- and upper-limb training, respectively), at the 24-week time-point in relation to baseline measures (P at least < 0.05; Figure 14) and control patients ($P < 0.01$). Peak $\dot{V}O_2$ during the ACT was greater in both training groups compared with the control group at the 6-, 12-, 18- and 24-week time-points (P at least < 0.05). However, an increase from baseline was only observed in the patients assigned to the upper-limb exercise training group (1.05 ± 0.05 vs. 1.19 ± 0.07 $l.min^{-1}$; $P < 0.05$; Figure 14).

3.7.2.3 Peak $\dot{V}CO_2$

Similarly, peak $\dot{V}CO_2$ responses were higher in both training groups following the 24-week intervention period, in both the LCT and ACT in relation to baseline measures (P at least < 0.05), and the control group ($P < 0.01$). The pattern of response resembled that of peak $\dot{V}O_2$ (Figure 15). In the LCT peak $\dot{V}CO_2$ increased by 22% and 21% (1.08 ± 0.05 vs. 1.32 ± 0.06 and 1.12 ± 0.06 vs. 1.36 ± 0.10 $l.min^{-1}$) and in the ACT by 14% and 18% (0.96 ± 0.04 vs. 1.09 ± 0.05 and 1.05 ± 0.06 vs. 1.24 ± 0.07 $l.min^{-1}$) following lower- and upper-limb training, respectively (P at least < 0.05; Figure 15).

3.7.2.4 Peak RER

There were no significant differences in peak RER within any of the study groups over the course of the intervention period. The only differences observed were between the lower- and upper-limb training groups, following 12-weeks and 24-weeks of the intervention period, respectively, compared to the control group of patients ($P < 0.05$; Figure 16).

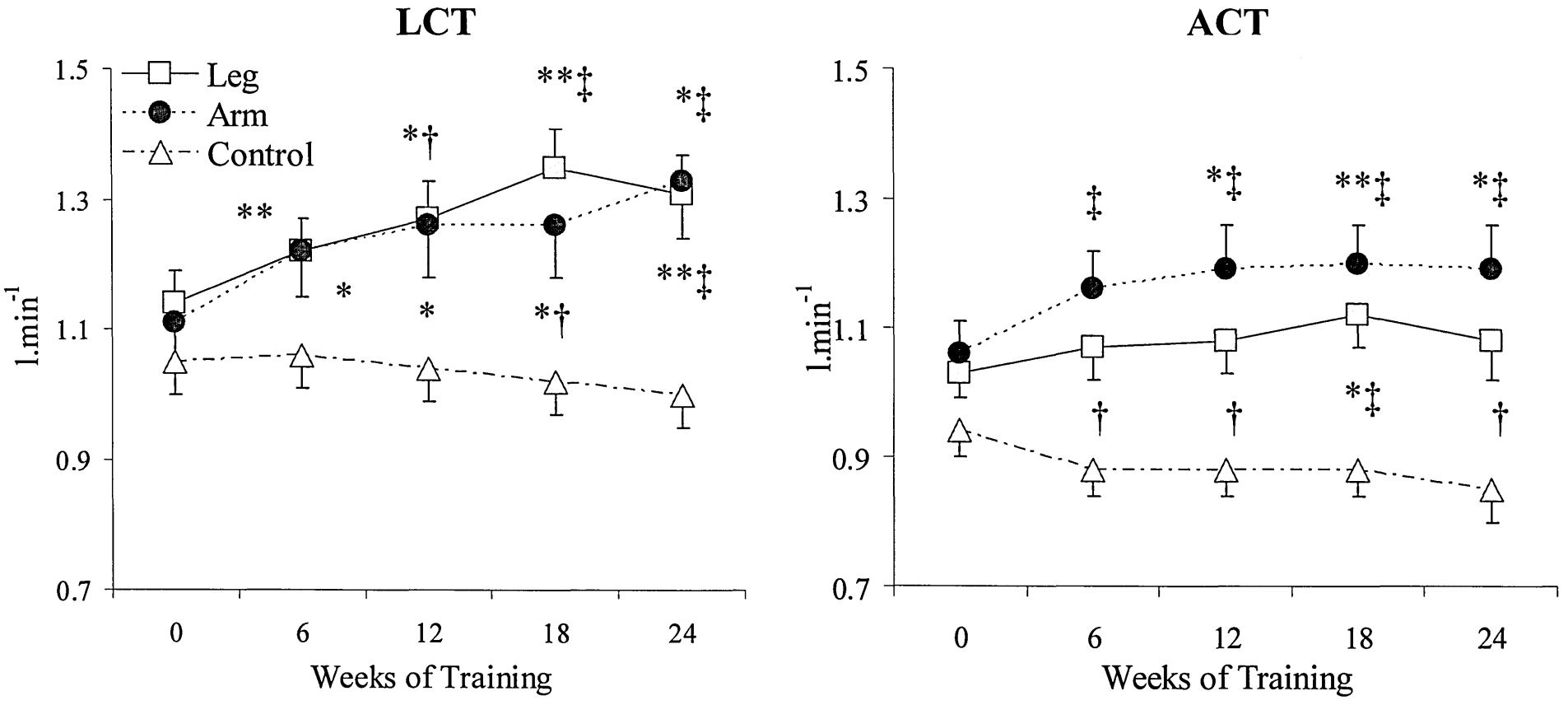


Figure 14. Changes in peak $\dot{V}O_2$ during the leg- and arm-cranking assessments during the intervention period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the intervention period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg or arm-training group and the control group of patients.

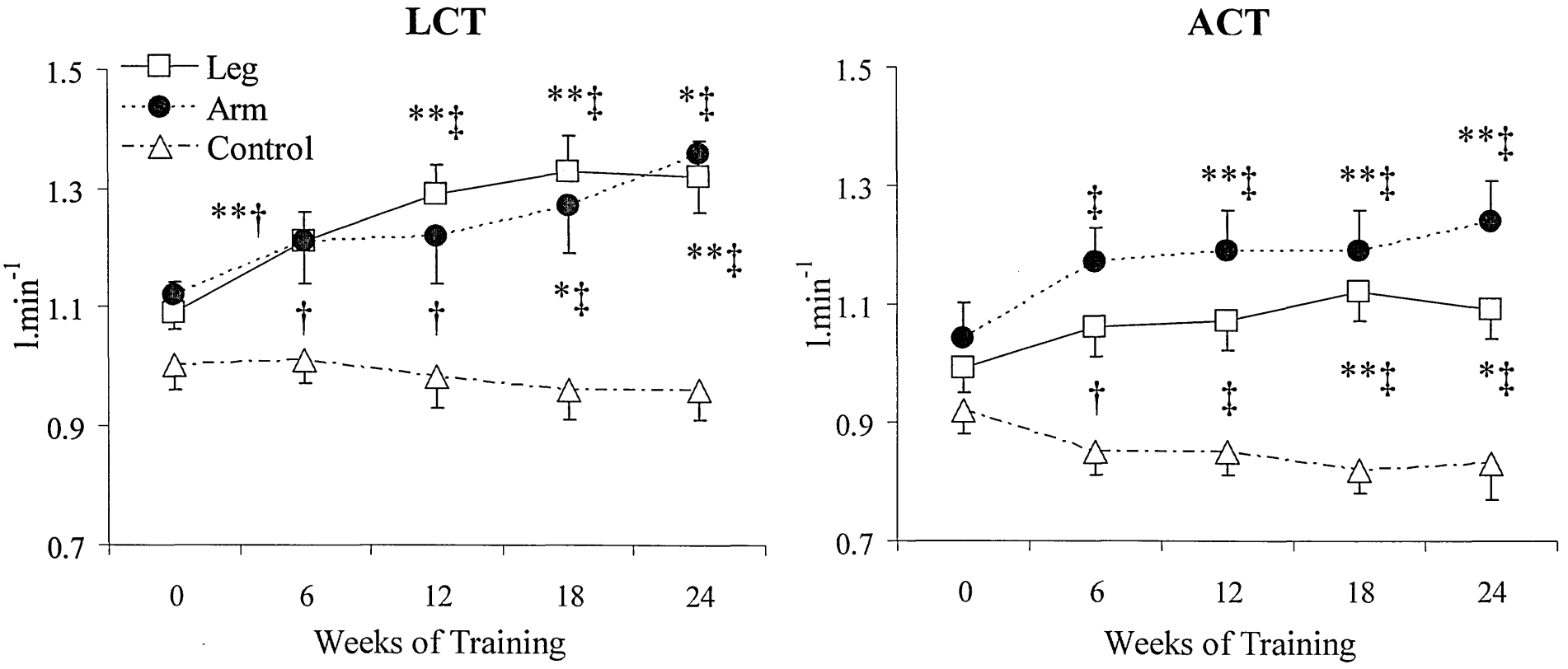


Figure 15. Changes in peak $\dot{V}CO_2$ during the leg- and arm-cranking assessments during the intervention period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the intervention period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

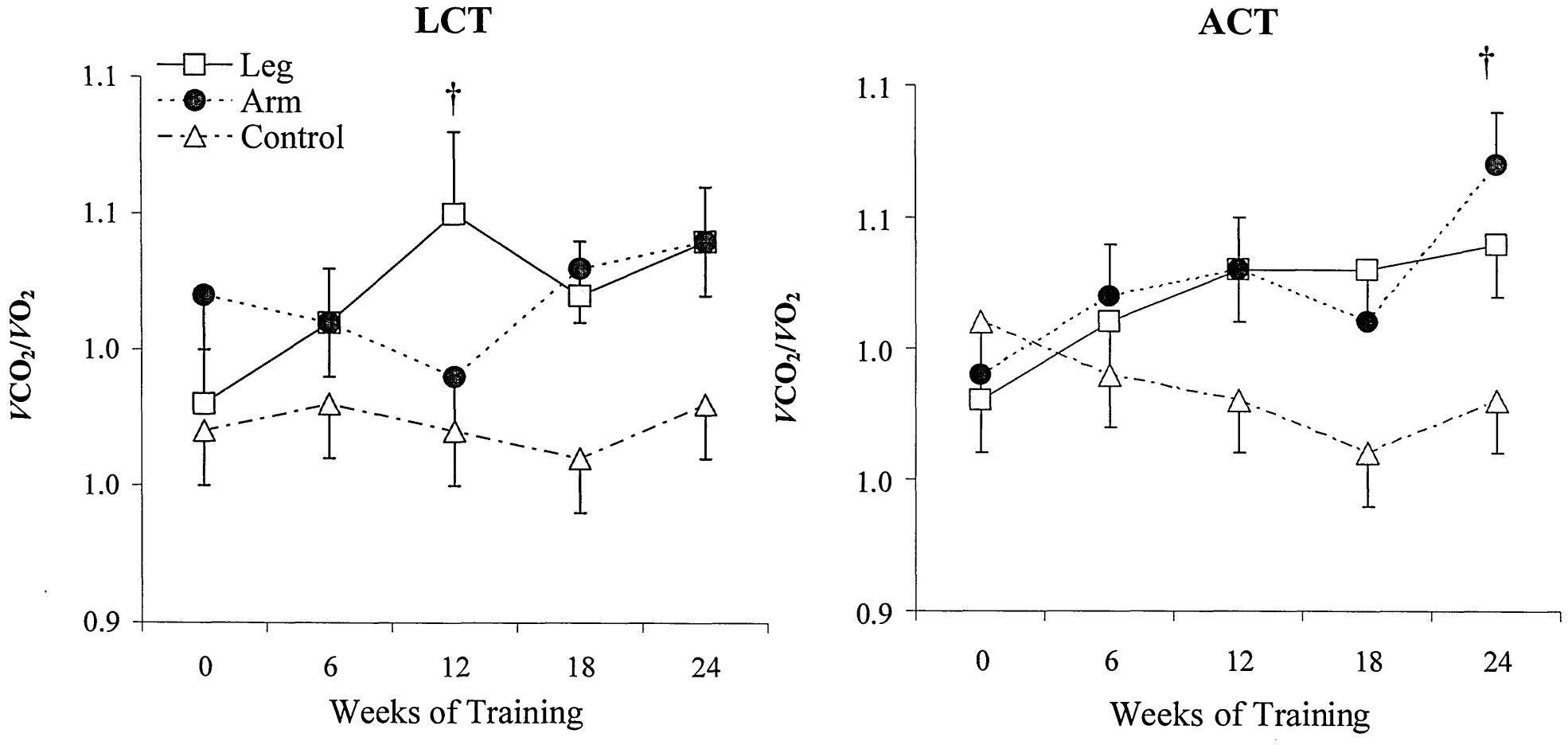


Figure 16. Changes in peak RER during the leg- and arm-cranking assessments during the intervention period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the intervention period. † $P < 0.05$ between the leg- or arm-training group and the control group of patients.

3.7.2.5 Peak $\dot{V}E$

The increases in peak $\dot{V}O_2$ were accompanied by increases in peak $\dot{V}E$ responses at maximum exercise tolerance in both training groups, at the 6-, 12-, 18- and 24-week time-points in both the LCT and ACT, in relation to baseline measures ($P < 0.01$) and the control group ($P < 0.01$). The pattern of response resembled that of peak $\dot{V}O_2$ (Figure 17). In the leg-cranking assessment, following the 24-week intervention period peak $\dot{V}E$ increased by 33% and 25% (39.0 ± 2.0 vs. 52.0 ± 2.6 and 39.5 ± 1.9 vs. 49.3 ± 2.9 $l.min^{-1}$) and in the arm-cranking assessment by 20% and 26% (37.7 ± 2.0 vs. 45.2 ± 2.7 and 37.6 ± 2.0 vs. 47.3 ± 2.7 $l.min^{-1}$) following lower- and upper-limb training, respectively ($P < 0.01$; Figure 17).

3.7.2.6 Peak $\dot{V}E/\dot{V}O_2$

Peak values for the ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) at maximum exercise tolerance were higher in both training groups in both the LCT and ACT, compared to the control group of patients (P at least < 0.05). The pattern of response at each time point resembled that of peak $\dot{V}O_2$ but with higher values attained in the lower-limb training group at each time point (Figure 18). In the leg-cranking assessment, following the 24-week intervention period peak $\dot{V}E/\dot{V}O_2$ had only significantly increased from baseline in the lower-limb training group (34.7 ± 1.3 vs. 40.6 ± 1.8; an increase of 17%). Whereas, in the arm-cranking assessment increases of 15 and 13 % (36.8 ± 1.5 vs. 42.5 ± 2.1 and 35.9 ± 1.2 vs. 40.5 ± 1.6) were observed following both lower- and upper-limb exercise training, respectively ($P < 0.01$).

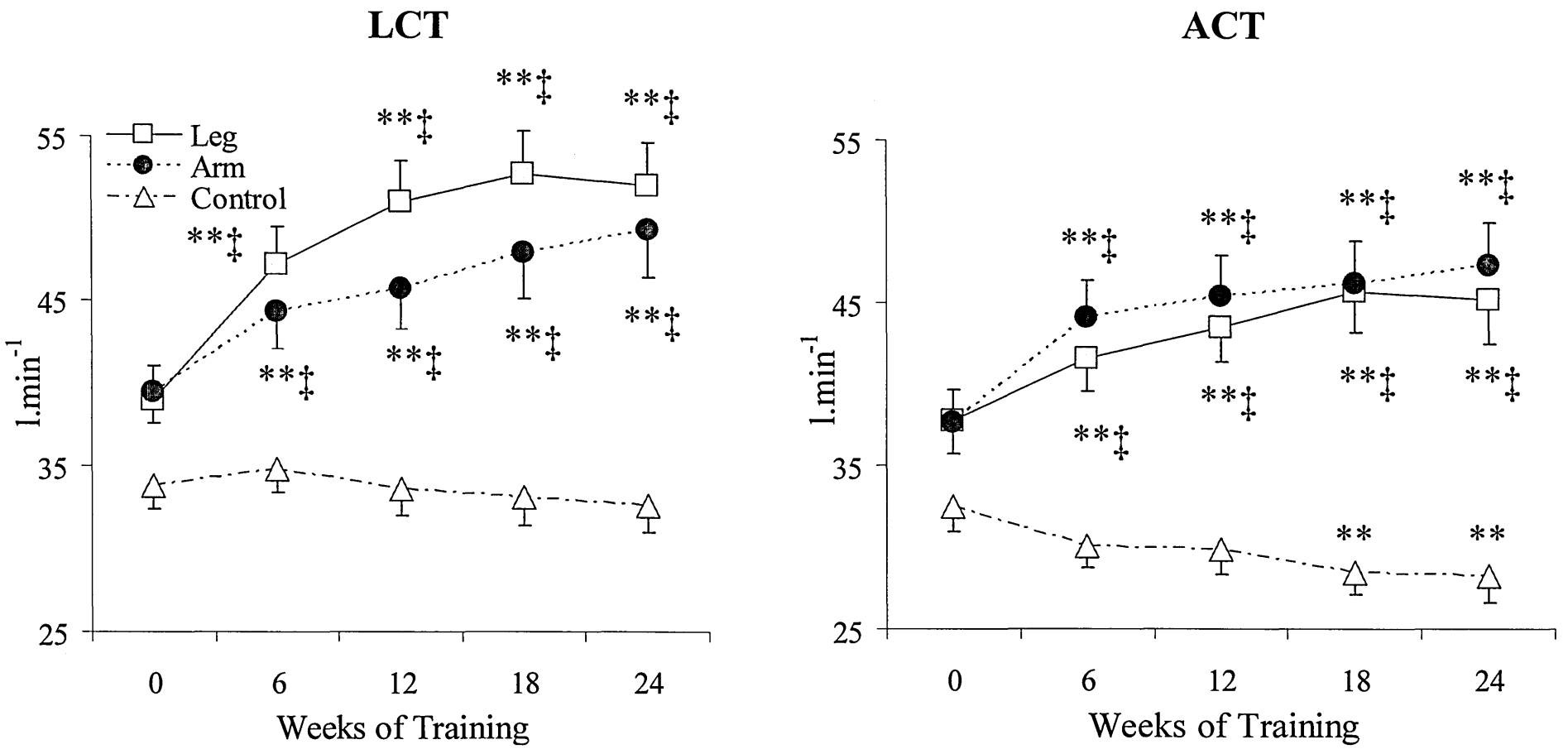


Figure 17. Changes in peak $\dot{V}E$ during the leg- and arm-cranking assessments during the intervention period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the intervention period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

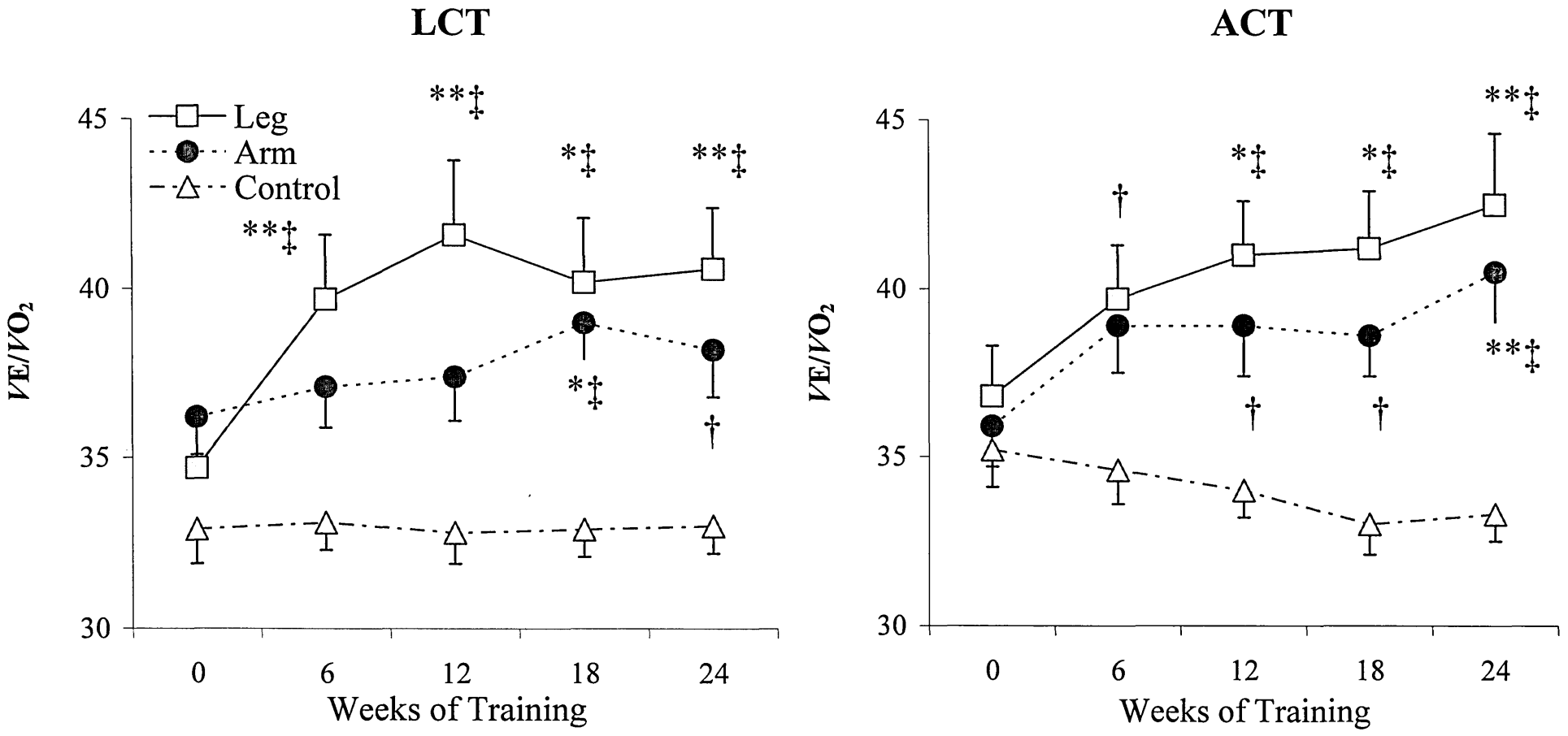


Figure 18. Changes in peak $\dot{V}E/\dot{V}O_2$ during the leg and arm cranking assessments during the intervention period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the intervention period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg or arm-training group and the control group of patients.

3.7.2.7 Peak breath frequency (Bf)

Peak Bf responses at maximum exercise tolerance were also higher in both training groups, in both the LCT and ACT, compared to the control group of patients ($P < 0.01$), the pattern of response resembling that of peak $\dot{V}O_2$. In the LCT peak Bf increased by 16% and 15% following the 24-week intervention period (29.7 ± 1.1 vs. 34.4 ± 1.2 and 30.4 ± 1.0 vs. 35.0 ± 1.2 $Br.min^{-1}$) and in the ACT by 15% and 10% (29.4 ± 1.0 vs. 33.8 ± 1.3 and 31.4 ± 0.9 vs. 34.6 ± 1.0 $Br.min^{-1}$) following lower- and upper-limb training, respectively ($P < 0.01$; Figure 19).

3.7.2.8 Peak tidal volume (Vt)

Peak Vt responses at maximum exercise tolerance were higher during both assessments following lower-limb training, but only higher during the arm-cranking assessment following upper-limb training, compared to the control group ($P < 0.01$). Significant differences from baseline values were observed in the lower-limb training group during LCT (1.41 ± 0.06 vs.1.55 ± 0.06 l) and in the upper-limb training group during the ACT (1.28 ± 0.08 vs. 1.42 ± 0.08 l; Figure 20) only.

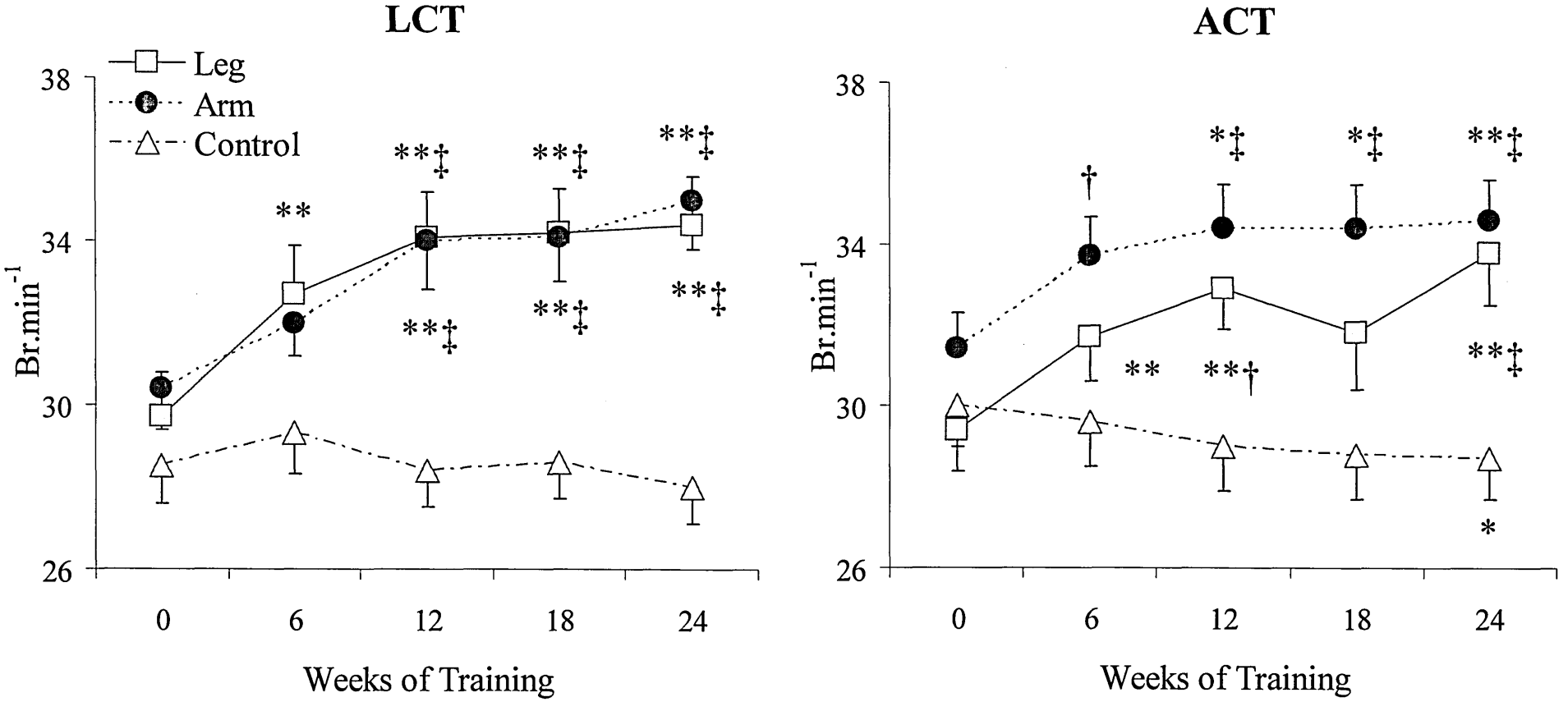


Figure 19. Changes in peak Breath Frequency during the leg- and arm-cranking assessments during the intervention period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the intervention period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

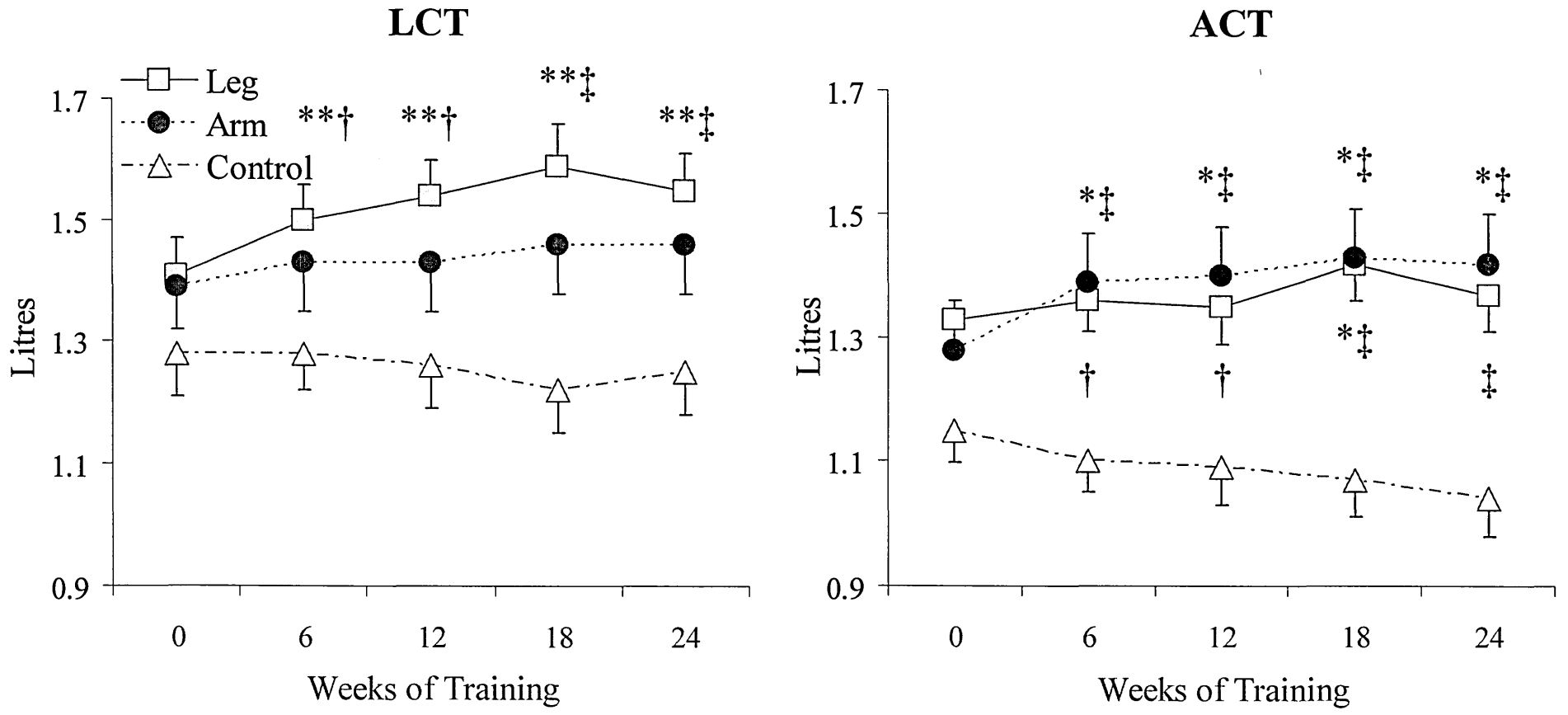


Figure 20. Changes in peak Tidal Volume during the leg- and arm-cranking assessments during the intervention period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the intervention period.. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

3.7.3 Peak cardiovascular responses throughout the intervention period

3.7.3.1 Peak systolic blood pressure (SBP)

There were no differences in SBP from baseline in any of the study groups during the course of the intervention period at any time-point, for either LCT or ACT. However, SBP was significantly greater in the upper-limb exercise training group at week 18 of the intervention period during the LCT and at week 6, 12 and 18 during the ACT, compared to the control group of patients (P at least < 0.05; Figure 21).

3.7.3.2 Peak diastolic blood pressure (DBP)

There were no differences in DBP between the study groups at any time-point during the intervention period, for either the LCT or ACT. A decrease in DBP from baseline was only observed during the ACT following 18-weeks of the intervention period in the upper-limb training group only ($P < 0.05$; Figure 22).

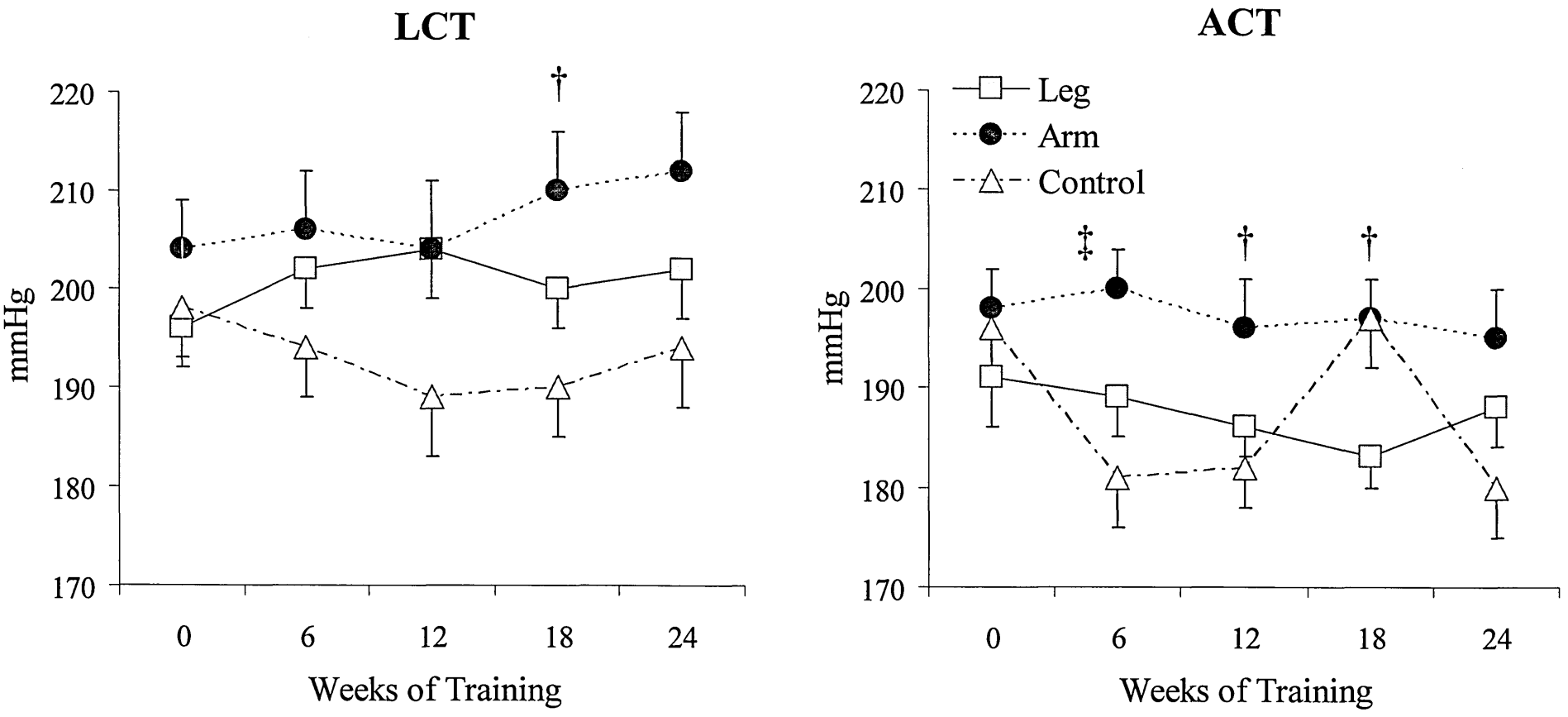


Figure 21. Changes in peak Systolic Blood Pressure during the leg- and arm-cranking assessments during the intervention. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the intervention period . * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

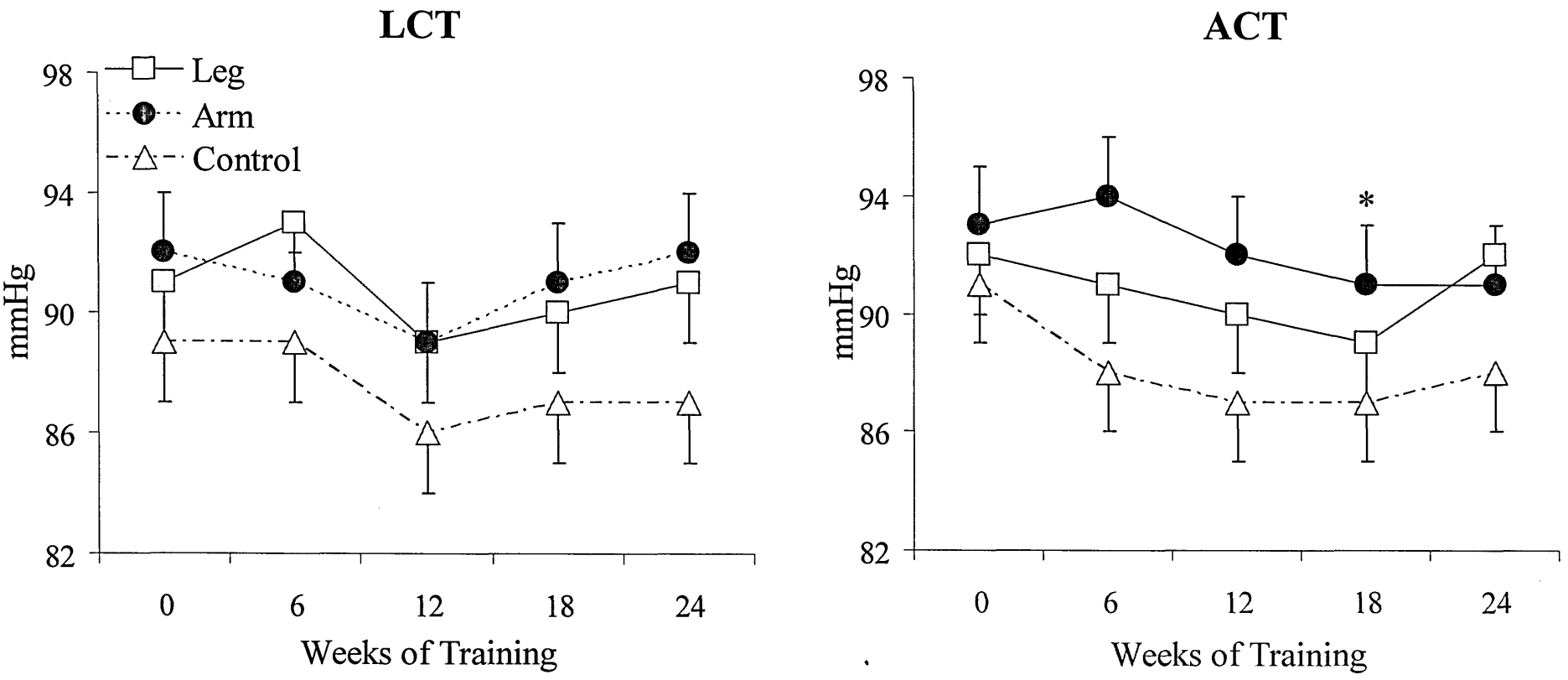


Figure 22. Changes in peak Diastolic Blood Pressure during the leg- and arm-cranking assessments during the intervention period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the intervention period * $P < 0.05$; ** $P < 0.01$ compared to baseline.

3.7.3.3 Peak heart rate (HR)

The increase in peak $\dot{V}O_2$ in the lower-limb exercise training group at maximum exercise tolerance during the LCT was accompanied by an increase in HR compared to baseline measures (113 ± 4 vs. 123 ± 4 beats.min $^{-1}$; $P < 0.01$; Figure 23). Higher HRs were observed in both training groups, in both the LCT and ACT at the 6-, 12-, 18- and 24-week time-points compared to the control group of patients (P at least < 0.01; Figure 23). A decrease in HR in the control group of patients was observed in the LCT and ACT following 12; and 18- and 24-weeks of the intervention period, respectively (P at least < 0.05). Pre-intervention peak HR responses at maximum exercise tolerance were not different between the three study groups for the LCT, but for the ACT there was a difference between the lower-limb exercise training and control group of patients ($P <$ 0.05).

3.7.3.4 Peak rate pressure product (RPP)

A similar pattern of response was observed in RPP, with values being higher in both training groups, in both the LCT and ACT compared to the control group of patients, following 6-, 12-, 18- and 24-weeks of the intervention period (P at least < 0.05; Figure 24). Similarly to HR, an increase in RPP from baseline (12 %) was only observed in the lower-limb training group during the LCT (22.3 x 10^3 ± 0.91 x 10^3 vs. 24.9 x 10^3 ± 0.97 x 10^3 beats.min^{-1}.mmHg), following the intervention period. Decreases in RPP in the control group in the LCT and ACT were observed following 12; and 12-, 18- and 24-weeks of the intervention period, respectively ($P < 0.01$).

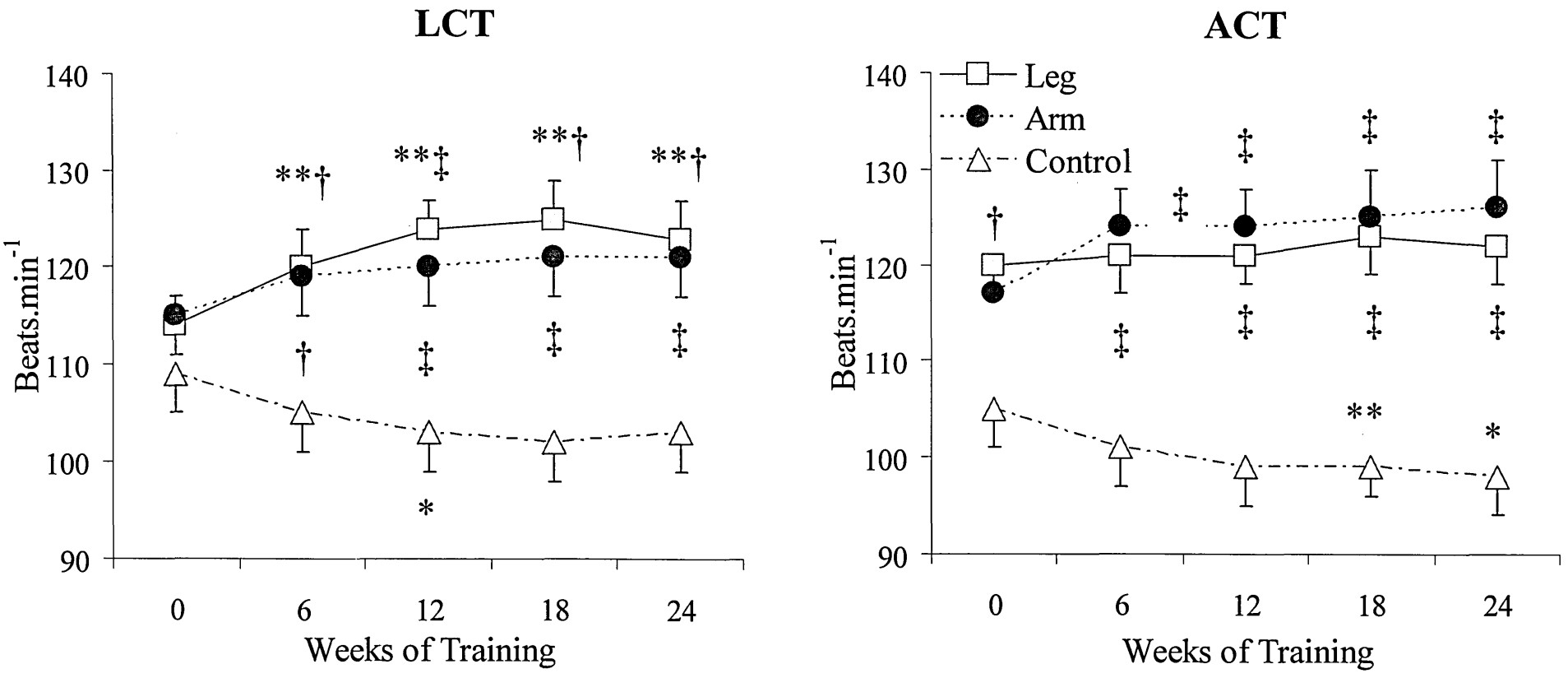


Figure 23. Changes in peak Heart Rate during the leg- and arm-cranking assessments during the intervention period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the intervention period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

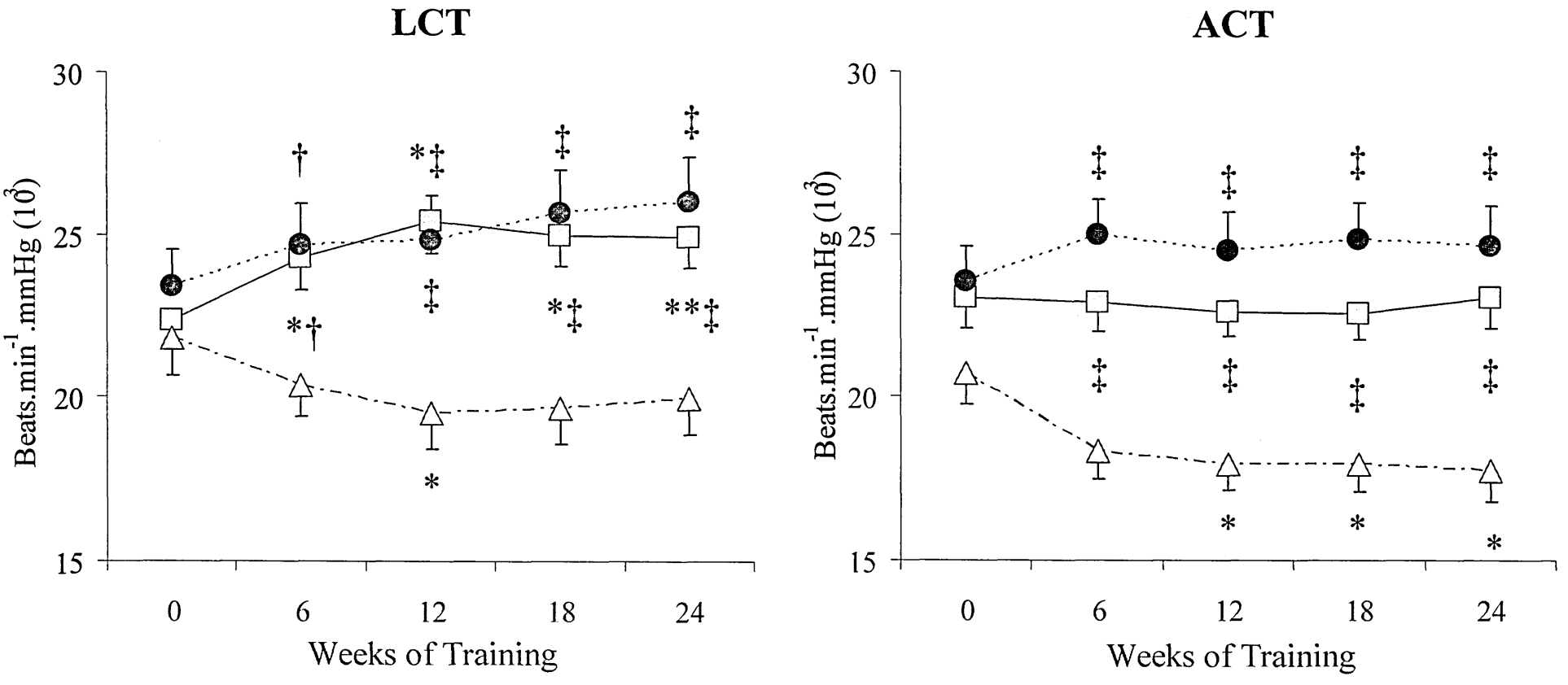


Figure 24. Changes in peak Rate Pressure Product during the leg- and arm-cranking assessments during the intervention period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the intervention period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

3.7.4 Peak blood lactate responses throughout the intervention period

Increases in peak HR were accompanied by comparable increases in peak blood lactate concentration in both training groups, in both the LCT and ACT compared to the control group of patients ($P < 0.01$; Figure 25). Peak blood lactate increased from 3.34 ± 0.16 to 4.05 ± 0.22 mM and 3.21 ± 0.18 to 3.91 ± 0.20 mM during the LCT in the lower- and upper-limb training groups, respectively ($P < 0.01$). During the ACT an increase in peak blood lactate was only observed in the upper-limb training group of patients (3.33 ± 0.21 to 4.42 ± 0.24 mM; $P < 0.01$). A significant decrease in peak blood lactate was observed in the control group of patients following 18-weeks of the intervention period ($P < 0.05$).

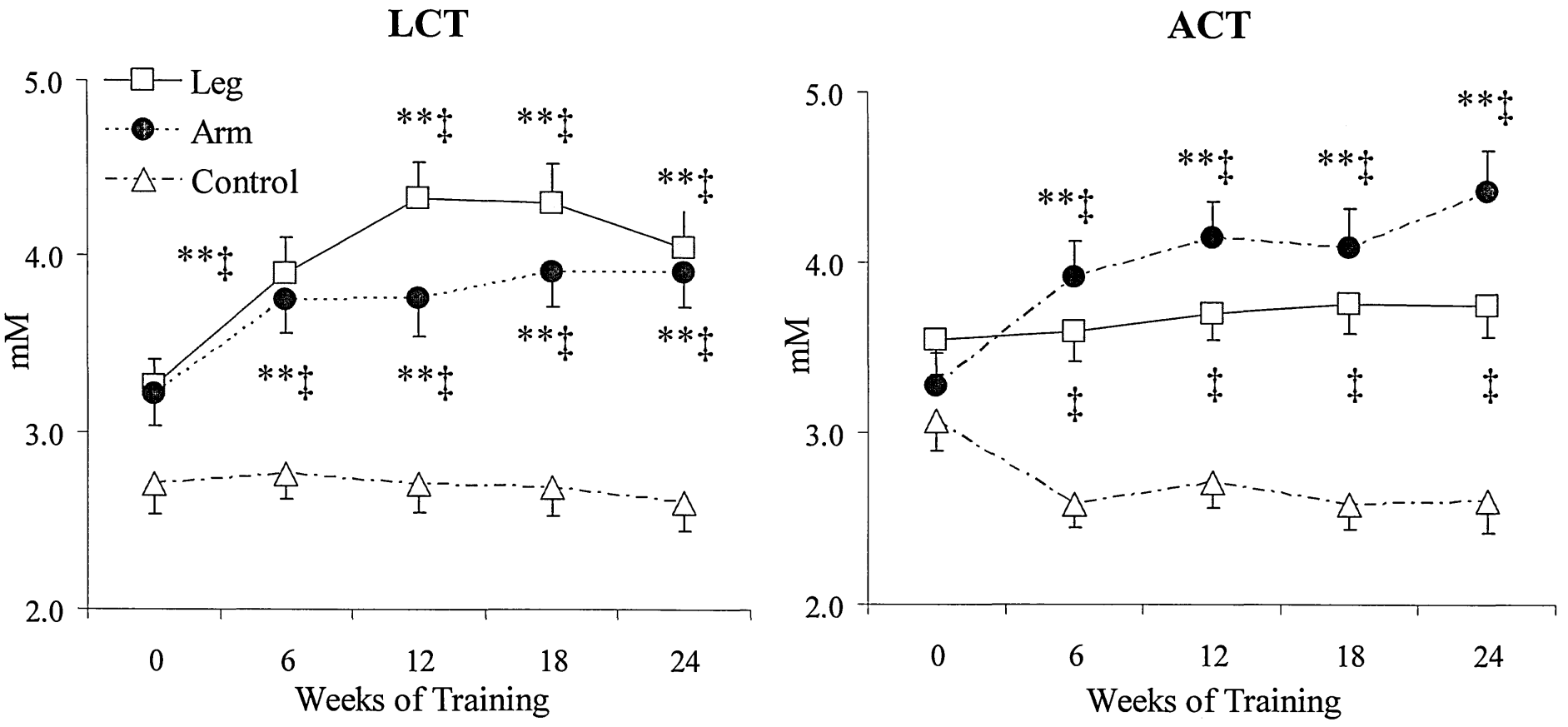


Figure 25. Changes in peak Blood Lactate during the leg- and arm-cranking assessments during the intervention period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the intervention period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

3.7.5 Peak Psycho-Physiological responses throughout the intervention period

Peak RPE responses for the ACT and LCT did not increase throughout the 24-week intervention period in any of the groups (Table 26). Similarly, there was no difference in peak pain perception during the LCT. However, peak perceived pain did increase in the upper-limb training group at the 6-, 12-, 18- and 24-week time-points (P at least < 0.05).

Table 26. Changes in perceived exertion and perceived pain at each assessment stage of the intervention period.

	Weeks of Training	Leg-Cranking Assessment			Arm-Cranking Assessment		
		LCT	ACT	Control	LCT	ACT	Control
Peak Exertion (RPE Scale)	Baseline	18 (13-20)	17 (12-20)	17 (13-20)	17 (13-20)	16 (10-20)	17 (13-20)
	6	17 (13-20)	15** (9-20)	17 (12-20)	17 (13-20)	16 (8-20)	17 (7-20)
	12	17 (13-20)	16 (10-20)	17 (10-20)	17 (13-19)	15 (13-20)	18 (12-20)
	18	17 (12-20)	15 (9-20)	16 (13-20)	17 (13-20)	16 (11-20)	17 (11-20)
	24	17 (12-20)	17 (7-20)	15 (12-20)	17 (10-19)	17 (8-20)	17 (11-20)
Peak Pain (CR-10 Scale)	Baseline	8 (0-11)	6 (3-11)	6 (0-11)	5 (0-10)	3† (0-10)	5 (0-11)
	6	7 (3-10)	5 (2-11)	8 (2.5-11)	7 Ψ (0-10)	4* (0-10)	6 (0-11)
	12	7 (0-10)	7 (1-11)	8 (2.5-11)	6 Ψ (0-11)	4*† (0-11)	7 (0-11)
	18	7 (0-11)	6 (2-11)	7 (3-10)	7 Ψ (0-11)	5** (0-11)	7 (0-10)
	24	8 (3-10)	7 (3-11)	7 (3-10)	7 (2-11)	5** (0-11)	7 (0-10)

Data are presented as the median (ranges). * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients. Ψ $P < 0.05$ between the leg- and arm-training group.

3.7.6 Changes in Haematocrit

Haematocrit was measured in 65 patients (N=23, 21 and 21 patients, from the leg-training, arm-training and control groups, respectively). No changes in haematocrit were

observed either between or within groups, at any time-point throughout the intervention period (Figure 26).

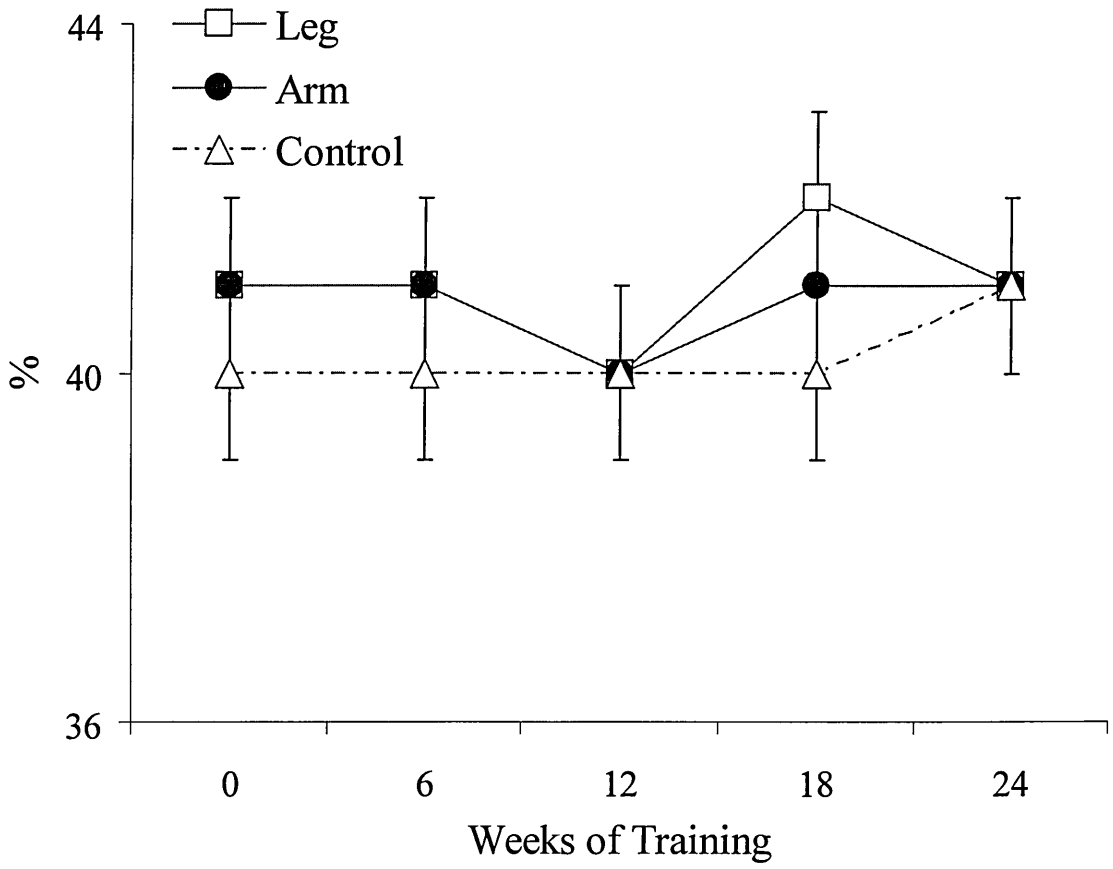


Figure 26. Changes in haematocrit during the intervention period. Data are presented as mean ± SEM at each assessment stage during the intervention period.

3.7.7 Changes in BMI

No changes in BMI within any of the study groups were observed at any time- point during the intervention period (Figure 27). However, differences between the lower- and upper-limb training groups were observed following 18- (26.6 ± 0.6 vs.26.1 ± 0.6 and 28.6 ± 0.7 vs. 29.2 ± 0.8) and 24-weeks of the intervention period (26.6 ± 0.6 vs. 26.1 ± 0.6 and 28.6 ± 0.7 vs. 29.3 ± 0.8), respectively ($P < 0.05$).

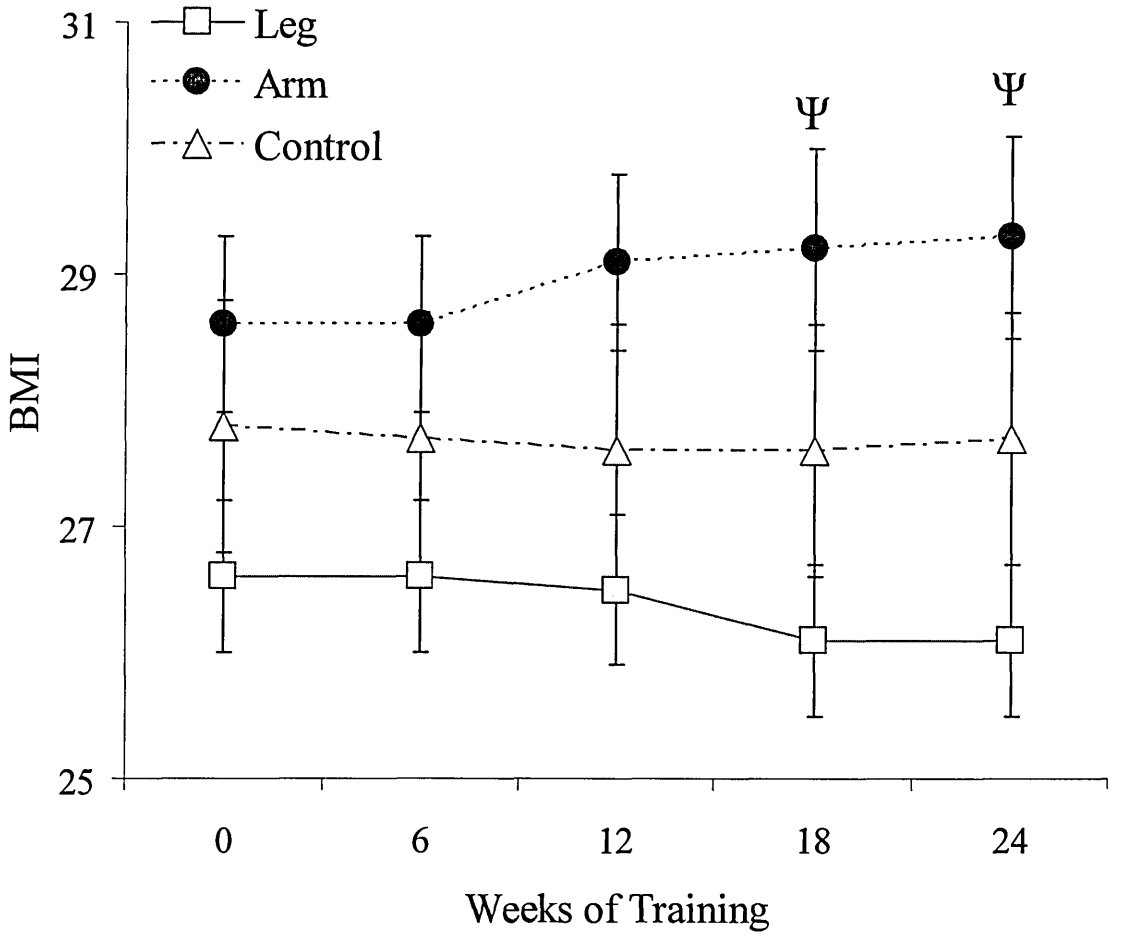


Figure 27. Changes in BMI during the intervention period. Data are presented as mean ± SEM at each assessment stage during the intervention period. $\Psi < 0.05$ between the lower- and upper-limb training groups of patients.

Chapter 4 – Intervention Study Discussion

Overview

Most randomised controlled studies are limited by their small size and have not assessed mechanisms for improved claudication distances (Gardner *et al.* 2001). The primary aims of this study were to determine the relative efficacies of a 24-week programme of twice weekly upper- and lower-limb aerobic exercise training on CD and MWD in a large cohort of patients with stable intermittent claudication, and to investigate the mechanisms which could influence symptomatic improvement. The influence of changes in walking performance and physical activity status on patients' quality of life, perceived walking impairment, pain tolerance and confidence in walking were also investigated.

This study indicates that upper- and lower-limb aerobic exercise training can induce a similar significant time-course of improvement in walking performance in patients with intermittent claudication, and that this improvement was associated with an improved confidence in walking. Improvements in MWD in both exercise training groups were accompanied by progressive increases in peak HR at MWD and a decrease in post shuttle-walk ABPI compared to baseline measures. The increase in peak HR suggests that either a greater exercise stimulus was required to elicit a claudication response or that patients were able to push themselves further beyond the 'pain barrier' after exercise training.

In the upper-limb training group, peak blood lactate concentration and perceived pain were higher at MWD compared to baseline measures, suggesting that an alteration in exercise pain tolerance accounted for more of the change in MWD than it did in the lower-limb exercise training group. In both exercise training groups, HR at CD remained unchanged, however perceived pain at CD was lower at the end of the intervention period in patients performing lower-limb exercise, possibly indicating an enhanced pain perception response in this group. Ninety-one and 93% of patients in the lower- and upper-limb training groups, respectively, stated that the study had provided them with an incentive to perform physical activity.

Community based walking ability was assessed using the WIQ, a disease-specific quality of life questionnaire for patients with symptomatic PAD (Regensteiner *et al.* 1990; Hiatt *et al.* 1995a). Both modes of exercise training induced increases in the walking distance, walking speed and stair climbing ability domains of the WIQ, and patients in the upper-limb training group also perceived an improvement in the claudication pain severity dimension of the WIQ. In accordance with the observation that walking ability was unchanged in the control group of patients over the course of the 24-week intervention period, WIQ responses were also unchanged in all domains from baseline measures in this group.

A short-period of exercise training (6-weeks) improved the general health status of patients in the lower-limb training group only, in relation to baseline measures, as assessed using the SF-36 *v2* questionnaire. Whereas 24-weeks of exercise training improved the general health status in both exercise training groups, in relation to the control group of patients. Physical function, bodily pain and energy and vitality were also improved in the upper-limb training group, whereas general health and role limitation emotional status had deteriorated in the control group following the 24-week intervention period. Upon comparing quality of life, as assessed using the EQ-5D questionnaire, general health status was perceived to be improved after 6- and 24-weeks in the upper-limb training group only. In addition, bodily pain was improved in the upper-limb training group, whereas mobility status had deteriorated in the control group following the 24-week intervention period. Differences in questionnaire design could account for the observed differences in response to the SF-36 *v2* and EQ-5D questionnaires.

In order to further understand the effects of the two training regimens on upper- and lower-limb exercise tolerance, the physiological responses to incremental arm- and leg-cranking exercise were also studied. In both exercise training groups, improvements in lower-limb peak aerobic power, peak $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, breath frequency and blood lactate concentration during the LCT accompanied the observed improvements in walking performance. The improvement of lower-limb peak $\dot{V}O_2$ in patients undertaking upper-limb exercise training was particularly interesting, indicating that upper-limb exercise can improve lower-limb function in patients with PAD. No changes in peak systolic or diastolic blood pressure, perceived exertion or perceived pain responses were observed in either group. Peak HR, RPP and $\dot{V}E/\dot{V}O_2$ during the LCT

were higher in the lower-limb training group in relation to baseline measures, and higher in both training groups in relation to control patients. Similarly, peak tidal volume was only increased in the lower-limb training group of patients.

At maximum exercise tolerance during the ACT, peak power output, $\dot{V}O_2$, tidal volume and blood lactate were higher in the upper-limb training group of patients in relation to baseline measures, but higher values were observed in both training groups in relation to the control patients. Other peak respiratory values ($\dot{V}E$, $\dot{V}E/\dot{V}O_2$, $\dot{V}CO_2$ and breath frequency) were higher in both exercise training groups at the end of the intervention period in relation to baseline measures. However, no changes in peak systolic or diastolic blood pressure, HR, RPP or perceived exertion responses were observed in either group. An increase in perceived pain was only observed in the upper-limb training group.

Outcome Measures – Walking Performance

The primary outcome measure in this study was walking performance. In patients with PAD, changes in exercise performance using the graded treadmill test have been shown to correlate with improved outpatient ambulatory function (Hiatt *et al.* 1990; Regensteiner *et al.* 1993a). This association is important because it allows even small-percentage improvements in treadmill performance to be interpreted as being clinically relevant (Hiatt *et al.* 1995b). In the lower- and upper-limb training groups following the 24-week intervention period, CD increased by 65% and 56% and MWD by 35% and 30% respectively, based on mean individual percentage difference of actual walking distances. Typically, a 25% to 50% increase in treadmill performance is considered to be of clinical significance (Hiatt, 1999). The apparent clinical relevance of these changes were confirmed as the majority of patients in the exercise training groups perceived that their day-to-day walking ability had also improved as a direct result of the 24-week intervention period.

Previous reports have suggested that patients with disease confined to the superficial femoral/popliteal arteries benefit most from exercise training (Binnie *et al.* 1999). In two-thirds of the patients in this present study, claudication was due to superficial femoral artery disease as determined by angiogram, duplex scanning or examination of pulses. The remainder of patients had tibial vessel disease. These proportions were fairly well balanced across the three study groups. Further suggestions have also

inferred that patients with an initial MWD of > 100m and those enrolled in a programme as a primary treatment rather than after failed intervention, also show a trend towards greater benefit (Binnie *et al.* 1999). Again, all patients in all three study groups had an initial MWD of > 100m.

The increase in CD and MWD reported in this study were lower than some reported in the literature following randomised controlled walking exercise interventions, which were in the range of 28-134% and 51-210% for CD and MWD, respectively (Robeer *et al.* 1998; Gardner *et al.* 2001; Brandsma *et al.* 1998). In these studies most patients gained an improvement in walking ability during the last 2 months of a 6-month walking program (Andriessen *et al.* 1989). Although the exercise stimulus in weight-bearing walking exercise programmes might be greater than in weight-supported upper- and lower-limb exercise, the use of constant-pace treadmill testing to assess walking performance in previous studies (Gardner and Poehlman, 1995) may have also had some bearing on the magnitudes of improvement previously reported.

Constant-load protocols have several potential limitations, in that a single workload may not be appropriate for a heterogeneous population of patients with different walking abilities (Regensteiner and Hiatt, 1995). If the workload remains constant at a low level, some patients may be claudication-limited on entry to a programme, but never reach a maximal level of claudication pain after an intervention from which they experience a large improvement (Regensteiner and Hiatt, 1995). For a graded test, the coefficient of variation of MWD is 12-13% compared with 30-45% for a constant-load protocol (Clyne *et al.* 1979; Gardner *et al.* 1991; Gardner *et al.* 1992b; Hiatt *et al.* 1988). In addition, constant-pace walking tests are considered less effective when compared to incremental assessments, as control patients who have multiple tests at the same constant workload can experience an increase in MWD (Porter *et al.* 1982; Clyne *et al.* 1979).

The mechanism underlying this observation is unknown, but may represent a "learning effect" as patients repeat the test, a classic placebo effect, or it may be due to improved walking biomechanics as patients become familiar with the treadmill apparatus (Hiatt *et al.* 1995b). In control patients the magnitude of improvement in walking distance from repetitive testing is typically 36% and 25% for CD and MWD respectively (Porter *et al.* 1982), but might be as great as 100% for MWD over a two week period (Skinner J.S.

and Strandness, 1967). In contrast, sequential testing of control patients with graded treadmill tests is not associated with temporal improvement in the initial or absolute CD's or times (Hiatt *et al.* 1988; Gardner *et al.* 1991).

In this study an incremental shuttle-walk test was used, which has good test-retest reproducibility (Zwierska *et al.* 2004). This test might better reflect changes in everyday walking ability compared to incline treadmill assessments (Zwierska *et al.* 2004) which have been criticised for not reflecting the influence of claudication on everyday functional activities (Montgomery and Gardner, 1998). Nor do they measure the true functional capacity of patients walking on level ground (Coughlin *et al.* 2001). Repetitive testing over a short time period can produce confounding problems, in that multiple testing may induce an improved walking performance or placebo response (Regensteiner and Hiatt, 1995). Such placebo responses on tests of physiological function are usually due to a learning or order effect which result from increased familiarity with the testing procedures. In this study, control patients were only required to attend the Centre on a 6-weekly basis, and the order of assessments (LCT, ACT and walking assessment) were performed on a random basis during each visit.

A review of previous exercise intervention studies in this area (Hiatt *et al.* 1995b) have reported placebo responses of 25-36% when patients were assessed using constant-pace tests, whereas no placebo response was observed where incremental testing had been used. In this study, all patients were fully accustomed with the testing procedures before undertaking the first walking assessment and our previous research (Zwierska *et al.* 2004) showed that responses on this test are stable over time. The shuttle-walk test is incremental (graded) and may yield less variability of response than has previously been observed for constant-pace assessments.

Interestingly, although no placebo response was observed in the control patients in this study, a psychological perception of improved walking performance was observed, as almost half of the control patients perceived a noticeable improvement in their walking ability when asked at the end of the intervention period. This perception can only be attributed to the fact that these patients were receiving emotional support through weekly telephone contact, during which their level of self-reported physical activity was monitored via the PAD-PAR questionnaire. These patients appreciated someone taking

an active interest in their walking ability and as a consequence believed their walking impairment was improving.

Mechanisms Underpinning Improved Walking Performance

Claudication occurs in muscles distal to arterial lesions at times when the metabolic demand of the active musculature exceeds the capacity of the peripheral circulation to deliver oxygen (Gardner *et al.* 2001). A better match between energy utilisation and energy delivery in the active leg musculature would delay the development of claudication pain and, as a consequence, increase the distance walked before intolerable pain ensued (Gardner *et al.* 2001). The mismatch between metabolic demand and the capacity of the peripheral circulation to deliver oxygen can be ameliorated either by decreasing metabolic demand, increasing oxygen delivery, or both (Gardner *et al.* 2001).

It is believed that an improved effect in walking performance is not based on one mechanism alone, but is induced by a combination of factors and mechanisms (Remijnse-Tamerius *et al.* 1999). Of the proposed mechanisms that could be involved in this beneficial effect, the most important include an adaptation or redistribution of the peripheral blood flow within the ischaemic tissues (collateral development), inhibition of the progression of the atherosclerotic disease (Remijnse-Tamerius *et al.* 1999), central cardiovascular adaptations (Walker *et al.* 2000; Hiatt *et al.* 1990; Brendle *et al.* 2001) and increases in muscle enzyme activity (Nehler and Hiatt, 1999b). It has been postulated that training enhances oxidative skeletal muscle metabolism in patients with PAD (Hiatt *et al.* 1996; Hiatt *et al.* 1992).

A decrease in blood viscosity has also been associated with increases in walking distance in these patients (Remijnse-Tamerius *et al.* 1999). Enzymatic changes including increases in the activity of cytochrome oxidase, citrate synthetase and 3-hydroxyacyl-CoA dehydrogenase, in conjunction with altered blood rheology (Whyman and Ruckley, 1998) have also been proposed. Furthermore, exercise-induced inflammation is ameliorated, cardiorespiratory function is improved and the oxygen cost of exercise decreases following exercise training (Tan *et al.* 2000b). It has been suggested that there are many interactions between the factors described above and most factors are not yet fully understood (Remijnse-Tamerius *et al.* 1999).

There is no agreement on the results of studies on the effect of training on calf blood flow in patients with PAD (Alpert *et al.* 1969; Johnson *et al.* 1989; Hiatt *et al.* 1990). Some studies have reported an increases in leg blood flow after programmes of walking exercise rehabilitation (Alpert *et al.* 1969; Hiatt *et al.* 1990; Gardner *et al.* 2000; Brendle *et al.* 2001) and the increase in blood flow could reduce muscle ischaemia by increasing oxygen delivery (Remijnse-Tamerius *et al.* 1999). However, in only two studies was a correlation between the increased blood flow and improved walking performance observed, and this correlation was low to moderate (Alpert *et al.* 1969; Gardner *et al.* 2000). Other studies have shown no changes in lower-limb blood flow following walking exercise rehabilitation, despite improvements in CD and MWD being observed (Larsen and Lassen, 1966; Johnson *et al.* 1989; Blumchen *et al.* 1970; Mannarino *et al.* 1989; Tan *et al.* 2000a).

The inhibition of atherosclerotic disease progression can also be a factor in reducing the amount of muscle ischaemia (Remijnse-Tamerius *et al.* 1999). It has been hypothesised that a normalisation of nitric oxide release can reduce claudication by enhancing the induction of flow-dependent vasodilation, both mechanisms causing an increase in muscle oxygen delivery (Remijnse-Tamerius *et al.* 1999). In this present study, localised metabolic adaptations within the lower-limb skeletal muscles could have contributed to the improvement in CD observed in the lower-limb exercise training group, which demonstrated progressive improvements in walking ability throughout the intervention period. However, it is not feasible that such a physiological adaptation accounted for the improvement in CD observed in the upper-limb exercise training group. The rate of improvement in CD in the upper-limb training group rose quite sharply up to the 12^{th} week of training, followed by a progressively slower rate of improvement thereafter, thereby suggesting a possible plateau effect. This observed improvement in CD was more likely to be related to central and/or systemic cardiovascular adaptations than improved lower-limb perfusion during exercise.

An increase in cardiac stroke volume is known to account for most of the rapid improvement in cardiorespiratory capacity observed after short-term programmes of aerobic training in previously sedentary individuals (Saltin *et al.* 1968). Furthermore, the increase in stroke volume observed after a programme of exercise training in patients with chronic heart failure appears to be accompanied by a decrease in total peripheral resistance at rest and during exercise (Hambrecht *et al.* 2000; Gielen *et al.*

2002). An improvement in cardiac stroke volume, combined with a decrease in total peripheral resistance would facilitate improved blood flow to lower-limb skeletal muscle groups during walking and might explain the improvement in CD observed in the upper-limb training group. However, a number of other systemic adaptations, including improved endothelial vasoreactivity (Brendle *et al.* 2001), nitric oxide metabolism (Arosio *et al.* 1999) and blood rheological adaptations (Ernst and Matrai, 1987) cannot be dismissed on the basis of the evidence presented herein. In addition, it has previously been suggested that a decrease in blood viscosity could be associated with an increase in walking ability in patients with PAD (Remijnse-Tamerius *et al.* 1999). Although rheological changes were not studied as part of this present study, haematocrit was determined in approximately two thirds of the patients in all groups, no change in which was observed.

Although the CD in both training groups improved as a result of the intervention period, the HR at CD was unchanged throughout the study period. This suggests that although patients could walk further and at a faster pace (because the shuttle-walk was incremental in nature) before the onset of claudication pain at the end of the exercise training programme, patients experienced a comparable level of cardiovascular stress at CD both before and after the programme. In addition, given that CD reflects the first perception of claudication pain, the onset of pain at CD was perceived to be in the main 'very weak' throughout the programme of exercise rehabilitation in both exercising groups, suggesting consistency of pain perception. However, despite being able to walk further prior to the onset of pain, patients in the lower-limb training group also reported the pain to be less intense at CD following the 24-week intervention period. These patients perceived their pain to be 'extremely weak' compared to 'very weak' at baseline.

This could suggest an enhanced pain perception in this lower-limb group, that is, these patients were possibly more aware of pain perception and the onset of claudication pain. The reason for this apparent difference in pain perception in the lower-limb training group is unknown. One explanation could be that these patients were being subjected to high levels of pain on a twice weekly basis during the supervised exercise training classes. The fact that these patients were experiencing the sensation of pain on such a frequent basis, in comparison to the upper-limb training group who were exercising relatively pain-free, and control patients who experienced claudication pain only during

walking, could explain the difference in pain perception threshold in the lower-limb training group.

The improvement in CD following exercise training in both exercise training groups, coupled with the perception of pain in the main being 'very weak' would suggest that the exercise-induced ischaemic pain response was delayed at sub-maximal intensities of walking, even though there was no change in resting ABPI. Although there was no change in resting ABPI following exercise training in either group, this does not preclude an increased perfusion of the lower-limb skeletal muscles during sub-maximal walking exercise. Previous reports have shown that a number of medical treatments can significantly improve treadmill exercise performance and functional status without a change in ABPI or leg blood flow (Hiatt *et al.* 1990). Furthermore, resting ABPI has been reported to be unrelated to walking performance in a number of studies (Gardner *et al.* 1992a; Hiatt *et al.* 1992; Leder *et al.* 2002) and the substantial change in walking performance which can be evoked by exercise rehabilitation is not always accompanied by a change in resting ABPI (Perkins *et al.* 1996).

As a means to understanding changes in MWD following upper- and lower-limb exercise rehabilitation, HR, blood lactate, perceived exertion and the pain responses at MWD were measured during the shuttle-walk test to assess consistency of effort and exercise pain tolerance. Improvements in MWD in both training groups were accompanied by progressive increases in peak HR over the course of the exercise interventions, suggesting that either a greater exercise stimulus was required to elicit a claudication response, or that patients were able to push themselves further beyond the 'pain barrier' after training.

The improvements in MWD were also accompanied by progressive increases in peak blood lactate concentration in both training groups of patients compared to the controls. However, increases from baseline were only observed in the upper-limb exercise training group. Blood lactate concentration reflects a balance between production within the working skeletal muscles and mechanisms of removal. This response may indicate an enhanced rate of lactic acid clearance from skeletal muscle after the programme of exercise training, perhaps associated with improved oxygen and substrate delivery, a mechanism which could help to control skeletal muscle acidosis.

Changes in the psychological approach to exercise and adjustments in gait to compensate for pain (Whyman and Ruckley, 1998), and a change in pain perception through an improved tolerance of claudication pain (Remijnse-Tamerius *et al.* 1999; Ernst and Matrai, 1987; Alpert *et al.* 1969) could also account for improved walking performance in patients with PAD (Nehler and Hiatt, 1999b). It is also possible that patients with PAD develop an increased supply of endorphins with exercise training (Remijnse-Tamerius *et al.* 1999). Interestingly, a higher rating of perceived pain at MWD after 18- and 24-weeks of the intervention was only observed in the upper-limb training group of patients. This indicates that patients in this group could tolerate a higher amount of pain, pushing themselves further beyond the pain barrier after exercise training. An increase in exercise pain tolerance might therefore be a possible mechanism of adaptation, which could account for the improvement in MWD in this patient group. Furthermore, a significant decrease in post shuttle-walk ABPI was observed in this group of patients, in relation to the control group, thereby providing further evidence that these patients were pushing themselves further beyond the pain barrier after the programme of exercise rehabilitation.

A possible criticism of this theory is that the investigator might have encouraged these patients to a greater extent and that this could explain the fact that they were pushing themselves harder. Operator encouragement has been reported to have a positive effect on walking performance in previous walking protocols, such as the 6-minute walk test (Guyatt *et al.* 1984). The advantage of the incremental shuttle-walk test is that it is standardised, externally paced and thereby diminishes the effect of operator influence (Singh *et al.* 1992). Although a limitation of this study is that assessors were not blinded to training group assignment, consideration of the peak HR, RPE and pain responses suggests that patients in both exercise training groups were equally motivated to perform well on tests of physical function. Furthermore, tests were conducted in a standardised manner, with equal encouragement given to all patients, irrespective of training group assignment.

Patients in both exercise training groups expressed an improved confidence in walking following the 24-week intervention period, which accompanied the improvements observed in MWD. This was an interesting finding and a further possible explanation for the improved walking ability in these patients. It has been suggested that before training, patients are often afraid to walk because of a possible negative effect, whereas

an increased confidence in walking ability after a training programme can stimulate patients to walk a greater distance (Remijnse-Tamerius *et al.* 1999).

Alternative lower-limb exercise rehabilitation strategies such as dynamic leg exercise (incorporating running, dancing and playing ball) (Dahllof *et al.* 1974; Lundgren *et al.* 1989b; Lundgren *et al.* 1989a; Holm *et al.* 1973; Ekroth *et al.* 1978), repeated heel raising (Hedberg *et al.* 1988), functional exercises related to common activities of daily living (Sorlie and Myhre, 1978; Clifford *et al.* 1980), lower-limb cycle ergometry exercise (Zetterquist, 1970), lower-limb gymnastics exercise (Ericsson *et al.* 1970) and lower-limb strength training (Hiatt *et al.* 1994) have been investigated. These training modalities are well-tolerated by patients with claudication and all have been shown to have a positive impact on walking performance. Two of these studies reported an increase in maximum calf blood flow using venous occlusion plethysmography, following the rehabilitation programme (Lundgren *et al.* 1989a; Ericsson *et al.* 1970).

The limitation of previous studies that have measured leg blood flow after lower-limb exercise rehabilitation programmes are that blood flow has typically been measured at rest after an ischaemic or exercise challenge, and not during exercise. In addition, it is possible that improved tissue perfusion results from changes in the distribution of blood flow or capillary surface area (Regensteiner and Hiatt, 1995; Delp, 1998), rather than from changes in total blood flow to the lower extremities. Consequently in the absence of a formal exercise training regimen, a trend towards a decrease in MWD following the 24-week intervention period was observed in the control group. This is consistent with expectations, since intermittent claudication is a leveraged disability i.e. pain increases with walking (Beebe, 2001). The degree of ischaemic pain evoked by walking might deter some patients from engaging in such exercise (McDermott *et al.* 2002a) and the muscle strength of patients with the condition erodes (Beebe, 2001). The reduced levels of physical activity could potentially contribute to subsequent disability (McDermott *et al.* 2002a), with walking capacity decreasing further over time (Beebe, 2001). Indeed, evidence suggests that self-reported walking ability declines at a rate of 9.2 yards per year (Aquino *et al.* 2001) in patients with intermittent claudication.

Physiological responses to incremental upper- and lower-limb aerobic exercise in the whole cohort of patients

Tolerance to upper- and lower-limb aerobic exercise

In order to further understand the effects of upper- and lower-limb exercise on tolerance to upper- and lower-limb exercise and the mechanisms underpinning the improvement in walking performance, the physiological responses to incremental arm- and leg-cranking exercise were also studied during the intervention period.

At maximal exercise tolerance peak $\dot{V}O_2$ is consistently lower during arm-crank compared to cycle exercise in healthy individuals. Values in the range of 36% to 89 %, with a mean of 73 % have been reported (Astrand *et al.* 1965; Bergh *et al.* 1976; Davis *et al.* 1976; Magel *et al.* 1978; Miles *et al.* 1983; Pollock *et al.* 1974; Sawka *et al.* 1982; Astrand *et al.* 1961; Reybrouck *et al.* 1975; Stenberg *et al.* 1967; Sawka, 1986). Maximal power output during arm-crank exercise is also lower compared to cycle exercise (Sawka *et al.* 1982; Vokac *et al.* 1975).

Peak $\dot{V}O_2$ values are dependent upon central (cardiac output) and peripheral (ability to extract and utilise oxygen) components (Sawka, 1986). Both upper- and lower-body exercise share the same control mechanisms to maintain cardiac output (Sawka, 1986). During maximal exercise, cardiac output values are lower for arm-crank compared to cycle exercise (Clausen, 1976), by approximately 30% (Reybrouck *et al.* 1975). This disparity in maximal cardiac output corresponds to the difference in peak $\dot{V}O_2$ between the two types of exercise (Sawka, 1986) in healthy individuals.

The relatively smaller skeletal muscle mass and thus, the exercise oxygen extraction capacity during upper-body exercise, further contributes to the reduced peak $\dot{V}O_2$ values relative to lower-body exercise (Sawka, 1986) reported in the literature. Nevertheless, although both modes of ergometry employ different muscle groups (Sawka, 1986), strong correlation coefficients (r=0.70 to 0.94) have been reported for peak $\dot{V}O_2$ responses between upper- and lower-body exercise (Bar-Or and Zwiren, 1975; DeBusk *et al.* 1978; Falkel *et al.* 1986; Sawka *et al.* 1983a). Thus, it is believed that in arm exercise, neither oxygen transport nor oxygen extraction in the tissues can exceed that reached in maximal leg work due to the larger skeletal muscle mass in the latter (Stenberg *et al.* 1967). However, although upper-body muscle groups are

relatively weaker than the lower-body muscle groups (Falkel *et al.* 1985), it has been suggested that, in theory, muscular strength could influence upper-body performance by enabling stronger individuals to achieve higher levels of cardiorespiratory stress prior to local fatigue and exercise termination (Sawka, 1986). Certainly, individuals who train their upper-body muscle groups can achieve arm-crank values approaching 90% of their cycle exercise peak $\dot{V}O_2$ values (Cerretelli *et al.* 1977; Seals and Mullin, 1982; Vrijens *et al.* 1975). Conversely, sedentary individuals may achieve approximately 60% of their cycle exercise peak $\dot{V}O_2$ values during arm-crank exercise (Sawka, 1986).

The findings of this current study have shown that when the entire cohort of patients was compared at baseline, peak $\dot{V}O_2$ during upper-limb aerobic exercise was 92% of that measured during lower-limb aerobic exercise, representing an absolute difference of less than 0.10 l min^{-1} between upper- and lower-limb aerobic exercise capacity. This supports the findings of Fardy *et al* (Fardy *et al.* 1977) who reported a similar aerobic exercise capacity between incremental arm-cranking exercise and treadmill walking in a single patient with intermittent claudication. The impaired blood flow through the peripheral arteries resulting from the condition (Bulmer and Coombes, 2004), undoubtedly accounts for this observation. Furthermore, in over one-third of our patient cohort (35%), peak upper-limb aerobic capacity was equal to or exceeded lower-limb aerobic capacity. This sub-group of patients exhibited a lower resting ABPI than the remaining patients with higher leg exercise tolerance (0.60 ± 0.03 vs. 0.69 ± 0.02, respectively; $P < 0.05$).

Other cardiovascular and metabolic stress responses such as HR (Pimental *et al.* 1984), $\dot{V}E$ and blood lactate levels are also lower following upper-limb exertion than lower-limb exertion at maximum exercise tolerance in healthy individuals (Sawka *et al.* 1982; Sawka, 1986; Astrand *et al.* 1965; Bergh *et al.* 1976; Sawka *et al.* 1982). The difference in blood lactate concentration is probably explained by the amount of muscle mass involved during the two exercise types (Sawka, 1986), and the subjective feeling of strain during exercise is related to the metabolic rate per unit mass of contracting muscle (Astrand and Rodahl, 1970). The association between selected physiological responses and ratings of perceived exertion (RPE) may also be different between upper- and lower-body exercise (Sawka, 1986).

In the present study, peak responses for $\dot{V}E$, Bf, RER, HR, SBP, RPP and blood lactate following incremental upper- and lower-limb exercise were equivalent in our cohort of patients with PAD. This is unusual, since in healthy individuals all these responses are greater in LCT. These results reflect the impact of impaired perfusion and ischaemic pain on the ability to support moderate to high intensity leg exercise in this patient group (Fardy *et al.* 1977). Peak HR during treadmill walking has also been observed to be much lower in claudicants than healthy controls (Regensteiner *et al.* 1993b), thereby reflecting the fact that exercise performance and peak $\dot{V}O_2$ are limited primarily by peripheral, rather than central blood flow to working muscles (Askew *et al.* 2002).

The level of leg pain experienced at maximal exercise intensity in the leg-cranking assessment further reflects the inability of these patients to support high intensity leg exercise due to their lower-limb impaired perfusion. The level of peak pain during leg-cranking was greater than the level of arm pain experienced in the arm-cranking assessment, despite similar levels of perceived exertion and blood lactate levels being increased during the arm-cranking assessment. Patients typically experienced ischaemic pain in the calf and thigh regions of the lower extremity during the leg-cranking assessment, which was described as being similar to the pain experienced during walking. Given that upper extremity arterial disease is reported to be 20 times less frequent than lower extremity involvement, (Laroche *et al.* 1976; Welling *et al.* 1981), the pain experienced in the arms during the arm-cranking assessment was more likely attributable to the fatiguing effects of unaccustomed exercise in upper extremity muscle groups.

Perceived pain experienced during the assessment sessions in this present study was short-lived, since for both the upper- and lower-limb assessment an intermittent protocol was utilised, despite the fact that a continuous exercise protocol would have required less time to administer (Sawka, 1986). Intermittent arm-crank protocols have previously incorporated rest periods between exercise bouts ranging from 1 min (DeBusk *et al.* 1978; Washburn and Seals, 1983) to 20 min (Miles *et al.* 1984; Sawka *et al.* 1982). Two studies have examined whether the selection of a continuous or intermittent protocol alters the physiological responses to maximal effort arm-crank exercise (Sawka *et al.* 1983b; Washburn and Seals, 1983). Neither study found a difference in peak $\dot{V}O_2$ response, although Sawka *et al* (Sawka *et al.* 1983b) reported

maximal power output to be greater during the intermittent than continuous arm-crank protocol. Arm-crank ergometry has been reported to be accurate and reproducible in eliciting physiological responses (Bar-Or and Zwiren, 1975; Davis *et al.* 1976; Lazarus *et al.* 1981). However, upper-limb exercise above the head level elicits greater physiological strain (compared to below the heart level) which results from increased sympathetic vasoconstrictor tone mediated by arm elevation as well as a contributing isometric exercise component (Sawka, 1986). The mid-point of the sprocket was set at shoulder height for all patients individually in the ACT for this reason.

It has been suggested that intermittent protocols have a particular application in arm-crank ergometry, in which exercise termination is frequently associated with local muscular fatigue (Sawka, 1986). It is believed that perceptual sensitivity to process physiological information may be enhanced during upper-body exercise (Sawka, 1986) as compared to exercise with large muscle groups (Gamberale, 1972). Such intermittent protocols may minimise the effects of accumulated localised fatigue and thus enable improved maximal performance during arm-crank exercise (Sawka, 1986). In this study, due to the severe pain encountered during lower-limb exercise in some patients, such an intermittent protocol at least in part alleviated pain and discomfort and allowed each patient to continue to maximum exercise tolerance during both exercise protocols.

Changes in upper- and lower-limb aerobic exercise capacity after upper- and lower-limb exercise training

It is well recognised that a decline in aerobic fitness contributes to decreased mobility (Buckwalter, 1997). Consequently an increase in aerobic fitness, as reflected by an increase in peak $\dot{V}O_2$ can lead to an increase in mobility. It has even been suggested that in healthy elderly patients, potentially rigorous training can achieve levels comparable to those of younger individuals (Buckwalter, 1997). In healthy 60-70 year olds, $\dot{V}O_2$ max can increase by 30% on average with 6-months of aerobic exercise (Seals *et al.* 1984).

In this study, peak $\dot{V}O_2$ increased by 17% and 19% in the lower- and upper-limb training groups during the LCT following the intervention period, respectively. In comparison, a programme of 45- min of walking, or running four days per week for 9-

12-months increased mean aerobic capacity in patients with intermittent claudication by 24% (Coggan *et al.* 1992). These findings further identify the impact of intermittent claudication on functional capacity. Although peak $\dot{V}O_2$ in this study was much lower than that observed with healthy individuals, it is important to note that even small improvements in peak $\dot{V}O_2$ can have considerable implications for patients walking performance, overall health and general well-being, all of which make a substantial difference to quality of life.

Some studies have reported that endurance training only affects the trained muscle groups (Bhambhani *et al.* 1991; Magel *et al.* 1978; McKenzie *et al.* 1978), whereas others have suggested that endurance training also increases the performance capacity of untrained muscles (Clausen *et al.* 1973; Lewis *et al.* 1980; Loftin *et al.* 1988). The observed improvement in walking performance in both exercise training groups in this study may in part be attributed to an increase in lower-limb peak power and peak $\dot{V}O_2$ during the leg-cranking assessment, since peak responses for perceived exertion and pain were similar for both groups.

It can be argued that the higher peak HR for the lower-limb exercise training group and higher blood lactate response for both exercise groups during the LCT suggest that these patients became more motivated to perform well and pushed themselves harder after the period of supervised exercise training. The level of encouragement during all assessments was identical for all patients, regardless of grouping. Patients were actively encouraged to keep going as long as possible, taking into account all criteria, including verifying that blood pressure, HR and ECG rhythms were within acceptable limits. All groups were treated equally, since the investigators were aware of the fact that a bias for any group could hamper the validity of the findings.

The improvement in lower-limb peak $\dot{V}O_2$ in the upper-limb exercise training group in this study is of particular interest, since this indicates that such an exercise regimen can improve lower-limb function in patients with PAD. Specific and transfer effects have previously been observed between arm- and leg-training (Tordi *et al.* 2001), however not in patients with intermittent claudication. Furthermore, transfer effects of endurance training (i.e. increase of performance measured during exercise with untrained muscles) are more controversial (Franklin, 1989) than specific training effects (Tordi *et al.* 2001). It is believed that in healthy individuals the magnitude of specific effects

depends on the pre-training level of peak $\dot{V}O_2$ of participants, and that this initial peak $\dot{V}O_2$ also indirectly influences the transfer effect (Tordi *et al.* 2001).

The occurrence of a transfer effect depends on the magnitude of the specific effect, with the transfer effect from legs to arms being more effective than transfer from arms to legs (Tordi *et al.* 2001) in healthy individuals. In arm training studies in which the peak $\dot{V}O_2$ improvement (measured in the arm test) is below 20%, no transfer effect has been reported (Bhambhani *et al.* 1991; Magel *et al.* 1978). Indeed, it has been suggested that an increase of more than 30% of peak $\dot{V}O_2$ is necessary to obtain a significant transfer effect (Lewis *et al.* 1980). In contrast, the findings in this present study suggest that a transfer effect from arms to legs had occurred in patients undertaking upper-limb exercise training, as indicated by the improvement in aerobic capacity and power output during the LCT.

The improvement in peak $\dot{V}O_2$ in these patients during the ACT (13%) was considerably less than that previously reported to generate a transfer effect. The patients in the present study were sedentary, elderly individuals. Perhaps, their low peak $\dot{V}O_2$ could account for the transfer effect of endurance training to untrained limbs, as previously suggested (Lewis *et al.* 1980; Loftin *et al.* 1988). These observations are consistent with the central circulatory changes observed after short periods of endurance training in individuals with low peak $\dot{V}O_2$ (Thompson *et al.* 1981), and may account for the observations in this study.

It has been suggested that when legs are trained, a 15% increase in $\dot{V}O_2$ (measured during the leg test) is generally sufficient to induce a significant transfer effect in the arms (Clausen *et al.* 1973; Lewis *et al.* 1980). In this study a 17% improvement in peak $\dot{V}O_2$ during the LCT by the lower-limb training group was observed, however no transfer effect, as suggested by an improved peak $\dot{V}O_2$ was observed by these patients in the ACT. Undoubtedly, due to the impairment in lower-limb perfusion in these patients, a greater increase in peak $\dot{V}O_2$ is required compared to those of healthy individuals. An increase in peak $\dot{V}O_2$ from baseline during the ACT was only observed in the upper-limb training group of patients, indicating the specificity of exercise training. The improvement in upper-limb peak $\dot{V}O_2$ following arm ergometer exercise is probably

attributable to enhanced oxygen utilisation resulting from an expanded arterio-venous oxygen difference (Magel *et al.* 1978).

Aerobic training substantially changes the respiratory response to exercise, with the dramatic increase in ventilation at maximal power output being accomplished by an increase in both maximal respiratory rate and maximal tidal volume (Wilmore, 2003). In the present study, increases in peak $\dot{V}O_2$ were associated with increases in peak $\dot{V}CO_2$, $\dot{V}E$ and breath frequency in both training groups, during both the LCT and ACT assessments, with no changes in systolic or diastolic blood pressure or perceived exertion from baseline values being observed.

Functional Status Measures

In order to evaluate functional status in patients with PAD comprehensively, it is important not only to consider laboratory-based measures, but also to examine data on community-based walking ability obtained from questionnaire responses (Regensteiner and Hiatt, 1995; Regensteiner *et al.* 1997b). The questionnaire data in this study, as in previous studies (Izquierdo-Porrera *et al.* 2005; Labs *et al.* 1999a) were collected as a secondary outcome measure, in order to further explore the effects of exercise rehabilitation on function in older patients with symptomatic PAD. Only relatively recently have questionnaires been used routinely in clinical trials in patients with PAD (Regensteiner *et al.* 1997b; Patterson *et al.* 1997; Whyman *et al.* 1997; Regensteiner *et al.* 1996; Hiatt *et al.* 1990), and therefore comparatively little is known about the effects of a treatment programme on community-based walking ability or quality of life (Regensteiner and Hiatt, 1995).

Physiological measures of PAD severity correlate with specific subscales (physical functioning) of the generic (SF-36 *v2*) measure and with the disease-specific measures (WIQ), suggesting that both generic and disease-specific questionnaires can provide insight into health related quality of life in patients with PAD (Izquierdo-Porrera *et al.* 2005). Both questionnaires describe the impact of claudication and treatment thereof, and provide insight into disease-specific and more global aspects of function, which are essential measures of therapeutic outcome in PAD clinical trials (Hiatt *et al.* 1995b). The information obtained from these questionnaires can provide a valuable adjunct to laboratory-based measures (Regensteiner and Hiatt, 1995). Furthermore, the European quality of life questionnaire (EQ-5D) has been specifically designed to complement

other health related quality of life questionnaires (Krabbe and Weijnen, 2004) such as the SF-36.

In accordance with previous recommendations (Regensteiner *et al.* 1990), in the main all questionnaires were administered before undertaking the shuttle-walk test in order to minimise the potential for bias in the self evaluation of walking ability and functional status, and to prevent shuttle-walk performance from influencing questionnaire response. In addition, both interviewer and patient were blinded to previous questionnaire scores (Regensteiner *et al.* 1996) so that patients could not answer based on previous experience (Regensteiner *et al.* 1990).

Walking Impairment Questionnaire (WIQ)

The WIQ has been referred to as a disease-specific health related quality of life questionnaire (Izquierdo-Porrera *et al.* 2005). It has been widely used to examine the effect of exercise rehabilitation on patients functional status in the PAD population (Regensteiner *et al.* 1990; Regensteiner *et al.* 1997b). Improvements in WIQ domains have been observed following supervised exercise (Regensteiner *et al.* 1997b) in the form of treadmill intervention (Hiatt *et al.* 1990; Regensteiner *et al.* 1996) and strength training (Regensteiner *et al.* 1996). In the WIQ, walking capabilities are quantified in terms of walking defined distances, speeds, stair climbing ability and severity of claudication pain during usual walking activities (Regensteiner *et al.* 1990). A score of 0 to 100 is used to measure each domain, with a score of 0 representing inability to perform the task and 100 representing no difficulty performing the task (Izquierdo-Porrera *et al.* 2005).

The WIQ has previously been used to detect changes in community based walking ability following two of the major intervention treatments used for patients with PAD (Regensteiner *et al.* 1990), namely exercise training (Hiatt *et al.* 1990) and peripheral bypass surgery (Regensteiner *et al.* 1994; Regensteiner *et al.* 1993a; Regensteiner *et al.* 1990). Changes in graded treadmill exercise performance (Regensteiner *et al.* 1990), the 6-minute and 4-m walk score all correlate with changes in questionnaire scores (McDermott *et al.* 1998a) and WIQ responses are stable when repeated over time in control patients (Hiatt *et al.* 1995b; Regensteiner and Hiatt, 1995). The findings of this present study also confirm that all WIQ domains correlate highly with MWD

determined using the shuttle-walk protocol, with correlation coefficients of 0.71 and 0.67 for walking distance and walking speed observed.

It has previously been argued that the WIQ should be able to measure walking impairment regardless of the type of intervention used or lack of intervention to improve walking ability (Regensteiner *et al.* 1996). Although the WIQ has been shown to accurately reflect treadmill performance, it does not duplicate it, since it asks questions about habitual walking patterns rather than walking performed in the laboratory setting (Regensteiner *et al.* 1990). The corroboration of shuttle-walk results by questionnaire results assumes great importance in this present study.

In some patients the onset of claudication pain can occur with even low-intensity physical activity, severely restricting the patient's ability to ambulate in the community setting (Nehler and Hiatt, 1999b). Upon commencing this present study all patients perceived a 50% degree of difficulty in walking, due to claudication severity, as assessed using the WIQ pain severity domain. This further confirms that patients are limited in their walking ability due to claudication, as opposed to angina or arthritis for example. Claudication severity may be regarded as a minor inconvenience, or alternatively, a significant handicap, imposing frustrating and sometimes distressing limitations on lifestyles (Binnie *et al.* 1999). Some patients with intermittent claudication experience a feeling of disability, due to having a moderate to severe impairment in walking ability that may limit their ability to meet the personal, social or occupational demands of daily living (Regensteiner *et al.* 1996; Regensteiner *et al.* 1990; Regensteiner, 1997).

Intermittent claudication causes both men and women to have poorer walking endurance and slower walking speeds (McDermott, 1998a; Hiatt *et al.* 1988). The WIQ includes questions specifically on both walking distance and walking speeds, since some patients may be limited selectively in either speed or distance, therefore the questionnaire is more applicable to a broad range of patients with PAD (Regensteiner *et al.* 1990). Individual questions about each defined distance or speed allow a close examination of the limitations of walking ability (Regensteiner *et al.* 1990) in these patients. The integrated summary scores provide a single value which can be related to an entire component of self-reported walking ability (Regensteiner *et al.* 1990).

Upon commencing the present study patients displayed a characteristic pattern of response to the WIQ, in that walking ability was rated as becoming increasingly difficult at longer distances and faster speeds. These findings were similar to those reported previously (Regensteiner *et al.* 1990). WIQ scores in patients with PAD are lower than those reported in non-PAD patients (Gardner and Montgomery, 2001). In the present study the degree of difficulty associated with walking distance was 27, 23 and 22% and walking speed was 28, 27, and 31% for the lower-, upper-limb and control groups, respectively, thereby indicating that patients perceived themselves as being functionally impaired (Izquierdo-Porrera *et al.* 2005). These scores are similar to those in previous reports (Regensteiner *et al.* 1990), but lower than those in others (McDermott *et al.* 1998a; Izquierdo-Porrera *et al.* 2005; Regensteiner *et al.* 1997b). Differences in patient numbers could account for the discrepancy in perceived abilities between studies.

No changes in the WIQ distance or speed domains were observed in either exercise training group following a 6-week period of exercise training. It is possible that perceived improvements in walking ability lag behind the physical improvements in ambulatory function achieved following 6-weeks of exercise training. It is equally possible that the WIQ is not sensitive to address small improvements in walking ability obtained through short-term exercise. A criticism of the WIQ has been that patient-specific factors such as depressed mood and perception of optimal walking speed and endurance are likely to affect the responses to the WIQ (McDermott *et al.* 1998a).

Following 12- and 18-weeks of exercise training, improvements in the WIQ distance and speed scores were observed in the upper-limb training group only. It is interesting that these improvements were not observed in the lower-limb training group of patients, since improvements in walking performance and functional capacity were observed in both exercise training groups at these time-points. It is possible that perceived improvements in walking ability in the lower-limb training group of patients in this present study continue to lag behind the physical improvements in ambulatory function induced in these patients. Conflicting findings in WIQ domains exist following short-term exercise training, since improvements in all WIQ domains have been observed in some studies following a 12-week period of treadmill training (Regensteiner *et al.* 1997b; Tsai *et al.* 2002; Regensteiner *et al.* 1990), but not in others (Regensteiner *et al.*

1996). Twelve weeks of strength training improved only walking speed and stair climbing ability, with no changes in other WIQ scores (Regensteiner *et al.* 1996).

These perceived differences between groups in the present study following 12- and 18-weeks of exercise training might also be explained by a greater confidence in walking in the upper-limb training group of patients at these time-points. Perceived confidence in walking was improved in both exercise training groups following the 24-week intervention period, however it was not assessed at intermediate time-points throughout the study. Equally, it is possible that differences associated with adaptations which contributed to improved walking performance between the two exercise training regimens could have influenced the perception of improved walking ability (WIQ domains of speed and distance) in these patients at these time-points. A further possibility which cannot be excluded is the fact that patients in the upper-limb exercise training group were participating in relatively pain-free, twice-weekly exercise, compared to the lower-limb training group. The frequent sensation of pain experienced during the training sessions in the lower-limb training group could have masked their perception of an improvement in the walking distance and speed domains at the 12- and 18-week time-points.

In contrast, stair climbing ability was improved following 12-weeks of exercise training only in the lower-limb exercise training group, whereas at the 18-week time-point an improvement in this domain was seen in both groups. It is possible that peripheral adaptations could account for the more rapid improvements observed in the lower-limb training group at the 12-week time point. The improvement in functional capacity through central/systemic cardiovascular function in the upper-limb training group could possibly account for the observed improvement in stair climbing ability following 18-weeks of exercise training.

At the end of the intervention period in this present study there was no change in the claudication pain severity domain of the WIQ from baseline measures in any group, indicating that perceived difficulty in walking due to calf pain was unchanged. However, an improvement in this domain was observed in the upper-limb training group compared to the control group of patients. Similarly, 12-weeks of treadmill exercise intervention have not resulted in changes in this domain (Regensteiner *et al.* 1990), although improvements have been observed following 24-weeks of treadmill

training (Regensteiner *et al.* 1996) and following surgical intervention (Regensteiner *et al.* 1990).

It has been suggested that when patients exit an intervention study, they are able to perform at a higher level than on entry, so that many of them can reach the upper limit of the questionnaire's distance scale (Regensteiner *et al.* 1990). In this present study and in parallel to the improvements in CD and MWD observed during the shuttle-walk assessment during standardised laboratory conditions, walking ability (distance, speed and stair-climbing ability) in the community setting was perceived to be improved following the intervention period in both exercise training groups, as determined by the WIQ. Furthermore, these patients also reported a self-observed noticeable improvement in walking ability in the community setting, stating that they could walk much further on the flat, but also up a hill following the intervention period.

Similarly, 24-weeks of treadmill training have also been associated with increases in the WIQ distance, speed and stair climbing scores (Regensteiner *et al.* 1996). However, the improvements in these domains were greater than those observed in the present study. The specificity of walking exercise might account for these findings. Although a proportion of the control group did perceive an improvement in their walking ability, no changes in WIQ domains were observed at any time-point throughout the intervention period. This further supports that WIQ responses are stable when repeated over time in control patients (Hiatt *et al.* 1995b; Regensteiner and Hiatt, 1995).

The perceived improvement in both walking distance and speed in both exercise training groups could be associated with a number of factors including an improvement in confidence in walking, which was shown to improve from baseline in both exercise training groups. The improved confidence in walking could account for the fact that patients felt that they could push themselves further or indeed that they felt able to tolerate the pain more when they were walking and this in itself could account for the improvement in walking performance. Walking distance and speed were also highly correlated with the shuttle-walk test and this was the case at each assessment stage of the intervention period.

Quality of Life

Although health related quality of life is thought to be an important measure of disability in patients with PAD, the severity of functional impairment in these patients only partially determines this (Breek *et al.* 2002), since PAD represents just one (peripheral) manifestation of a generalised atherosclerotic status (Labs *et al.* 1999a). Usually, affected patients have multiple morbidities, and the assessment of quality of life may give a more representative picture of the patients' perception of health than the exclusive measurement of walking performance (Labs *et al.* 1999a). It might be expected that all claudication therapies would alleviate pain and improve walking capacity, however such an improvement could, but might not necessarily, lead to an improved quality of life (Hiatt, 1997b).

Health-related quality of life is reduced in older patients with PAD (Breek *et al.* 2001) (Izquierdo-Porrera *et al.* 2005), and this might be attributable to their ambulatory dysfunction (Feinglass *et al.* 1996), degree of bodily pain and reduction in physical function (Bartman *et al.* 1998). Several non-disease specific questionnaires have been used to measure health related quality of life in these patients (Izquierdo-Porrera *et al.* 2005). These have included amongst others the Medical Outcomes Study (MOS) Short Form 36 (SF-36) (Pell, 1995; Bosch and Hunink, 1996; Bartman *et al.* 1998) and the European Quality of Life Instrument (Chetter *et al.* 1997; Cook *et al.* 1997; De Vries *et al.* 1998).

Data from the SF-36 questionnaire (Izquierdo-Porrera *et al.* 2005) indicate that the self-perceived physical performance such as physical functioning, role limitation due to physical health and bodily pain subscales in these patients is *impaired*, supporting previous findings (Gardner *et al.* 2001). The present study also supports these findings. In addition, lower scores in energy and vitality were also observed. This is in agreement with previous studies, since when compared with national norms (Ware, 2004), patients with PAD not only scored lower in the subscales of vitality, but also in the subscales of mental health and social functioning (Izquierdo-Porrera *et al.* 2005).

The SF-36 and EQ-5D questionnaires

In contrast to the WIQ and PAD-PAR, which measure only walking ability and physical activity, respectively, the SF-36 assesses multiple functional domains (Hiatt, 1997b; Izquierdo-Porrera *et al.* 2005). The SF-36 is a reliable, valid, generic health related

quality of life instrument (Ware and Sherbourne, 1992). It measures eight health domains of physical function, social function, role limitations due to physical dysfunction, role limitations due to emotional problems, mental health, bodily pain, general health and vitality (Izquierdo-Porrera *et al.* 2005). For each subscale, several item scores are standardised into a scale from 0 to 100, with better health states resulting in higher scores (Izquierdo-Porrera *et al.* 2005). Another questionnaire which is being increasingly incorporated in randomised controlled trials as a secondary outcome measure is the European quality of life (EQ-5D) questionnaire (Krabbe and Weijnen, 2004). In the EQ-5D questionnaire, general health state, mobility, self-care, ability to perform usual activities, pain and discomfort, and anxiety and depression are assessed on a scale from 0 to 100, indicating worst imaginable and best imaginable states, respectively (Health Policy, 1990) .

Short-term influence of exercise rehabilitation on Quality of Life

Therapeutic interventions which improve ambulatory function such as exercise rehabilitation, may improve quality of life (Izquierdo-Porrera *et al.* 2005). In this present study, 6-weeks of exercise training improved the general health status of patients in the lower-limb exercise training group only, despite improvements in walking ability and functional capacity in both exercise training groups during this period. It is possible that in the upper-limb training group, a patient's perceived improvement in general health status might lag behind the physiological improvements in walking ability and functional capacity observed.

Equally, it is possible that patients in the upper-limb training group initially perceived their training intervention negatively. Upon commencing the exercise intervention the majority of patients undertaking upper-limb exercise training felt sceptical regarding the possible benefits which they might receive from such an intervention. Such negative feelings might have had an impact when answering the questions which contributed to the scoring of the general health domain in the SF-36 *v2*. These questions included 'I expect my health to get worse' and 'my health is excellent'. It is possible that these patients did not perceive that an upper-limb training intervention could generate improvements and as such answered these questions accordingly, anticipating a decline in their general health. A further possibility is that a 6-week period of upper-limb exercise training is insufficient to generate feelings of improvement in general health status in these patients.

Although trends were observed, there were no significant differences within or between the study groups, in the physical functioning, role limitation physical, bodily pain, mental health, energy and vitality, social functioning or role limitation emotional domains in either exercise training group. As a consequence, this study failed to support the findings of a preliminary 6-week study of both upper-and lower-limb exercise training which reported improvements in the physical functioning and role limitation physical domains of the SF-36 in both exercise training groups (Walker *et al.* 2000). Other studies have also reported improvements in these domains after exercise training in these patients (Regensteiner *et al.* 1996). There are several possible explanations which could possibly account for differences between studies.

Firstly, it is possible that the patients in this present study were more sedentary than those in previous studies, since physical activity status was not assessed in the Walker *et al* study (Walker *et al.* 2000). Thus, it is feasible that 6-weeks of exercise training might be insufficient to generate improvements in these domains if patients in this present study were more sedentary at baseline, since questions which contribute to the physical functioning domains included questions about performing vigorous activities and walking long distances. In addition, questions contributing to the role limitation physical domain, ask questions regarding the amount of time spent performing activities and the degree of difficulty in doing so.

Furthermore, it is possible that patients in the present study were severely affected by their claudication and thus a longer period of exercise training was required to generate any improvement in physical functioning domains. It is also feasible that differences in patient number between studies and patients age, and types of physical activities typically undertaken by patients could all account for the discrepancies between studies. In contrast to another study (Currie *et al.* 1995), Walker *et al* (Walker *et al.* 2000) and the findings of this present study found no improvement in the bodily pain domain of the SF-36 *v2* following 6-weeks of either upper- or lower-limb exercise training. One possibility for this might be that exercise delays the onset of, rather than eliminates claudication pain (Walker *et al.* 2000).

For comparison, in this study quality of life was also assessed using the EQ-5D questionnaire. Following 6-weeks of the intervention period no changes in any of the questionnaire domains were observed, however the general health of patients in the

upper-limb training group was higher compared to the control group of patients. Differences in general health perception between the SF-36 *v2* and EQ-5D questionnaire can be explained by differences in questionnaire design. The EQ-5D uses a scale, rather like a thermometer, on which best imaginable state is marked by 100 and worst imaginable marked by 0 (Health Policy, 1990). The SF-36 *v2* on the other hand asks a series of specific questions, regarding a patient's perceptions of health, asking them to compare themselves to other people. It might be that such differences between the SF-36 *v2* and EQ-5D questionnaire could account for the discrepancies in perception of health status by both exercise training groups.

Long-term influence of exercise rehabilitation on Quality of Life

Intermittent claudication is associated with increased mortality as well as decreased functional status (Regensteiner, 2004) and a substantial limitation in the quality of life of patients is the reduction in walking ability (Remijnse-Tamerius *et al.* 1999). It is of interest therefore that the observed improvement in walking ability following exercise training in this present study, similarly to previous findings, coincided with an improvement in both the patients' physical aspect and quality of life (Tan *et al.* 2000b).

In this present study, in agreement with previous findings (Clifford *et al.* 1980) the improved functional capacity and walking ability in both exercise training groups was associated with an improvement in perceived general health status of these patients following 24-weeks of the intervention period, compared with the control group of patients, whose general health deteriorated over the study period. The physical function aspects examined in an earlier version of the SF-36 have also been shown to improve with exercise training (Regensteiner *et al.* 1996). Although patients who perform exercise training might not obtain the level of function of healthy aged-matched individuals, even small improvements in function may have practical relevance for patients with PAD (Regensteiner *et al.* 1996). It is believed that patients feel much healthier following exercise training, having unduly restricted their activities before, fearing the onset of ischaemic leg pain, thereby suggesting that exercise training is simple and effective in treating intermittent claudication (Clifford *et al.* 1980).

Improvements in other physical functioning domains of the SF-36 *v2* following 12- (Tsai *et al.* 2002; Regensteiner *et al.* 1997b) and 24-weeks of treadmill training (Regensteiner *et al.* 1996) have also been reported, thereby corroborating the treadmill

findings observed in these studies. A 38% to 67% gain in the physical functioning domain have been reported in smaller samples of claudicants following exercise programmes (Regensteiner *et al.* 1996; Regensteiner *et al.* 1997b). However, one study (Gardner *et al.* 2001) reported no change in the physical and mental health components of the SF-36 survey following exercise rehabilitation. Several factors may account for this discrepancy, including the fact that in the Garder *et al* study, the sample of patients was older and incorporated a higher percentage of patients with low socio-economic status (Gardner *et al.* 2001).

In this present study, further to the improvement in general health, improvements in the physical functioning and bodily pain domains of the SF-36 *v2* were observed in the upper-limb training group of patients only, however no significant changes in the role limitation physical domain were observed either between or within study groups. The upper-limb training group also showed an improvement in the energy and vitality domains compared with the control group of patients. Why such an improvement in bodily pain, physical functioning and energy and vitality should be achieved in the upper-limb training group only and not both training groups could result from limitations of the SF-36 *v2* questionnaire. Although the questionnaire is suitable in a broad field and extensively used in previous studies with patients with intermittent claudication, the SF-36 *v2* could have drawbacks when upper- and lower-limb exercise training are directly compared.

In the SF-36 *v2*, questions that relate to the scoring of the physical functioning domain, incorporate questions regarding the ability to perform 'vigorous activities such as lifting heavy objects' and 'moderate activities such as moving a table, vacuuming, bowling etc', and the degree of difficulty involved with 'lifting or carrying groceries', and 'bathing or dressing' oneself. Such activities predominantly involve the use of the upper-body. It could thus be argued that patients who performed upper-limb exercise training felt an improvement in their upper-body strength and function, and that this could account for differences in response and thereby perceived improvement in the physical functioning domain by this group of patients.

Furthermore, only two questions in the SF-36 *v2* questionnaire contribute to the bodily pain domain (Ware *et al.* 1993). One question asks the patient about 'the intensity of bodily pain' experienced in the last 4-weeks. It could be argued that the patients in the

upper-limb training group experienced less pain on a twice weekly basis compared to the lower-limb training group of patients. The second question contributing to the bodily pain domain asks about 'the extent pain interfered with their normal work' (including both work outside the home and housework). Due to the structure and regular pattern which the exercise training classes established, incorporating group sessions and also the frequency of attendance involved at the Centre, the majority of patients classed their participation in the study on a similar par to their previous working experience. As such, it is possible that patients in the upper-limb training group answered the questionnaire perceiving that they had been subject to minimal bodily pain and that this minimally interfered with their normal work, i.e. attending the Centre. Consequently, the lower-limb training group was subjected to more pain than normal through attending the twice weekly training sessions and this could explain why there was no change in this domain from baseline measures.

Similarly questions in the SF-36 *v2* which relate to the energy and vitality domain, specifically ask questions, if patients 'feel worn out', 'have a lot of energy' and if they 'feel tired'. It could also be argued that the patients in the lower-limb training groups were subject to higher intensity pain levels on a twice weekly basis and as such they could have perceived to be tired and worn out as a result of this. This might therefore explain why no improvements in the energy and vitality domain in this patient group were observed compared to the control group of patients.

It has previously been reported that improvements in the physical functioning domains are more pronounced than changes in the mental health component of the questionnaire (Tsai *et al.* 2002), with no changes in the social and role function domains reported following treadmill training in patients with PAD (Regensteiner *et al.* 1996). Longer exercise rehabilitation programmes of 3-6 months in duration, equally have found no change in the mental health domain in these patients (Menard *et al.* 2004; Patterson *et al.* 1997; Gardner *et al.* 2001). This present study agrees with these findings, since both lower- and upper-limb exercise training failed to alter a patient's perception of mental health, social function and role limitation emotional status. Several factors may account for this. In chronically ill patients with PAD, ambulatory dysfunction may be the most important factor influencing self perceived health related quality of life (Tsai *et al.* 2002). It is also possible that the perceived improvements in the mental health

component of quality of life may lag behind the improvements in ambulatory function (Tsai *et al.* 2002).

Therefore, in agreement with hospital-based treadmill training the primary effects of this present study have all been in physical functioning (Regensteiner *et al.* 1997b), suggesting that improved walking ability does not alter other domains of functional status (Regensteiner *et al.* 1996). This is not surprising since physical functioning domains enable patients to become more functionally independent (Tsai *et al.* 2002); after all PAD is a disease wherein the symptom of intermittent claudication limits walking ability. This is important, since unsupervised exercise programmes are unlikely to significantly improve patient's quality of life (Currie *et al.* 1995).

The patients in the control group, were given general lifestyle advice and an in depth consultation regarding ways of increasing physical activity which were identical to those given to patients undertaking exercise training. Some of the patients in the control group who heeded this advice increased their level of physical activity. However, this was unstructured and short-lived, indicating a lack of motivation and did not result in an improvement in quality of life. It is noteworthy that many patients frequently commented that they felt that they were insufficiently motivated to perform exercise at home. Indeed, patients with PAD frequently associate specific barriers to exercise including; comorbidity, lack of specific advice and lack of supervision (Bartelink *et al.* 2004). Many patients do not feel safe or comfortable in undertaking unsupervised exercise. Hence, in the absence of increased physical activity the patients in the control group perceived that their general health status and role limitation emotional status had deteriorated following the 24-week intervention period. This is what one would expect, since intermittent claudication is a progressive deteriorative condition and general health status would be expected to progressively decline.

Similarly to the SF-36 *v2* questionnaire, an improvement in the general bodily pain and discomfort domain of the EQ-5D was only observed in the upper-limb training group of patients, following the 24-week intervention period. However, an improvement in the general health domain of this questionnaire was only observed in the upper-limb training group of patients, compared to the control group, whereas improvements were observed in both exercise training groups in the SF-36 *v2* questionnaire. Again, differences in questionnaire design could account for this observation. The SF-36 *v2*

asks a series of specific questions, regarding patient's perceptions of general health, asking them to compare themselves to other individuals, whereas the EQ-5D uses a scale, rather like a thermometer, on which best imaginable state is marked by 100 and worst imaginable marked by 0 (Health Policy, 1990). It is possible that the lower-limb training group could relate to specific questions on general health better using this style of response and that this could account for the differences between questionnaires following the 24-week intervention period.

As previously suggested, intermittent claudication typically affects the physical functioning domains of the SF-36 questionnaire, and it is therefore not surprising that no significant differences were observed either between or within groups in the domains of perceived self care, the ability to perform usual activities or in anxiety and depression status following the intervention period in the EQ-5D questionnaire. Equally, it is not surprising that in the absence of a structured exercise training programme, patients in the control group perceived a deterioration in mobility status in the EQ-5D. The extremely sedentary lifestyle of patients with intermittent claudication (Sieminski and Gardner, 1997) places them at high risk for subsequent decline in mobility and physical function (Visser *et al.* 2002), even if symptoms remain unchanged (Gardner *et al.* 2004b). This was observed in these control patients since although they perceived a deterioration in mobility, their measured CD and MWD were unchanged. Decreased mobility undermines the capacity for activities of daily living such as the ability to feed and dress oneself and attend to personal hygiene (Buckwalter, 1997). However, despite their perception of decreased mobility, the overall self-care perception of these patients was unaffected.

Compliance to the assessments and exercise training sessions

Compliance to an exercise intervention can be a problem for any patient (Buckwalter, 1997). However, considering that intermittent claudication is a frequent complaint among the elderly (Perakyla *et al.* 1998), compliance can be particularly problematic for these older individuals who have been sedentary for decades (Buckwalter, 1997). Given the age of the patients in this study (median age 69 years, range 50-85 years), an excellent level of compliance to the assessment and twice-weekly training sessions (98.9 % and 99.9 %, respectively) was observed. Attendance to exercise rehabilitation studies of similar duration has been reported to be 75% of the possible exercise training classes (Gardner *et al.* 2004a), yet it can be as low as 45% (Creasy *et al.* 1990). High

attendance nevertheless has been reported for a 24-week resistance training programme in these patients (90 ± 6%), but the high level of compliance was attributable to the transportation service that was provided to and from the training and evaluation sessions in that study (McGuigan *et al.* 2001). This present study was unable to offer such a service, and therefore patients had to utilise both public and private transport, in order to attend the *Centre*.

The level of compliance in this present study contrasts with those reported in previous exercise studies of 12-weeks to 6 months in duration which have reported compliance to range from 65% to 87% (Carter *et al.* 1989; Ekroth *et al.* 1978; Gardner *et al.* 2004a) (Gardner *et al.* 2001; Tsai *et al.* 2002). However, shorter studies of 6-12 weeks in duration have reported high attendance and low patient dropout figures (Walker *et al.* 2000; Tsai *et al.* 2002). Studies with fewer patients (61 to 64 patients) have reported patient dropout to be 17% (Gardner *et al.* 2001; Tsai *et al.* 2002). The patient dropout rate in this present study was also low (~ 9.6 %), with only 10 of the 104 patients recruited withdrawing within the course of the 24-week intervention period. As detailed in the Results section, these were primarily for medical reasons. Previous randomised controlled studies of similar magnitude to the present study have experienced a dropout rate in the region of 31%, with 29 out of 94 patients recruited dropping out (Andriessen *et al.* 1989).

The high compliance rates experienced in this present study can be attributed to the strong emphasis placed on providing good group training sessions, reinforced with social adhesion where possible. Previous recommendations have suggested that elderly patients should be urged to exercise with like-minded companions and be educated to obtain realistic expectations, as they will become discouraged and discontinue if anticipated swift and dramatic improvements are not forthcoming (Buckwalter, 1997). Assessing and accommodating a patient's time of day preferences to undertake exercise was undoubtedly beneficial.

The high attendance rates in this present study can be attributed to the determination of the training/assessment session supervisor and the degree of flexibility applied in accommodating patients who were, for various reasons such as hospital, GP or dental appointments, unable to attend a pre-arranged meeting. A strong emphasis was always placed on such appointments being a priority. Patients unable to attend their particular

group session, were always allocated a further similar time of day group session, without being made to feel that they were inconveniencing anyone, and thus eliminating any feelings of guilt which might otherwise have arisen. Patients were seen on an individual basis, if alternative group sessions were not possible.

The value of group sessions, can not be dismissed. The social success in this study, could be attributable to the fact that PAD is not widely known about among the general public, and the intermittent and largely hidden symptoms of claudicants are not easily understood by others, including their own families (Binnie *et al.* 1999). Thus patients during an exercise class often report that the opportunity to talk to fellow sufferers is helpful and reassuring (Binnie *et al.* 1999). Indeed, as in previous observations some patients may have undoubtably benefited more from its psychological dimension than from the exercise (Binnie *et al.* 1999). Recognizing the value of this aspect of an exercise class, the exercise supervisor consciously but unobtrusively promoted and facilitated it (Binnie *et al.* 1999).

Maintaining motivation, providing advice, encouragement and ensuring that each and every patient, regardless of grouping felt at ease with the investigator were undoubtedly the strongest factors which contributed to the high compliance figures observed for the assessment and exercise training sessions. Indeed, these proved to be essential in overcoming the barriers to exercise. Patients were actively encouraged to approach the investigator if they experienced any difficulty or concern or potential problem at any time-point during the intervention period of the study.

Additional factors, which could have contributed to the high compliance to the assessment and exercise training sessions, included the structure of the interval training regime. Interval training regimens enable a greater amount of higher-intensity work to be performed in a given time than could be achieved with continuous exercise of a similar nature and therefore optimise the stimulus for cardiovascular adaptations (Astrand and Rodhal, 1986). Thus, training regimens based on short, higher-intensity interval exercise which include interpolated rest intervals may be more effective at producing rapid, symptomatic improvement in patients with symptomatic PAD (Walker *et al.* 2000) and other cardiovascular conditions including chronic heart failure, than continuous exercise regimens.

During the supervised exercise training sessions all patients were motivated to exercise to their optimum capability within the limits previously defined. However, the 2-min rest period which followed each 2-min exercise bout was sufficient to allow any pain or discomfort to pass. This was particularly important for patients in the lower-limb exercise training group, who experienced some instances of extreme pain in the buttock, thigh or calf regions, depending on the site of their atherosclerotic lesions. Patients were urged to express their feelings of exertion and pain as honestly as possible during all training sessions.

The initial consultation session in this present study, undoubtedly played a major role regarding this studies success. Though comprehensive, it was lengthy and time consuming, lasting on average approximately 1.5 hr per patient. However, it is believed that without such an investment of time during the initial visit, the patient dropout rate during this present study would have been considerably higher and similar to those observed in other studies. Similarities can be drawn here with physician counselling, in which positive instruction and encouragement can make the difference between progressive immobility and deterioration, and an active, rewarding old age (Buckwalter, 1997). The initial consultation session served primarily to inform and educate patients on realistic expectations, however a degree of trust and a rapport between patient and investigator was developed and also a feeling of ease in the new surroundings. The regular contact and excellent rapport between the patients undergoing exercise training and the investigator undoubtedly played a major role and was crucial to the success of this present study. Regular contact with the control group of patients was achieved via weekly telephone contact.

Patient attrition was also minimised in the control group of patients who were only required to attend the Centre at 6-weekly intervals for assessment purposes. All patients in the control group were actively encouraged to "keep walking and stop smoking" (Housley, 1988), as per the advice which they would have received in the hospital setting and initial consultation visit in the *Centre*. Weekly telephone calls with the control patients provided them with emotional support which was comparable to that being received by patients randomised to the supervised exercise training classes. During the weekly phone calls, physical activity status was assessed via completion of the PAD-PAR questionnaire. Patients also had an opportunity to discuss anxieties concerning their walking impairment.

Physical activity status between groups

This study indicates that increases in self-reported physical activity were well-balanced between both supervised exercise training groups, as assessed using the PAD-PAR questionnaire. Physical activity is an important variable to consider in these patients given its potential role in subsequent cardiovascular disease morbidity and mortality (Otis *et al.* 2000). Knowledge of physical activity levels and tight control of the exercise training stimulus allows more robust conclusions to be drawn about the relative efficacy of different exercise regimens, and the extent to which symptomatic improvement can be attributed to supervised exercise, as opposed to changes in home-based physical activity.

Despite their advancing years, some patients continued to be in full or part-time employment. Over the course of the intervention period there were no observed changes in either the work or household activity domains of the PAD-PAR questionnaire, further highlighting that in the main, elderly patients maintain regular routines with regards to shopping activities, gardening, cleaning and general household chores, with very little fluctuation observed in any of the study groups over time. In a previous study of 51 patients with PAD, the PAD-PAR questionnaire indicated that approximately 94% of activities performed by PAD patients with intermittent claudication are either of low or very low intensity and less than 2% of activities are of high intensity (Otis *et al.* 2000). This is in line with the findings of this present study, since patients with intermittent claudication initially felt reluctant to engage in high intensity exercise.

The overall amount of physical activity undertaken by patients in both training groups increased throughout the intervention period, as indicated by an increased score in the leisure time (recreational) domain of the PAD-PAR questionnaire. This amounted to around 11 MET-h.wk^{-1}. Although increased scores in this domain of the PAD-PAR have been reported after 24-weeks of treadmill exercise training, following which scores increased by 39 MET-h.wk^{-1} (Regensteiner *et al.* 1996), no changes in PAR scores have been observed following 12-weeks of strength training (Regensteiner *et al.* 1996). In the latter study (Regensteiner *et al.* 1996), the improvement in peak walking time was 123% following 24-weeks of treadmill exercise training, as measured by a graded treadmill protocol. Increases in the overall amount of physical activity undertaken by patients in the exercise training groups in the present study might, in some way at least, explain the observed improvements in both CD and MWD.

The values for self-reported physical activity levels presented in this study (151 ± 8 and 158 ± 7 MET-h.wk^{-1} for the lower- and upper-limb exercise training groups, respectively) are in agreement with the values reported by Regensteiner *et al.* (1996) (Regensteiner *et al.* 1996) for patients with PAD (155 ± 31 MET-h.wk^{-1}), but considerably higher than those presented by other authors, who have reported PAD-PAR scores in the range of 109 – 119 MET-h.wk^{-1} (Otis *et al.* 2000; Gardner *et al.* 2001). One explanation for this discrepancy may be the fact that some activities may have gone unreported in some patients due to poor recall (Otis *et al.* 2000). By comparison, healthy older subjects from a previous population study (San Luis Valley Diabetes study) have been reported to have a PAR score of 268 ± 49 MET-h.wk^{-1} (Regensteiner *et al.* 1991).

A further possible explanation for the discrepancy in physical activity between studies is that in this study during the initial consultation session, a patient's current physical activity status and exercise habits (walking, utilising an exercise bike in the home setting, swimming, dancing, bowling etc) were thoroughly investigated. During the consultation session, and prior to study group randomisation, the general hospital advice of "stop smoking and keep walking" (Housley, 1988) was given to all patients, with the emphasis being placed on increasing patients level of physical activity. At this stage and throughout the study period all patients were treated equally with regards to the advice given to them. With each patient their interest in the various types of physical activity were more deeply explored. Suggestions were made to each patient for increasing their level of physical activity within safe limits of perceived exertion in the home setting. Some patients requested and were given copies of the Borg RPE scales, since some patients initially expressed an interest in increasing their level of physical activity, thus these scales could help patients gauge their intensity of physical activity in the home setting.

When questioned, three-quarters of the patients randomised to the control group felt that the study had provided them with an incentive to perform physical activity. This was probably due to the fact that patients had taken on board the "stop smoking and keep walking" recommendation (Housley, 1988) and heeded the encouragement which was given to all patients during the consultation session. This advice was re-enforced on a weekly basis through telephone contact with these control patients. These patients increased their leisure time physical activity level in the home environment through

increased participation in community based physical activities such as walking, dancing, swimming, bowling and the use of personal exercise bikes.

Despite this encouragement, an increase in leisure time physical activity (as assessed by the PAD-PAR questionnaire) was only observed up to the 12th week of the intervention period in these control patients. This indicates that self motivation is short-lived. Furthermore, at the end of the 24-week intervention period these patients did not perceive any change in their physical activity status, despite increases in physical activity being observed up to the 12th week. An increase in self-reported physical activity is not necessarily reflected by an improvement in walking performance, since no difference in actual walking ability (CD or MWD) was observed in these patients at any assessment time-point. It therefore appears that the form of exercise which is undertaken has to be specific and at an appropriate intensity to generate any defined clinical improvement.

The PAD-PAR has been criticised as not being an accurate measurement of free-living daily physical activity when compared to energy expenditure using the criterion method of doubly labelled water, and the PAD-PAR questionnaire measures have been reported to correlate poorly with clinical measures of PAD severity (Otis *et al.* 2000). One plausible reason why PAD-PAR responses are poorly correlated with the energy expenditure of physical activity is that the majority of physical activity performed by patients with claudication is unstructured (walking in and around the home) and more difficult to accurately report than more structured types of activities (Otis *et al.* 2000). It has also been suggested that the PAD-PAR responses are prone to over-reporting bias, resulting from an average of approximately 9 hr of self-reported physical activity per day (Otis *et al.* 2000). Indeed Otis *et al* (Otis *et al.* 2000) believe that the PAD-PAR questionnaire is not a clinically useful tool in determining the physical activity level of patients with intermittent claudication.

The main reason for using the PAD-PAR measure in this study was to ensure that self-reported physical activity was balanced between the two exercising groups, rather than being used to precisely quantify the level of physical activity performed by any one group. As it is likely that any reporting bias would be controlled for by randomisation, our results show that the increase in self-reported physical activity level was well-balanced across the supervised exercise training groups. In addition to the supervised

exercise classes, a few patients undertook extra leisure time walks or other activities such as swimming or cycling on an exercise cycle in the home setting. This may raise the question whether changes in lifestyle, rather than the exercise regime itself influenced the results. Additional changes in lifestyle were only observed in the initial weeks of the intervention study. Patients reported that due to the time commitment involved in attending the *Centre* on a twice weekly basis for the supervised training sessions, they had difficulty in physically committing themselves to extra physical activity in the community setting. Furthermore, it is believed that the improvement in walking performance in both exercise training groups can be attributable to the supervised exercise classes and not to changes in lifestyle, since for reasons stated these were minimal in only a few patients.

The self-perception of physical activity status was increased in both exercise training groups, in relation to baseline and control patients following the 24-week intervention period. When questioned, the majority of patients (91% and 93% of patients in the lower- and upper-limb training groups, respectively) stated that the study had provided them with an incentive to perform physical activity. These patients thus suggested that they were more inclined to continue keeping active in the home environment and community-setting through physical activities such as walking, dancing, swimming, bowling and the use of personal exercise bikes. These patients expressed an interest in pursuing such activities following the 24-week intervention period.

The use of the penultimate power output achieved in the respective arm- or leg-cranking assessments enabled exercise training intensity, used in the supervised training sessions to be balanced between the groups, equating to 85-90% of the respective limb specific peak $\dot{V}O_2$, ensuring a similar cardiovascular stimulus between training modalities. In addition to peak power output, monitoring of HR, perceived exertion and perceived pain ensured that the correct training intensities were used in the supervised exercise sessions. The reassessment of patients at 6-weekly intervals ensured that the exercise stimulus was maintained at this level throughout the intervention period and the interval style training regimen enabled exercise of this intensity to be well tolerated by the patients.

Chapter 5 - Intervention Study Conclusions

This is the first study to comprehensively examine the influence of upper- and lower-limb aerobic exercise training on walking performance in patients with PAD and the effects that these have on functional capacity, community-based walking ability, pain tolerance, confidence in walking, quality of life and physical activity status. Knowledge of physical activity levels and tight control of the exercise training stimulus allow more robust conclusions to be drawn about the relative efficacy of both exercise regimens. Furthermore increases in self-perceived physical activity status as observed in this study, might be associated with patients being more physically independent (Gardner *et al.* 2001).

The findings of this randomised controlled trial indicate that the time course of improvement in walking performance following both exercise training regimens were similar throughout the 24-week intervention period. These results confirm earlier preliminary findings (Walker *et al.* 2000) that both upper- and lower-limb weight supported aerobic exercise training provide an adequate stimulus for evoking improvements in walking performance in patients with PAD. In this present study improved walking performance was associated with an improvement in a patient's general health status, self-perceived walking ability, with perceived improvements in walking distance, speed and stair climbing ability. This study also suggests that the improvements in walking performance following upper-limb training are due to a combination of central cardiovascular and/or systemic mechanisms, in addition to an improvement in walking confidence and an adaptation in exercise pain threshold, which might enable patients to walk further beyond the 'pain barrier'. Such an adaptation in pain threshold might also explain the perceived improvement in bodily pain, physical functioning and energy and vitality domains of quality of life observed in these patients.

These findings demonstrate the effectiveness of alternative aerobic exercise interventions for patients with PAD. Arm-cranking was very well tolerated by our patient cohorts, who were able to exercise at high exercise intensities using the interval training regimen. At this point in time, we do not envisage that arm-crank training would ever be used in isolation from leg-crank training, nor be considered the preferential treatment of choice. Rather, that arm-crank training might be used in

conjuction with a program of other alternative exercise training modalities such as leg-cranking, or that a staged rehabilitation approach might be taken. Arm-crank training could be a very useful strategy for improving cardiovascular function and exercise pain tolerance in patients that have become physically inactive due to the discomfort that they encounter during walking, and may be particularly beneficial during the early stages of a rehabilitation program.

Chapter 6 – Follow-Up Study Results

6.1 Patient attendance and compliance to the follow-up assessment sessions

Of the 94 patients (32, 30 and 32 from the lower-, upper-limb and control groups, respectively) who completed the 24-week intervention period, compliance to the 6-, 12-, 24- and 48-week follow-up assessments was high (Table 27), since only 16% of patients were unable to attend the 48-week follow-up time-point, primarily for medical reasons.

Table 27. Number of patients attending at each follow-up assessment time-point.

Follow-up assessment	**Lower-limb training**	**Upper-limb training**	**Control group**
6 weeks	28	30	28
12 weeks	29	30	28
24 weeks	29	26	28
48 weeks	27	25	27

Four patients from the lower-limb training group were unable to attend at the 6-week follow-up stage. One sustained a stroke, one developed bowel cancer, one underwent knee replacement surgery and one went on holiday to Australia. At the 12-week time-point, the patient who had gone on holiday to Australia had returned and was re-assessed. Two patients had sustained an M.I. prior to the 48-week follow-up assessment.

All patients that had completed the intervention in the upper-limb training group were able to attend the 6- and 12-week follow-up assessments. However, four patients were unable to attend at the 24-week time-point. One patient developed a back problem, due to a slipped disc, one had sustained an M.I., one developed bowel cancer and a further patient developed lung cancer. Prior to the 48-week-time point a further patient underwent surgery for a ruptured aortic aneurysm.

Four patients from the control group were unable to attend at 6-week's follow-up. One had sustained a stroke, one an M.I., one received surgery for an aortic aneurysm repair and one was too ill, due to flu. At the 12- and 24-week follow-up time-points the patient who was ill with flu at 6-weeks attended, however a further patient sustained a stroke. Prior to the 48-week follow-up session a further patient developed bowel cancer.

6.2 Post-intervention study walking performance

6.2.1 Claudication distance

The CD of patients assigned to the lower- and upper-limb exercise training programme remained increased up to the 24- and 48-week follow-up assessment time-points, respectively, in relation to baseline measures (P at least < 0.05). However these observed increases were not significantly different from the patients assigned to the control group (Table 28). Data were not normally distributed and are presented as median, with range in parentheses. Statistical analyses were performed on log transformed data.

Table 28. Claudication distance data at each assessment stage of the follow-up period.

	Post-intervention follow-up period	Lower-limb training	Upper-limb training	Control group
Claudication Distance (m), (range)	**Baseline Data**	67 (20 - 274)	104 (25 - 430)	94 (28 - 408)
	6 weeks post	106** (26 - 312)	164** (53 - 402)	94 (23 - 503)
	12 weeks post	104** (27 - 287)	159** (34 - 425)	96 (37 - 438)
	24 weeks post	96** (35 - 317)	149** (58 - 513)	100 (17 - 396)
	48 weeks post	80 (31 - 301)	151* (33 - 455)	106 (20 - 350)

Data are presented as median value (with ranges). Statistical significance: * $P < 0.05$; ** $P < 0.01$ indicate significantly higher than baseline.

Considering the mean individual percentage difference data, compared to baseline, at the 48-week follow-up time-point, CD in the lower- and upper-limb exercise trained groups remained improved by 48% and 39%, respectively ($P < 0.05$; Figure 28). The difference between the two exercise trained groups was not significant.

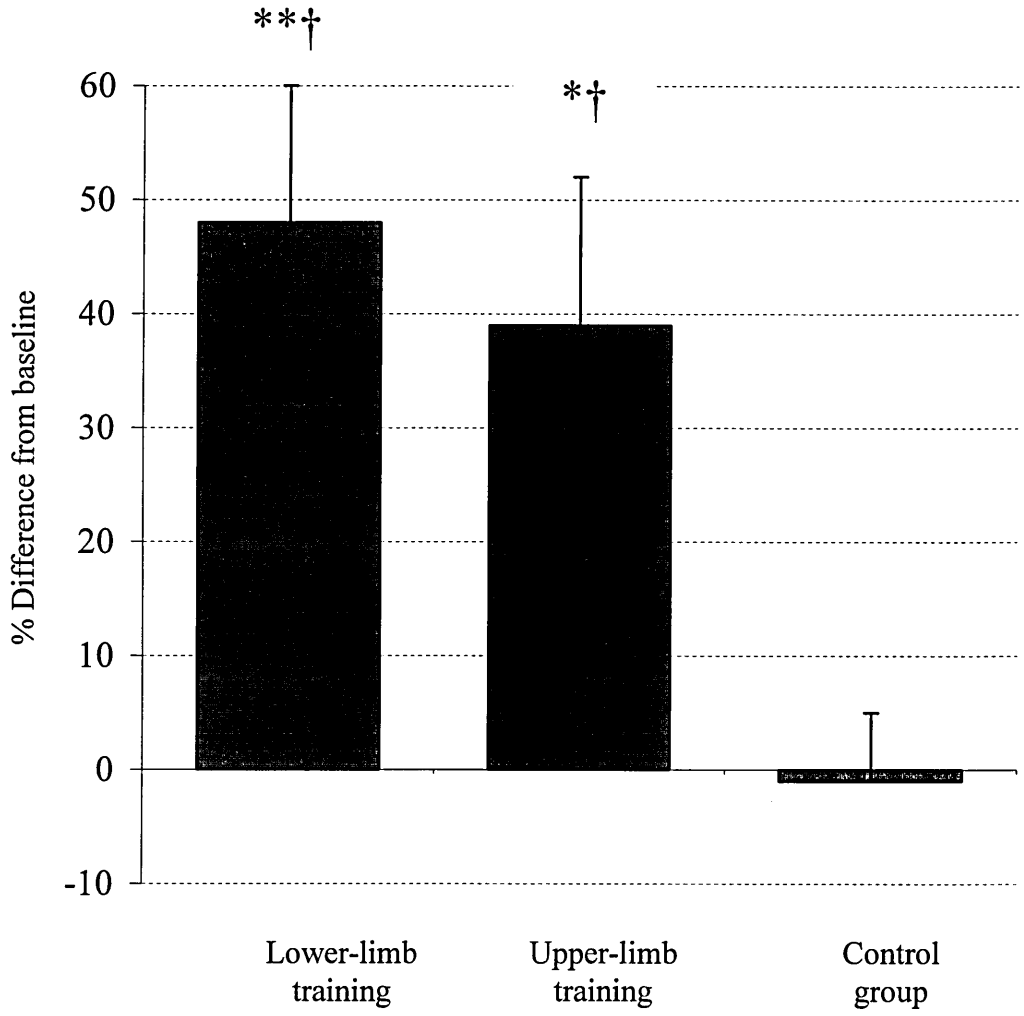


Figure 28. Claudication Distance at 48-weeks follow-up. Data are presented as the mean % difference at the 48-week follow-up time-point, in relation to baseline measures, ± SEM. † $P < 0.05$ indicates significance between the lower- or upper-limb exercise trained groups and the control group of patients.

Up to 12-weeks following the 24-week intervention period, CD remained improved to a greater extent in the group of patients who had undertaken lower-limb exercise training, compared to baseline values (Table 29).

Table 29. Mean percentage change in CD from baseline at each assessment stage of the follow-up period.

	Post-intervention follow-up period (weeks)	Lower-limb training	Upper-limb training	Control group
% Difference in CD from Baseline	6	+ 57**‡	+ 43*‡	- 2
	12	+ 61**‡	+ 39**‡	2
	24	+ 46**†	+ 45*†	1
	48	+ 48*†	+ 39*†	- 1

Data are presented as the mean % difference from baseline. * $P < 0.05$; ** $P < 0.05$ indicate significance from baseline. † $P < 0.05$; ‡ $P < 0.01$ indicates significance between the leg- or arm-training group and the control group of patients.

Heart rate, blood lactate, perceived exertion and perceived pain responses were assessed during the incremental walking test to assess the consistency of effort and level of pain experienced between walking assessments at the different time-points during the follow-up period.

6.2.1.1 Heart rate at claudication distance during the follow-up period

HR at CD was unchanged in all groups at each assessment time-point during the follow-up period (Figure 29).

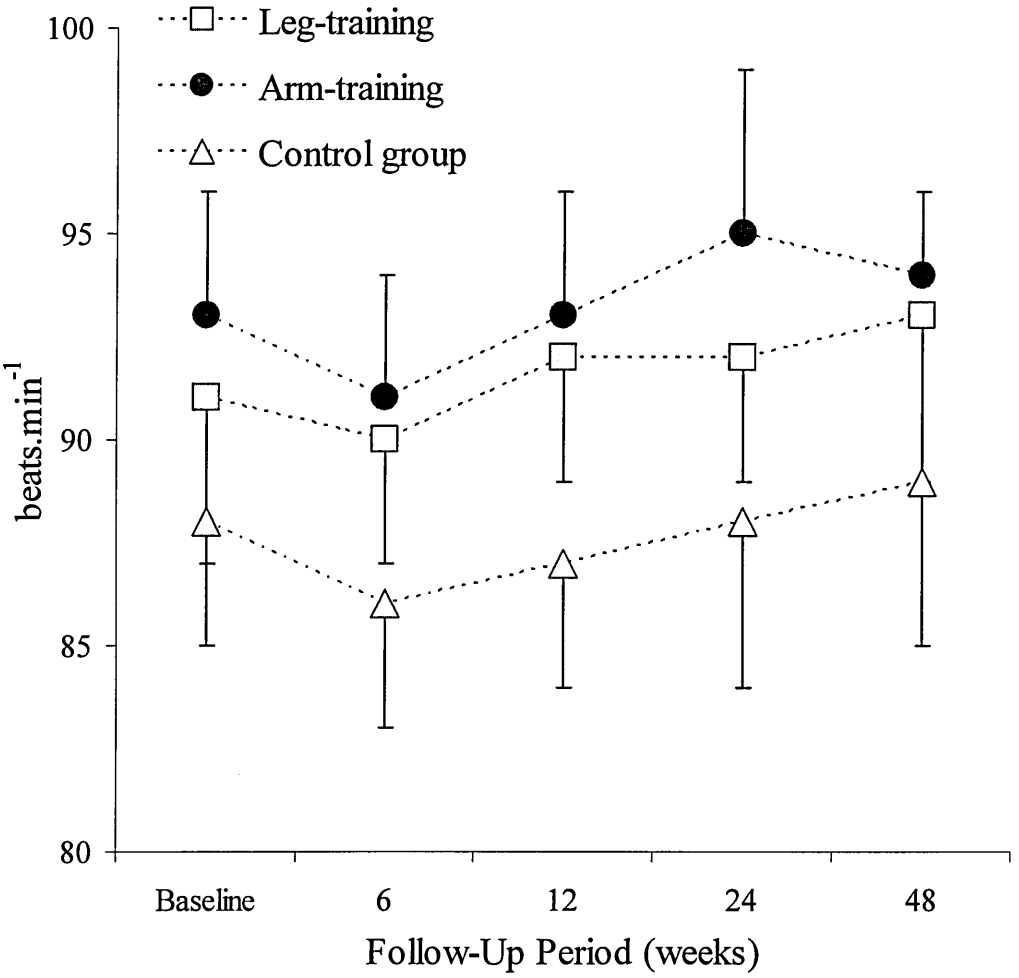


Figure 29. HR at claudication during the follow-up period. Data are presented at mean ± SEM at each assessment time-point during the follow-up period.

6.2.1.2 Perceived pain at claudication distance during the follow-up assessments

The degree of pain experienced at CD in the main was rated to be between 'extremely' and 'very weak' (i.e. 0.5 and 1 on the Borg CR-10 scale) and was consistent between groups, at the 6- and 12-week follow-up assessments. Interestingly, at the 24-week time-point, pain was rated to be less intense by both groups who had undertaken exercise training during the intervention period, compared to the control group of patients (P at least < 0.05). Furthermore, the observation in the lower-limb training group that pain was rated as less intense at CD upon completing the 24-week intervention study, in relation to baseline measures, was also observed at each follow-up assessment time-point. These patients perceived their pain to be "extremely weak" (i.e. 0.5 on the Borg CR-10 scale) compared to "very weak" at baseline ($P < 0.05$). A similar observation was also observed in the upper-limb training group up to the 24-week follow-up assessment time-point ($P < 0.05$; Table 30).

Table 30. Perceived pain (Borg CR-10 scale) at CD, at each stage of the follow-up period.

	Post-intervention follow-up period (weeks)	Lower-limb training	Upper-limb training	Control group
Perceived Pain (Borg CR-10 Scale) at CD	**Baseline**	1.0 (0.3 - 3.0)	1.0 (0.5 - 3.0)	2.0 (0.5 - 3.0)
	6	0.5** (0.3 - 3.0)	1.0* (0.3 - 2.0)	0.8 (0.3 - 3.0)
	12	0.5* (0.3 - 3.0)	0.5* (0.3 - 3.0)	0.8 (0.3 - 4.0)
	24	0.5**† (0.3 - 2.0)	0.5*† (0.3 - 2.0)	1.0 (0.3 - 3.0)
	48	0.5** (0.3 - 2.0)	1.0 (0.3 - 4.0)	1.0 (0.3 - 4.0)

Data are presented as median (range). * $P < 0.05$; ** $P < 0.01$ indicates significance from baseline measures. † $P < 0.05$ indicates significance between the leg- or arm-training group, compared with the control group of patients.

6.2.2 Maximum walking distance during the follow-up assessments

The pattern of sustained improvement in MWD at each follow-up assessment (Figure 30) was similar to that observed for CD. At the 48-week follow-up time-point, MWD remained improved by 26% and 18% in the patients who had undertook lower- and upper-limb exercise training, respectively, compared with baseline measures (P at least < 0.05; Table 31) and control patients (P at least < 0.05; Table 31). A trend indicating deterioration in MWD was observed in the control group of patients at each assessment time-point.

Table 31. Mean percentage change in MWD from baseline at each assessment stage of the follow-up period.

	Post-intervention follow-up period	Lower-limb training	Upper-limb training	Control group
% Difference in MWD from Baseline	6 weeks post	+ 33**‡	+ 23**‡	- 6
	12 weeks post	+ 29**‡	+ 25**‡	- 4
	24 weeks post	+ 27**‡	+ 22**‡	- 2
	48 weeks post	+ 26**‡	+ 18*†	- 2

Data are presented as mean % difference from baseline. * $P < 0.05$; ** $P < 0.01$ indicates significance from baseline measures. † $P < 0.05$; ‡ $P < 0.01$ indicate significance between the leg- or arm-training group and the control group of patients.

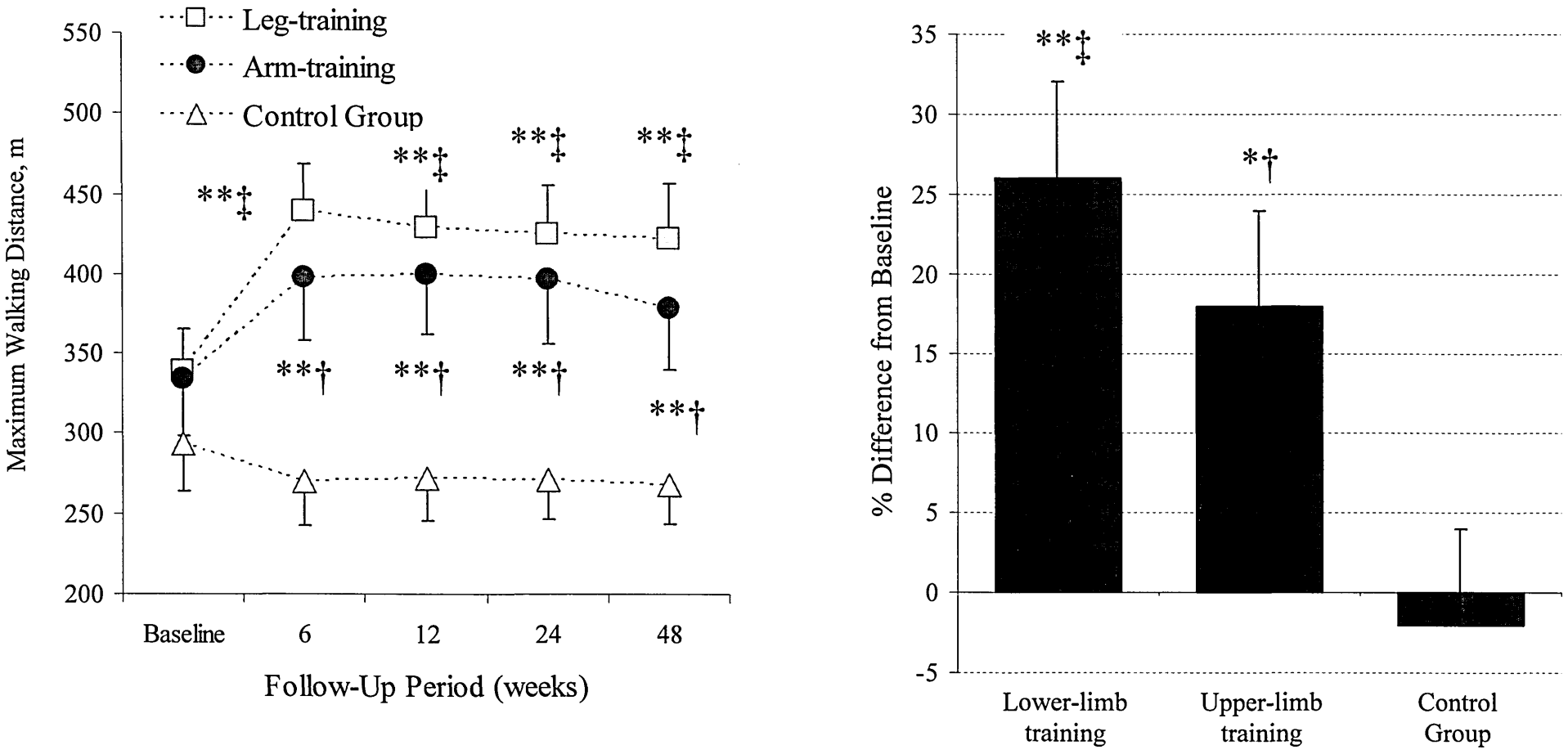


Figure 30. Maximum Walking Distance during the follow-up period. Changes in MWD (left) at 6-, 12-, 24- and 48-weeks following the intervention period, and mean difference in MWD at the 48-week follow-up time point (right). Changes in MWD data are presented as mean ± SEM. * $P < 0.05$; ** $P < 0.01$ indicates significance from baseline. † $P < 0.05$; ‡ $P < 0.01$ between leg- or arm-exercise training and the control group of patients.

6.2.2.1 Peak heart rate at MWD

The sustained improvements in MWD in both groups of patients who had undertaken exercise training were associated with HR at MWD being greater compared to the control group of patients at each follow-up assessment time-point (P at least < 0.05; Figure 31). However compared to baseline measures, HR at MWD only remained increased in the group who had undertaken lower-limb exercise training (109 ± 4 vs. 121 ± 5 beats.min^{-1}; comparing pre-intervention and data at the 48-week follow-up time-point), indicating these patients were continuing to attain a higher level of cardiovascular stress at MWD up to 48-weeks follow-up. The differences in HR between the two training groups were not significant.

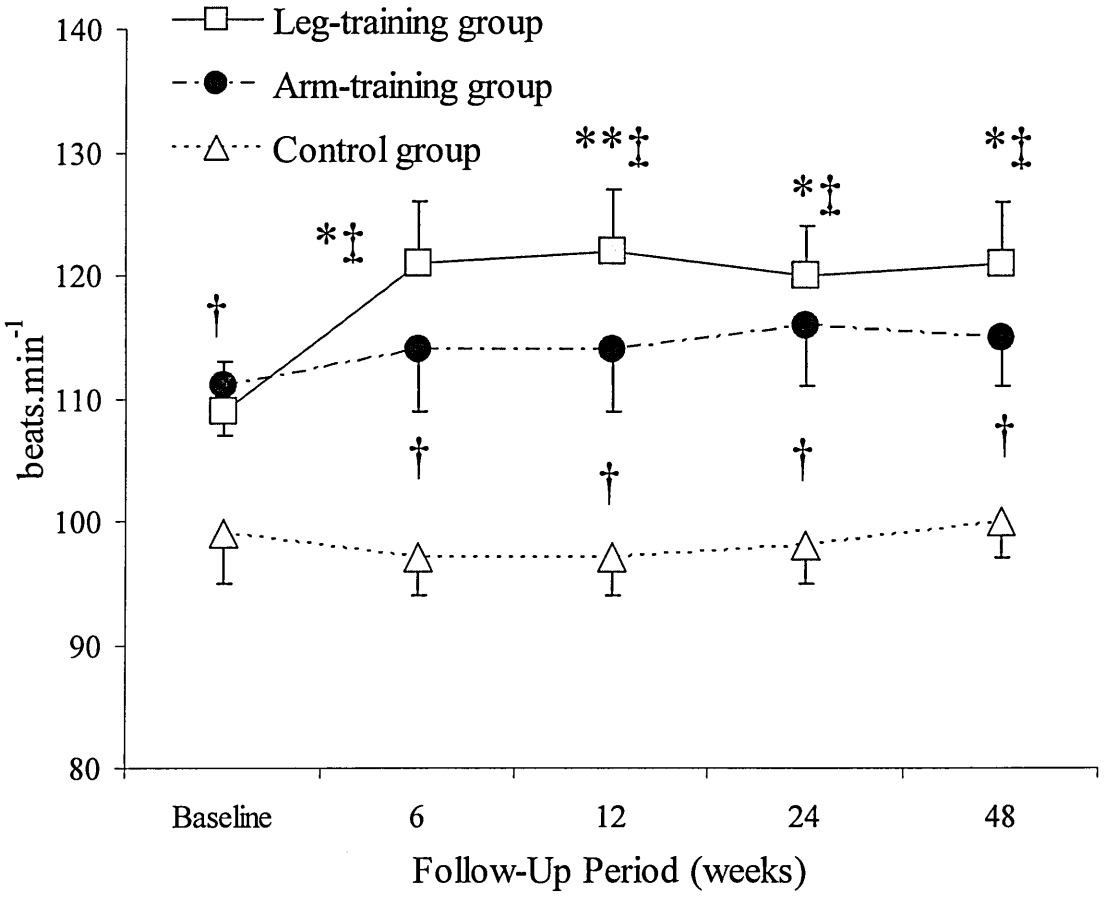


Figure 31. HR at MWD during the follow-up period. Data are presented as mean ± SEM at each assessment stage, during the follow-up period. * $P < 0.05$; ** $P < 0.01$ indicates significance compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ indicates significance between the leg- or arm-training group and the control group of patients.

6.2.2.2 Peak blood lactate at MWD

At the 12-week follow-up assessment time-point, blood lactate concentration at MWD was higher in both groups who had undertaken exercise training, compared to the control group of patients (P at least < 0.05). At the 24-week follow-up time-point, blood lactate was only higher in the patients who had undertaken upper-limb exercise training, in relation to control patients ($P < 0.05$), whereas at the 48-week follow-up time-point the concentration of blood lactate at MWD was only higher in the patients who had undertaken lower-limb exercise training compared to the control group of patients ($P < 0.05$; Figure 32). No changes in these parameters were observed in the control group of patients.

6.2.2.3 Peak blood lactate 5-min post MWD

At the 6- and 12-week follow-up time-points, the concentration of blood lactate taken 5-min post MWD was higher in the group of patients who had undertaken lower-limb exercise training only, in relation to baseline measures (P at least < 0.01) and control patients ($P < 0.05$). At the 24- and 48-week follow-up time-points blood lactate 5-min post MWD remained increased in these patients, in relation to baseline measures only ($P < 0.05$). In the group of patients who had undertaken upper-limb exercise training, differences were only observed at the 12- and 24-week follow-up time-points, in relation to the control group ($P < 0.05$). No changes in these parameters were observed in the control group of patients (Figure 32).

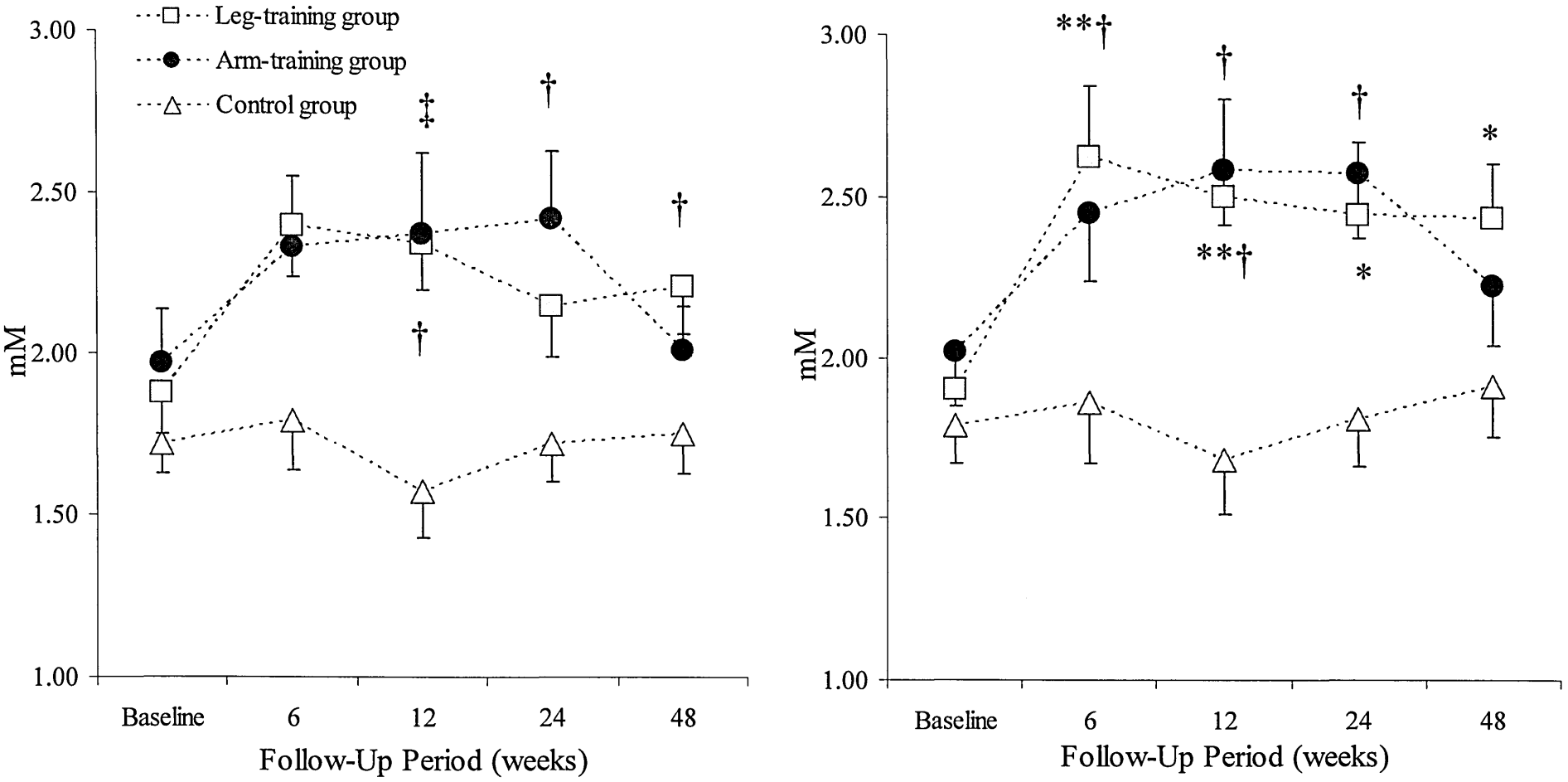


Figure 32. Blood lactate concentration at MWD and 5-min post MWD during the follow-up period. Data are presented as mean ± SEM, at each assessment stage during the follow-up period. * $P < 0.05$; ** $P < 0.01$ indicates significance from baseline. † $P < 0.05$; ‡ $P < 0.01$ indicates significance between the leg-or arm-training group and the control group of patients.

6.2.2.4 Perceived exertion and perceived pain at MWD

At the 12-week follow-up time-point an increase in the amount of pain experienced at MWD was observed in both groups who had undertaken exercise training, compared to the control group of patients ($P < 0.05$). An increase in RPE was associated with this increase in perceived pain at this time-point, in patients who had undertaken lower-limb exercise training, compared to the upper-limb training and control group of patients ($P < 0.05$). However compared to baseline measures, at each follow-up time-point perceived pain at MWD only remained increased in the group who had undertaken upper-limb exercise training (P at least < 0.05; Table 32).

Table 32. Perceived pain (Borg CR-10 scale) and perceived exertion (Borg RPE scale) at MWD at each assessment stage of the follow-up period.

	Follow-Up period (weeks)	Lower-limb training	Upper-limb training	Control group
Perceived Pain (Borg CR-10 Scale) at MWD	**Baseline**	7.0 (3.0 - 11.0)	5.0 (3.0 - 11.0)	6.0 (3.0 - 11.0)
	6	7.0 (2.5 - 11.0)	7.0* (1.0 - 11.0)	5.0 (2.0 - 10.0)
	12	7.0† (3.0 - 11.0)	7.0**† (3.0 - 11.0)	5.0 (1.0 - 10.0)
	24	7.0 (3.0 - 11.0)	9.0* (2.0 - 11.0)	6.0 (2.5 - 11.0)
	48	7.0 (3.0 - 11.0)	7.0* (3.0 - 11.0)	5.0 (2.0 - 10.0)
Perceived Exertion (Borg RPE Scale) at MWD	**Baseline**	13.0 (11.0 - 20.0)	15 (7.0 - 20.0)	15.0 (7.0 - 19.0)
	6	15.0 (11.0 - 20.0)	15.0 (6.0 - 20.0)	15 (9.0 - 20.0)
	12	17.0 †Ψ (12.0 - 20.0)	14.0 (6.0 - 20.0)	14.5 (7.0 - 19.0)
	24	16.0 (13.0 - 19.0)	15.0 (6.0 - 20.0)	15.0 (11.0 - 19.0)
	48	16.0 (12.0 - 20.0)	15.0 (6.0 - 20.0)	14.5 (8.0 - 20.0)

Data are presented as median (range). * $P < 0.05$; ** $P < 0.01$ indicate significance compared to baseline. † $P < 0.05$ indicates significance between the leg- or arm-training group and the control group of patients. Ψ indicate significance between the leg- and arm-training group of patients.

6.2.3 Confidence in walking during the follow-up period

The retained improvement in walking ability observed in both patient groups that had undertaken exercise training was also associated with a continued improved confidence in walking at all follow-up assessment time-points compared to baseline measures ($P < 0.01$). However, the increased confidence in walking was not significant when compared with the control group of patients. Furthermore, walking confidence was also improved in the control group of patients at 6-, 12- and 24-week follow-up time-points ($P < 0.05$; Table 33), but not at the 48-week follow-up time-point.

Table 33. Patients perceived confidence in walking at each assessment stage of the follow-up period.

	Post-intervention Follow-Up period (weeks)	Lower-limb training	Upper-limb training	Control group
Confidence in Walking	**Baseline**	5.0 (2.0 - 10.0)	5.0 (2.0 - 10.0)	8.0 (1.0 - 10.0)
	6	9.0** (4.0 - 10.0)	9.0** (1.0 - 10.0)	9.0* (3.0 - 10.0)
	12	9.0** (4.0 - 10.0)	10.0** (5.0 - 10.0)	9.0* (3.0 - 10.0)
	24	9.0** (4.0 - 10.0)	10.0** (5.0 - 10.0)	9.0* (3.0 - 10.0)
	48	9.0** (3.0 - 10.0)	10.0** (3.0 - 10.0)	9.0 (3.0 - 10.0)

Data are presented as the median (range). * $P < 0.05$; ** $P < 0.01$ indicates significance from baseline. Data are presented from 19, 15 and 17 patients from the lower-, upper-limb training and control groups, respectively.

6.2.4 Changes in ABPI during the follow-up period

Although walking ability remained improved over baseline measures in the patients who had undertaken exercise training, resting ABPI was unchanged at each assessment time-point throughout the post-intervention follow-up period in all study groups. A significant decrease in post shuttle-walk ABPI was observed 6- and 12-weeks post-intervention in both groups that had undertaken exercise training (P at least < 0.05), and

at 24-weeks follow-up in the group that had undertaken upper-limb exercise training, compared to baseline measures ($P < 0.05$; Table 34). These data again suggest that these patients were pushing themselves further beyond the pain barrier at these time-points.

Table 34. Resting, post shuttle-walk and mean individual difference in ABPI at each assessment stage of the follow-up period.

	Post-Intervention Follow-Up Period (weeks)	Lower-limb training	Upper-limb training	Control group
Resting ABPI	**Baseline**	0.67 (± 0.03)	0.66 (± 0.03)	0.72 (± 0.04)
	6	0.65 (± 0.03)	0.66 (± 0.03)	0.69 (± 0.04)
	12	0.64 (± 0.03)	0.64 (± 0.03)	0.67 (± 0.03)
	24	0.65 (± 0.03)	0.65 (± 0.04)	0.68 (± 0.04)
	48	0.65 (± 0.03)	0.62 (± 0.04)	0.62 (± 0.04)
Post Shuttle-Walk ABPI	**Baseline**	0.45 (± 0.04)	0.42 (± 0.03)	0.50 (± 0.05)
	6	0.34 (± 0.03)**	0.32 (± 0.02)**†	0.45 (± 0.05)
	12	0.34 (± 0.03)**†	0.34 (± 0.03)*†	0.47 (± 0.04)
	24	0.36 (± 0.04)	0.32 (± 0.03)*†	0.45 (± 0.04)
	48	0.36 (± 0.04)	0.36 (± 0.04)	0.42 (± 0.04)
Mean Difference in ABPI (Post - Resting)	**Baseline**	- 0.22 (± 0.03)	- 0.26 (± 0.03)	- 0.23 (± 0.03)
	6	- 0.32 (± 0.02)**	- 0.34 (± 0.03)†	- 0.24 (± 0.03)
	12	- 0.31 (± 0.03)**†	- 0.30 (± 0.03)	- 0.21 (± 0.03)
	24	- 0.29 (± 0.03)	- 0.34 (± 0.03)*†	- 0.23 (± 0.02)
	48	- 0.29 (± 0.04)	- 0.26 (± 0.03)	- 0.21 (± 0.03)

Data are presented as mean ± S.E.M, at each assessment stage of the post-intervention period. * $P < 0.05$; ** $P < 0.01$ indicate significance from baseline. † $P < 0.05$ indicates significance between the leg or arm-training group and the control group of patients.

6.3 Walking Impairment Questionnaire domains

6.3.1 Claudication pain severity, walking distance, walking speed and stair climbing ability during the follow-up period

Claudication pain severity remained unchanged in all groups throughout the follow-up period. Both groups who had undertaken exercise training continued to perceive an improvement in walking distance throughout the follow-up period, compared to baseline measures (P at least < 0.05). Compared to the control group, a retained improvement in walking distance was perceived up to the 24- and 48-week follow-up time-points in the lower- and upper-limb exercise training groups, respectively ($P < 0.05$). Both groups who had undertaken exercise training perceived a retained improvement in walking speed at 12- and 24-week follow-up time-points, in relation to control patients (P at least < 0.01). However, compared to baseline measures this improvement was only significant in patients who had undertaken upper-limb exercise training ($P < 0.01$). Stair climbing ability also continued to be improved in both groups who had undertaken exercise training up to the 24-week follow-up time-point, in relation to baseline measures (P at least < 0.05). This perceived improvement was only significant at the 24-week and at the 12-, 24- and 48-week time-points in patients who had undertaken lower- and upper-limb exercise training, respectively ($P < 0.05$; Table 35).

Table 35. Changes in WIQ domains at each assessment stage of the follow-up period.

	Post-intervention period (weeks)	Lower-limb training	Upper-limb training	Control group
Claudication Pain Severity	**Baseline**	50 (25-75)	50 (0-75)	50 (25-75)
	6	50 (25-75)	50 (0-75)	50 (25-100)
	12	50 (25-75)	50 (25-75)	50 (25-75)
	24	50 (25-75)	50 (0-75)	50 (25-75)
	48	50 (25-75)	50 (0-100)	50 (25-75)
Walking Distance	**Baseline**	26 (4-89)	27 (0-100)	18 (2-89)
	6	44 (7-89)*†	51 (2-100)*†	21 (2-89)
	12	54 (10-83)*†	51 (1-100)*†	24 (3-83)
	24	40 (9-83)*†	55 (2-100)*	15 (2-100)
	48	34 (5-89)*	62 (5-100)**†	18 (3-100)
Walking Speed	**Baseline**	28 (0-89)	28 (0-93)	28 (3-89)
	6	50 (15-89)	50 (0-89)	29 (10-89)
	12	39 (25-78)†	50 (3-93)**‡	26 (0-83)
	24	43 (22-89)†	50 (0-100)**‡	32 (0-83)
	48	36 (7-89)	50 (0-100)	33 (3-89)
Stair Climbing Ability	**Baseline**	42 (8-88)	42 (8-100)	30 (0-100)
	6	67 (8-100)**	67 (8-100)	33 (0-100)
	12	67 (8-100)*	79 (4-100)**†	33 (0-100)
	24	67 (13-100)*†	67 (0-100)*†	42 (0-100)
	48	50 (8-100)	79 (0-100)†	38 (0-100)

Data are presented as median (range), at each assessment stage of the intervention period. * $P < 0.05$; ** $P < 0.01$ indicates significance from baseline. † $P < 0.05$; ‡ $P < 0.01$ indicate significance between the leg- or arm-training group and the control group of patients.

6.4 Physical activity

6.4.1 Self perception of physical activity status during the follow-up period

An increase in physical activity status was observed in all three study groups at 6-, 12- and 24-week follow-up time-points, relative to baseline measures ($P < 0.01$). However, at the 48-week follow-up time-point physical activity status remained increased in both groups that had undertaken exercise training, relative to baseline measures ($P < 0.01$; Table 36).

Table 36. Patients self-assessed physical activity status.

	Post-Intervention Follow-Up Period (weeks)	Lower-limb training	Upper-limb training	Control group
Physical Activity Status	**Baseline**	2.0 (0-10)	6.0 (0-10)	6.0 (0-10)
	6	6.0** (2-10)	6.0** (2-10)	6.0** (0-10)
	12	6.0** (2-10)	6.0** (2-10)	6.0** (0-10)
	24	6.0** (2-10)	6.0** (2-10)	6.0** (0-10)
	48	6.0** (2-10)	6.0** (0-10)	6.0 (0-10)

Data are presented as the median (range). ** $P < 0.01$ from baseline measures.

6.4.2 Global PAD-PAR physical activity during the follow-up period

There was no change in global physical activity status, either within or between study groups at any time-point throughout the follow-up period (Figure 33).

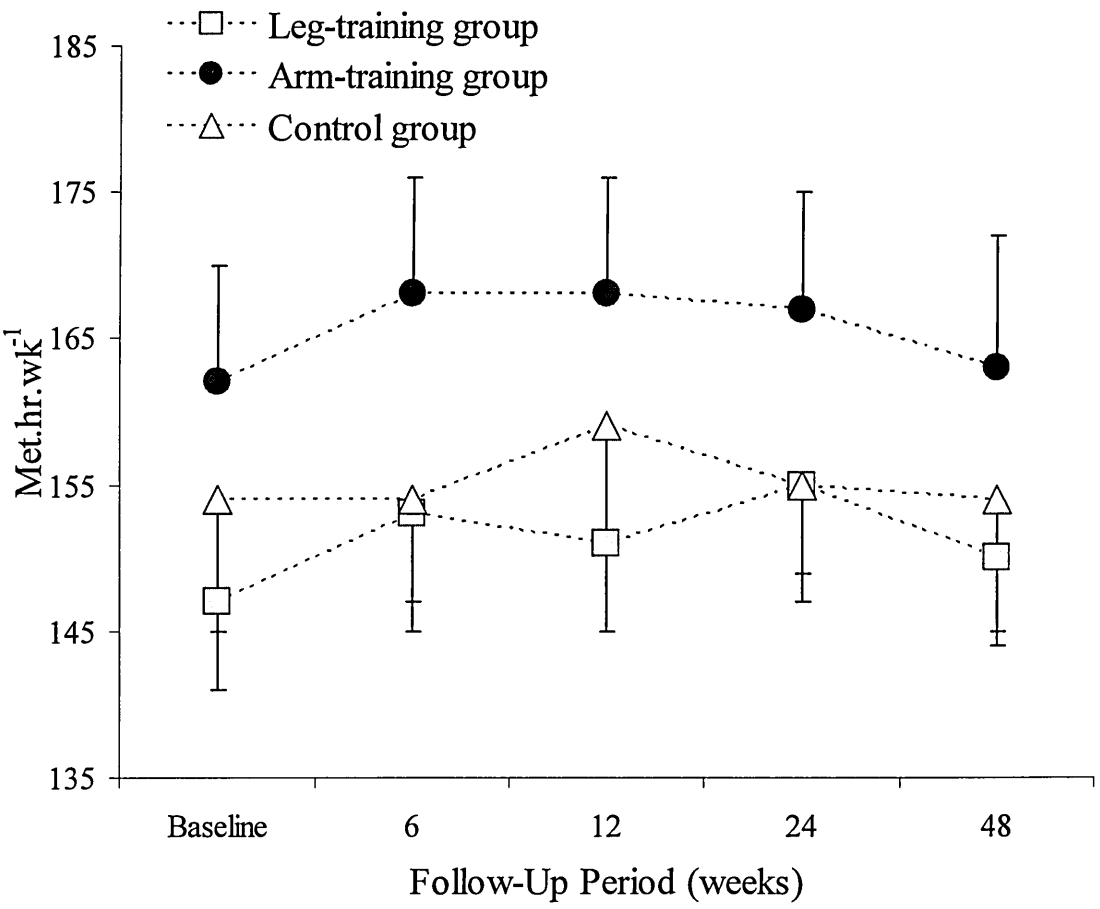


Figure33. PAD-PAR Global Physical Activity during the follow-up period. Data are presented as mean ± SEM.

6.4.2.1 PAD-PAR work, household and leisure-time physical activity

There was no difference between or within study groups in the level of work activities or in the household chores domain of the PAD-PAR questionnaire throughout the follow-up period (Figure 34). An increase in the leisure-time domain of the PAD-PAR questionnaire at the 24-week follow-up time-point relative to baseline measures was only observed in patients who had undertaken upper-limb exercise training (64 ± 5 vs. 69 ± 5 MET-h.wk^{-1}; $P < 0.05$; Figure 34).

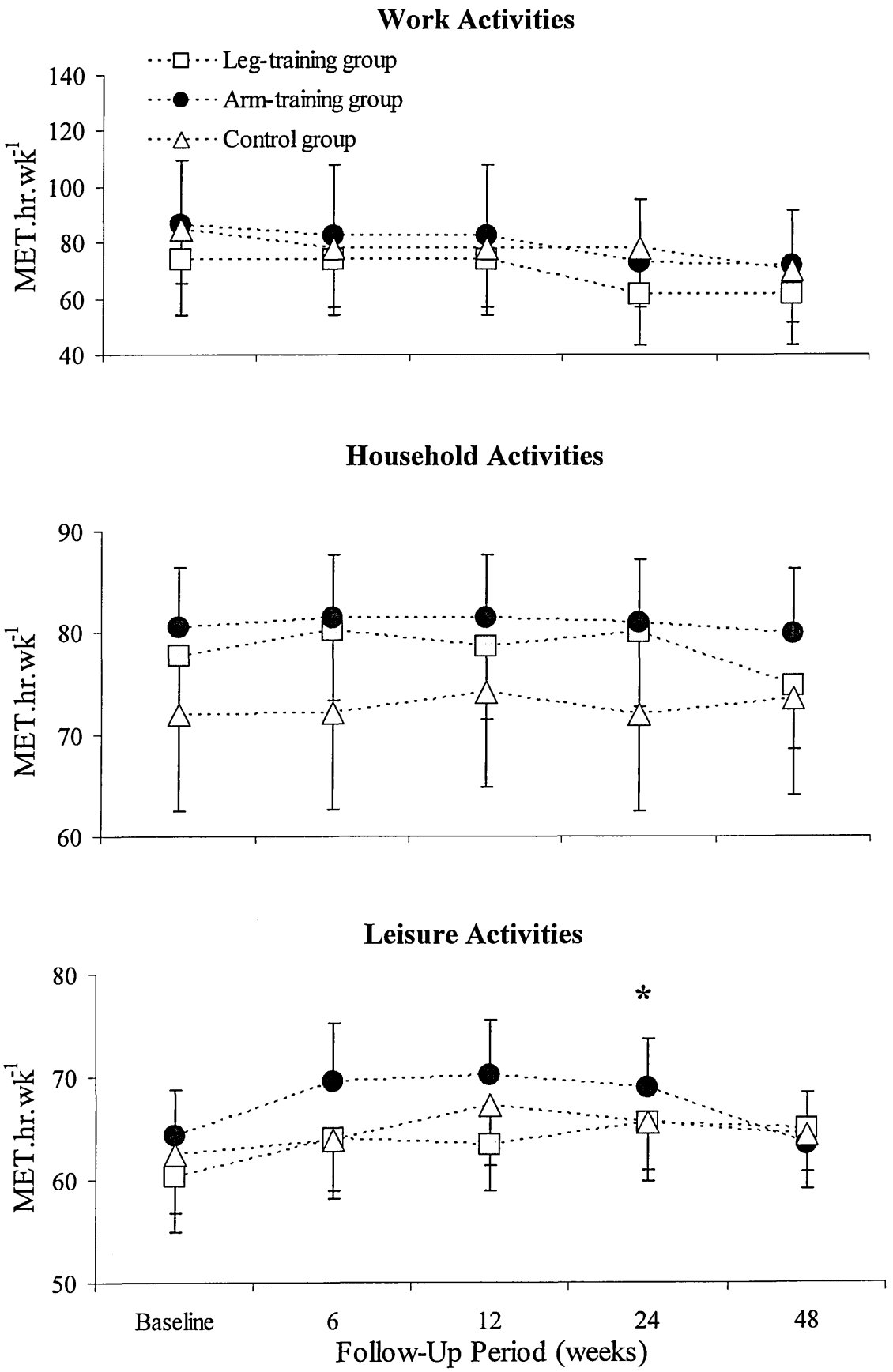


Figure 34. PAD-PAR scores relating to work, household and leisure activities during the follow-up period. Data are presented as mean ± SEM. * $P < 0.05$ indicates significance from baseline.

6.5 Quality of life – SF-36 *v2* questionnaire

6.5.1 The influence of exercise on the domains of physical function during the follow-up period

The general health of patients in the upper-limb exercise training group continued to be perceived to be better than that in the control group at 12- and 48-week follow-up time-points ($P < 0.05$). However, a persistent improvement in this domain was not observed throughout the follow-up period. The degree of bodily pain experienced by patients following the intervention period was no different to that present at baseline, although compared to the control patients, an improvement at the 12-week follow-up time-point was perceived in the group of patients who had undertaken upper-limb exercise training only ($P < 0.05$). No difference in the physical function and the role limitation physical domains of the SF-36 *v2* were observed either between or within study groups at any follow-up assessment time-point (Figure 35).

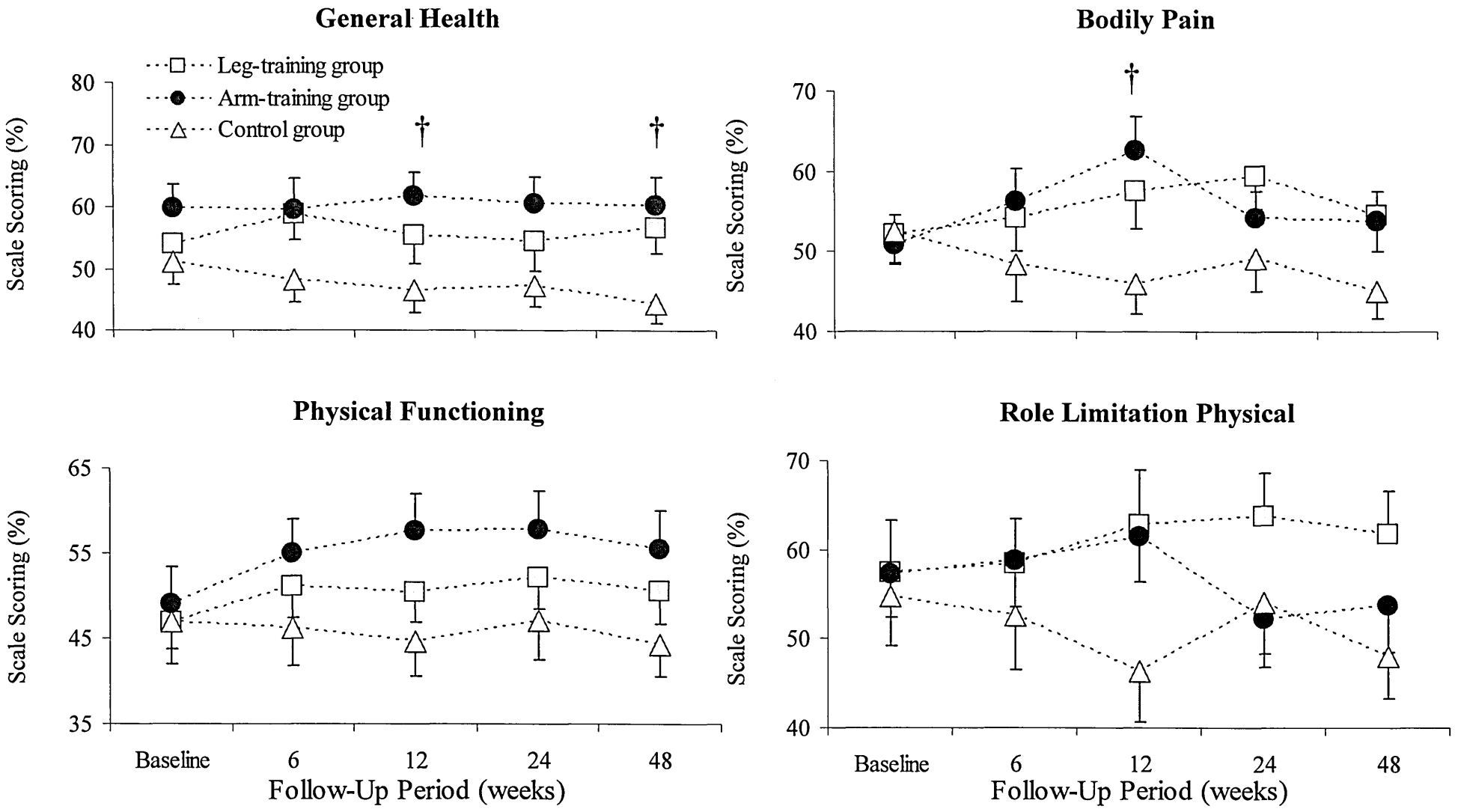


Figure 35. Physical Function domains of the Quality of Life SF-36 v2 questionnaire during the follow-up period. Data are mean ± SEM. † $P < 0.05$ indicates significance between the leg- or arm-training group and the control group of patients.

6.5.2 *The influence of exercise on the domains of mental health during the follow-up period*

Energy and vitality remained improved at 12-, 24- and 48-week follow-up time-points in patients who had undertaken upper-limb exercise training as compared to the control group of patients ($P < 0.05$; Figure 36). However, although improved, these changes were not of statistical significance when comparisons were made with the baseline measures. There was no significant difference in the mental health, social functioning or role limitation emotional domains of the SF-36 *v2* during the follow-up period, either within or between the study groups (Figure 36).

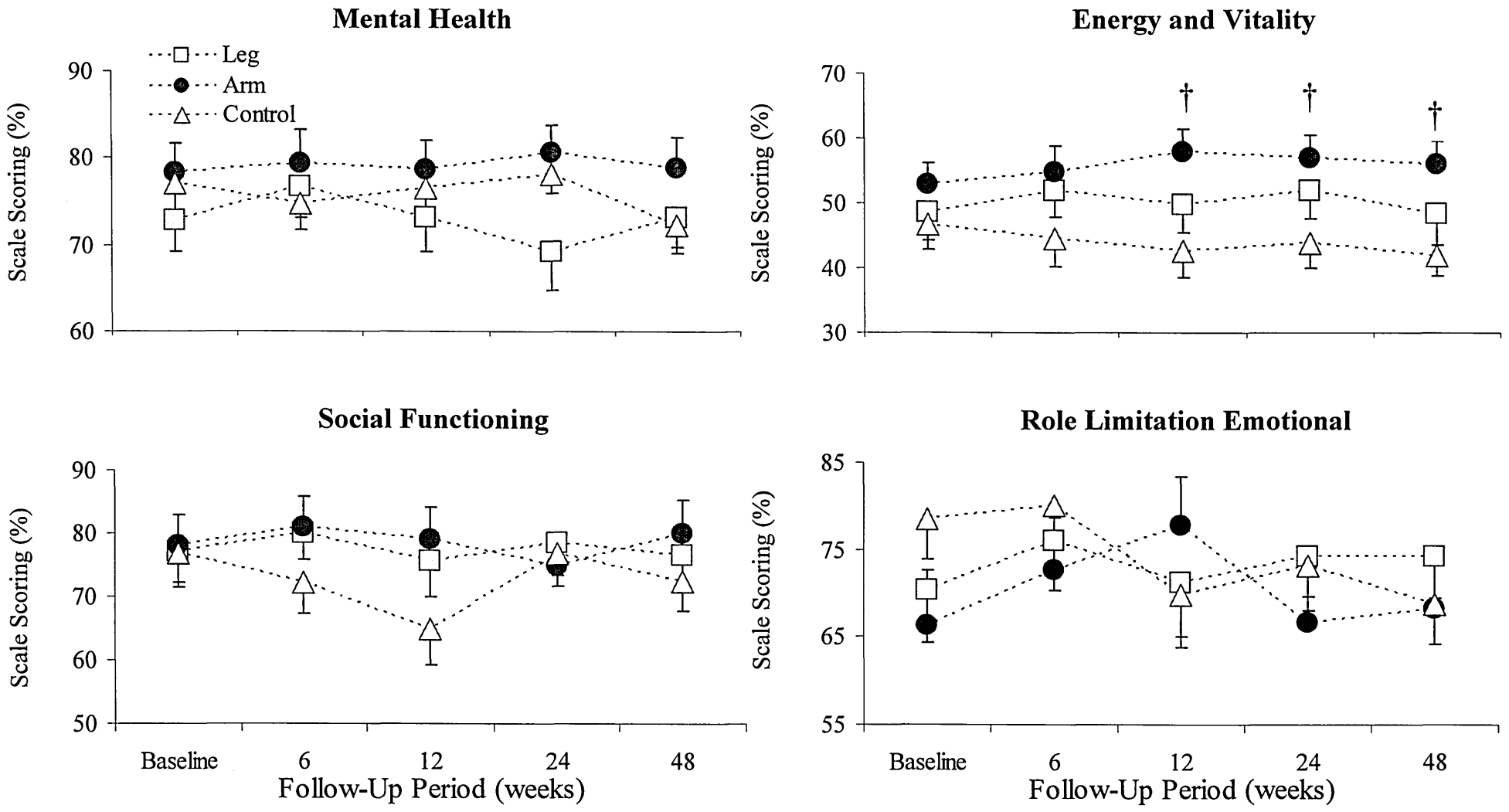


Figure 36. Mental Health domains of the Quality of Life SF-36 *v2* questionnaire during the follow-up period. Data are means ± SEM. † $P < 0.05$ indicates significance between the leg- or arm-training group and the controls.

6.6 General Health Status - EuroQol (EQ-5D) Questionnaire

The general health of patients who had undertaken lower-limb exercise training was perceived to be better at 6-, 12- and 24-week follow-up time-points, compared to baseline measures (P at least < 0.05) and up to the 12-week follow-up time-point in relation to control patients ($P < 0.05$; Table 37). Patients who had undertaken upper-limb exercise training perceived an improvement in general health and ability to perform usual activities at the 12-week follow-up time-point, compared to control patients (P at least < 0.05; Table 37). However, the difference from baseline measures in these domains, in these patients, was not significant. No changes in the domains of mobility, self care, bodily pain and discomfort, and anxiety and depression were observed at any follow-up assessment time-point, either between or within study groups (Table 37).

Table 37. EuroQol (EQ-5D) questionnaire domains throughout the follow-up period.

	Follow- Up Period (weeks)	Lower-limb Training	Upper-limb Training	Control Group
Health Status	**Baseline**	65 (40 – 95)	70 (35 – 90)	60 (40 – 95)
	6	70 (45 – 95) **†	70 (45 – 90)	55 (25 – 90)
	12	70 (40 – 100) *†	75 (50 – 90) ‡	60 (40 – 95)
	24	70 (38 – 100) *	80 (40 – 90)	60 (40 – 95)
	48	75 (35 – 95)	70 (30 – 94)	58 (40 – 94)
Mobility	**Baseline**	65 (25 – 100)	75 (50 – 100)	73 (35 – 100)
	6	60 (35 – 100)	75 (50 – 90)	70 (50 – 100)
	12	70 (45 – 100)	80 (50 – 90)	63 (50 – 95)
	24	70 (40 – 95)	80 (40 – 100)	70 (35 – 90)
	48	70 (30 – 95)	70 (40 – 90)	70 (40 – 100)
Self Care	**Baseline**	100 (70 – 100)	100 (75 – 100)	100 (30 – 100)
	6	100 (60 – 100)	98 (75 – 100)	100 (60 – 100)
	12	100 (60 – 100)	98 (70 – 100)	99 (50 – 100)
	24	100 (60 – 100)	95 (50 – 100)	93 (50 – 100)
	48	100 (10 – 100)	95 (70 – 100)	94 (70 – 100)
Usual Activities	**Baseline**	70 (25 – 100)	70 (25 – 95)	50 (30 – 100)
	6	70 (25 – 100)	70 (25 – 100)	59 (25 – 95)
	12	70 (25 – 100)	80 (25 – 100) †	60 (28 – 90)
	24	75 (25 – 100)	70 (30 – 90)	75 (30 – 100)
	48	60 (30 – 95)	75 (10 – 95)	50 (10 – 90)
Bodily Pain and Discomfort	**Baseline**	65 (25 – 90)	70 (5 – 95)	58 (25 – 100)
	6	75 (25 – 100)	75 (25 – 95)	70 (20 – 95)
	12	75 (30 – 100)	75 (25 – 90)	60 (25 – 80)
	24	65 (25 – 95)	75 (30 – 95)	70 (25 – 90)
	48	70 (25 – 95)	75 (20 – 90)	69 (20 – 90)
Anxiety and Depression	**Baseline**	80 (50 – 100)	95 (30 – 100)	90 (50 – 100)
	6	80 (40 – 100)	90 (50 – 100)	93 (75 – 100)
	12	82 (30 – 100)	92 (50 – 100)	90 (25 – 100)
	24	85 (60 – 100)	90 (60 – 100)	90 (70 – 100)
	48	80 (40 – 100)	95 (55 – 100)	90 (60 – 100)

Data are presented as median (range), at each assessment stage of the follow-up period, where 0% and 100% indicate severe difficulty and no difficulty, respectively. * $P < 0.05$; ** $P < 0.01$ indicate significance from baseline. † $P < 0.05$; ‡ $P < 0.01$ indicate significance between the leg- or arm-training group and the control group of patients.

6.7 Cardiorespiratory function throughout the follow-up period as assessed during the leg-and arm-cranking assessments

6.7.1 Peak power output

The retained improvement in walking performance observed during the follow-up period in both exercise groups was accompanied by a continued increase in peak power output at maximum exercise tolerance during the LCT up to the 48-week follow-up time-point, compared to baseline measures ($P < 0.01$) and control patients ($P < 0.01$; Table 38). Similarly, peak power output during the ACT also remained increased in both exercise groups at each follow-up time-point, compared to baseline measures ($P < 0.01$) and control patients ($P < 0.01$; Table 38).

The training effect continued to be most apparent for the specific training apparatus, although there was some cross over improvement with respect to the alternative exercise modality. As compared to baseline, maximum power output during the LCT and ACT remained increased by 21% and 14%, and by 15% and 30 % in the lower- and upper-limb training groups, respectively. These findings indicated that the improvement in peak power output for both trained and untrained skeletal muscle groups, in trained patients persisted.

Table 38. Peak power output at maximum exercise tolerance during the LCT and ACT at each assessment stage of the follow-up period.

	Follow-Up Period (weeks)	Power Output (W)	
		LCT	ACT
Lower-limb Training	Baseline	67 (38 – 96)	46 (31 – 67)
	6	81**‡ (53 – 139)	53**‡ (31 – 74)
	12	96**‡ (53 – 139)	53**‡ (31 – 81)
	24	81**‡ (53 – 124)	53**‡ (31 – 81)
	48	81**‡ (53 – 124)	53**‡ (24 – 74)
Upper-limb Training	Baseline	71 (9 – 140)	46 (17 – 82)
	6	81**‡ (38 – 153)	60**‡ (31 – 103)
	12	96**‡ (38 – 153)	53**‡ (24 – 110)
	24	96**‡ (38 – 139)	60**‡ (31 – 103)
	48	81**‡ (24 – 139)	60**‡ (31 – 110)
Control Group	Baseline	67 (24 – 105)	38 (17 – 60)
	6	53 (9 – 110)	35 (17 – 67)
	12	53 (9 – 110)	35 (17 – 67)
	24	67 (9 – 110)	38 (17 – 67)
	48	53 (9 – 110)	38 (9 – 74)

Data are presented as median (range), at each assessment stage of the follow-up period. ** $P < 0.01$ indicates significance from baseline. † $P < 0.05$; ‡ $P < 0.01$ indicate significance between the leg- or arm-training group and the control group of patients.

6.7.2 Peak $\dot{V}O_2$

During the LCT peak $\dot{V}O_2$ at maximum exercise tolerance remained improved in both exercise trained groups at the 6-week follow-up time-point, compared to baseline ($P < 0.05$) and control patients (P at least < 0.05), but at 48-weeks follow-up peak $\dot{V}O_2$ was unchanged from baseline measures in all study groups. Throughout the follow-up period, during the ACT peak $\dot{V}O_2$ was unchanged from baseline measures in both exercise trained groups. However, compared to control patients, peak $\dot{V}O_2$ remained improved in the upper-limb exercise trained patients up to 48-weeks follow-up during both the LCT and ACT ($P < 0.01$). Peak $\dot{V}O_2$ remained unchanged in the control group of patients, during both the LCT and ACT throughout the follow-up period (Figure 37).

6.7.3 Peak $\dot{V}CO_2$

The pattern of peak $\dot{V}CO_2$ responses was similar to those of peak $\dot{V}O_2$. At maximum exercise tolerance during both the LCT and ACT peak $\dot{V}CO_2$ remained increased in both exercise trained patients at the 6-week follow-up time-point compared to baseline (P at least < 0.05), but at 48-weeks follow-up peak $\dot{V}CO_2$ was unchanged from baseline measures in all study groups. Compared to control patients peak $\dot{V}CO_2$ remained increased in both exercise trained patients during the LCT at 6-weeks follow-up ($P < 0.05$). At 48-weeks follow-up during both the LCT and ACT an increase was only observed in the upper-limb trained patients, compared to the control patients ($P < 0.01$). Peak $\dot{V}CO_2$ remained unchanged during both the LCT and ACT in the control group of patients throughout the follow-up period (Figure 38).

6.7.4 Peak RER

No significant differences were observed in peak RER during the LCT, within any of the study groups over the course of the follow-up period (Figure 39). During the ACT, peak RER was higher at the 48-week follow-up time-point, compared to the control group of patients ($P < 0.01$). No other differences between or within groups were observed during the ACT (Figure 39).

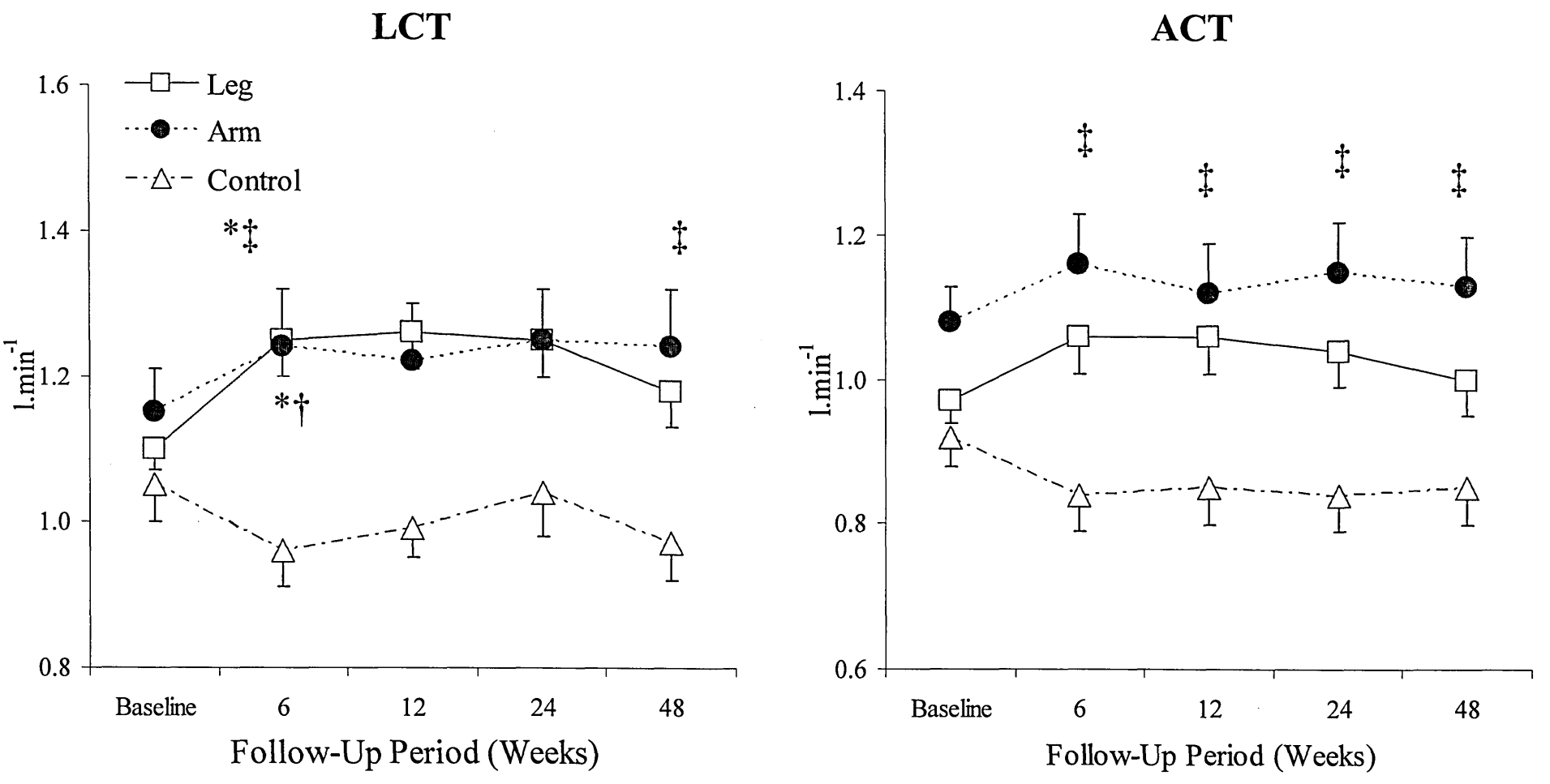


Figure 37. Changes in peak $\dot{V}O_2$ during the leg- and arm-cranking assessments during the follow-up period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the follow-up period. * $P < 0.05$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

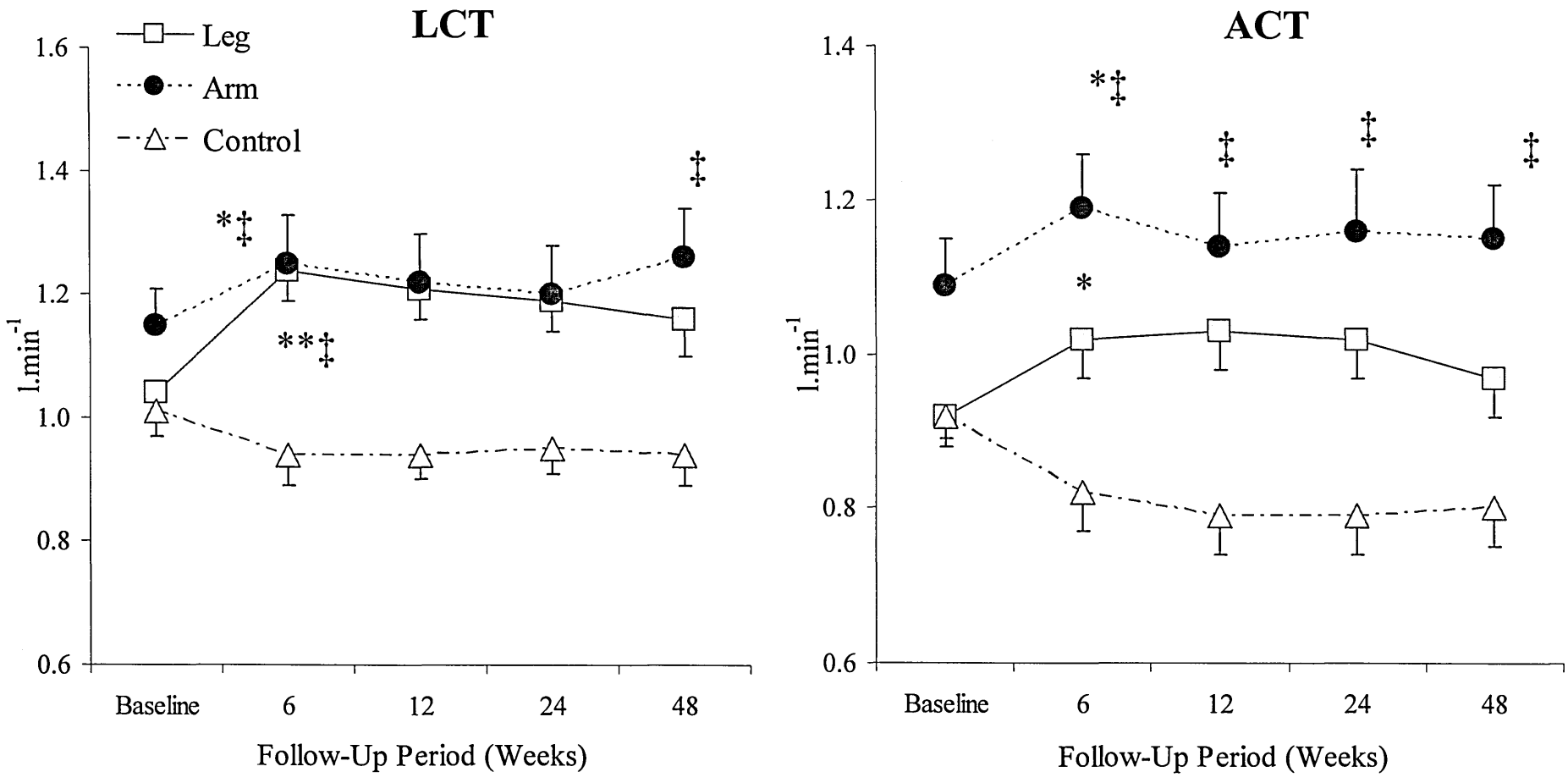


Figure 38 Changes in peak $\dot{V}CO_2$ during the leg-and arm-cranking assessments during the follow-up period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the follow-up period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

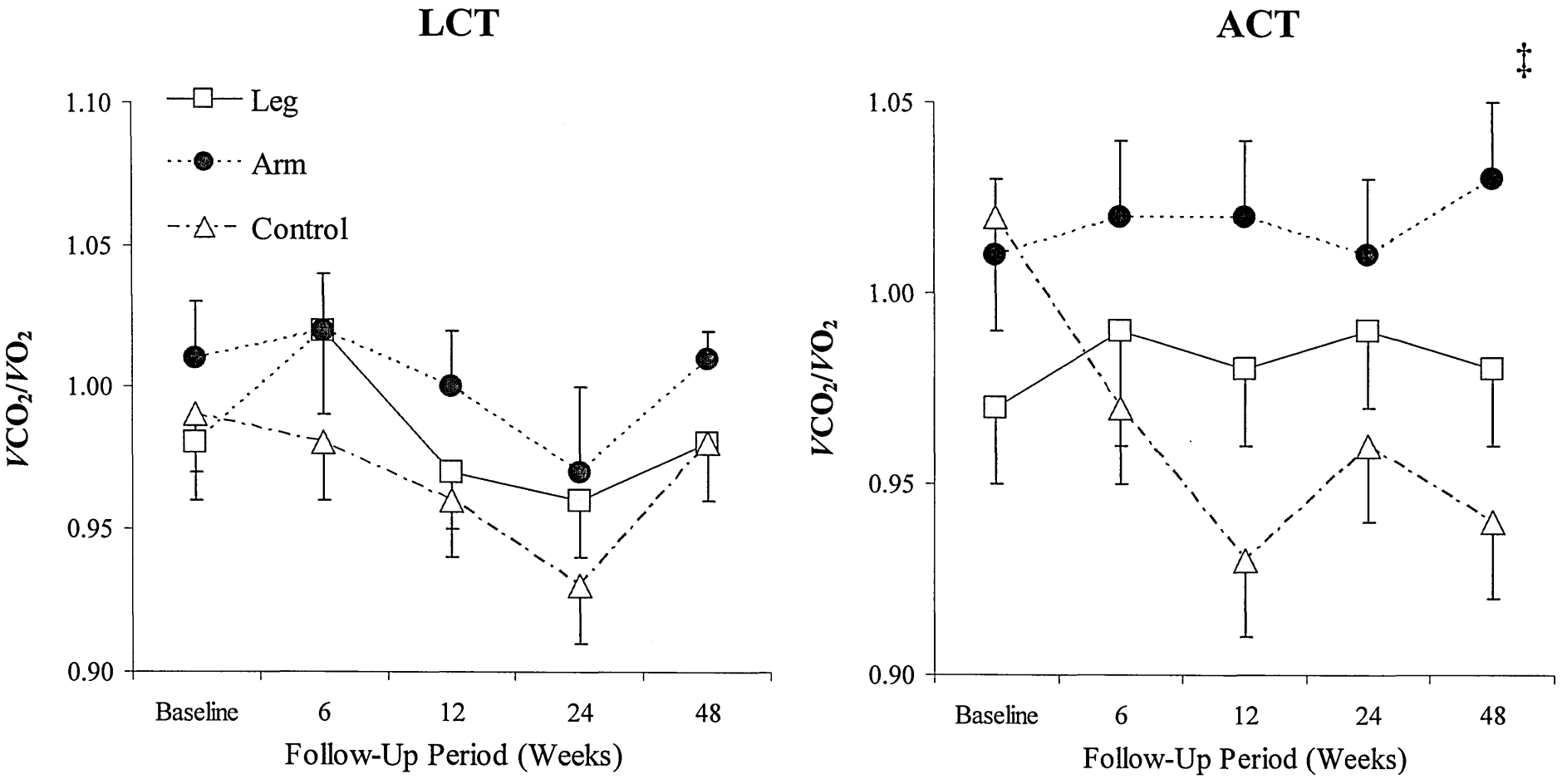


Figure 39. Changes in peak RER during the leg- and arm-cranking assessments during the follow-up period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the follow-up period. ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

6.7.5 Peak $\dot{V}E$

At maximum exercise tolerance during both the LCT and ACT, at 6-weeks follow-up peak $\dot{V}E$ remained increased in both exercise trained groups of patients, compared to baseline (P at least < 0.05). At 48-weeks follow-up an increase compared to baseline was only observed during the LCT in the group of patients who had undertaken lower-limb exercise training (38.1 ± 2.3 vs. 43.1 ± 2.7 $l.min^{-1}$; $P < 0.05$; Figure 40). Compared to control patients peak $\dot{V}E$ remained increased upto 48-weeks follow-up in both exercise trained groups, during both the LCT and ACT (P at least < 0.05). No change in peak $\dot{V}E$ was observed in the control group of patients during the LCT or ACT throughout the follow-up period (Figure 40).

6.7.6 Peak $\dot{V}E/\dot{V}O_2$

Peak values for the ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) during the LCT at maximum exercise tolerance at 6-weeks follow-up remained increased in the lower-limb trained group of patients only, compared to baseline ($P < 0.05$) and control patients ($P < 0.05$). At the 48-week follow-up time-point peak $\dot{V}E/\dot{V}O_2$ was unchanged from baseline measures in these patients (Figure 41). During the ACT peak $\dot{V}E/\dot{V}O_2$ remained increased at 6-weeks follow-up in patients who had undertaken upper-limb exercise training only, compared to baseline ($P < 0.05$) and control patients ($P < 0.05$),. However at 48-weeks follow-up this retained increase was only significant compared to the control group of patients ($P < 0.05$). No change in peak $\dot{V}E/\dot{V}O_2$ was observed in the control group of patients during the LCT or ACT throughout the follow-up period (Figure 41).

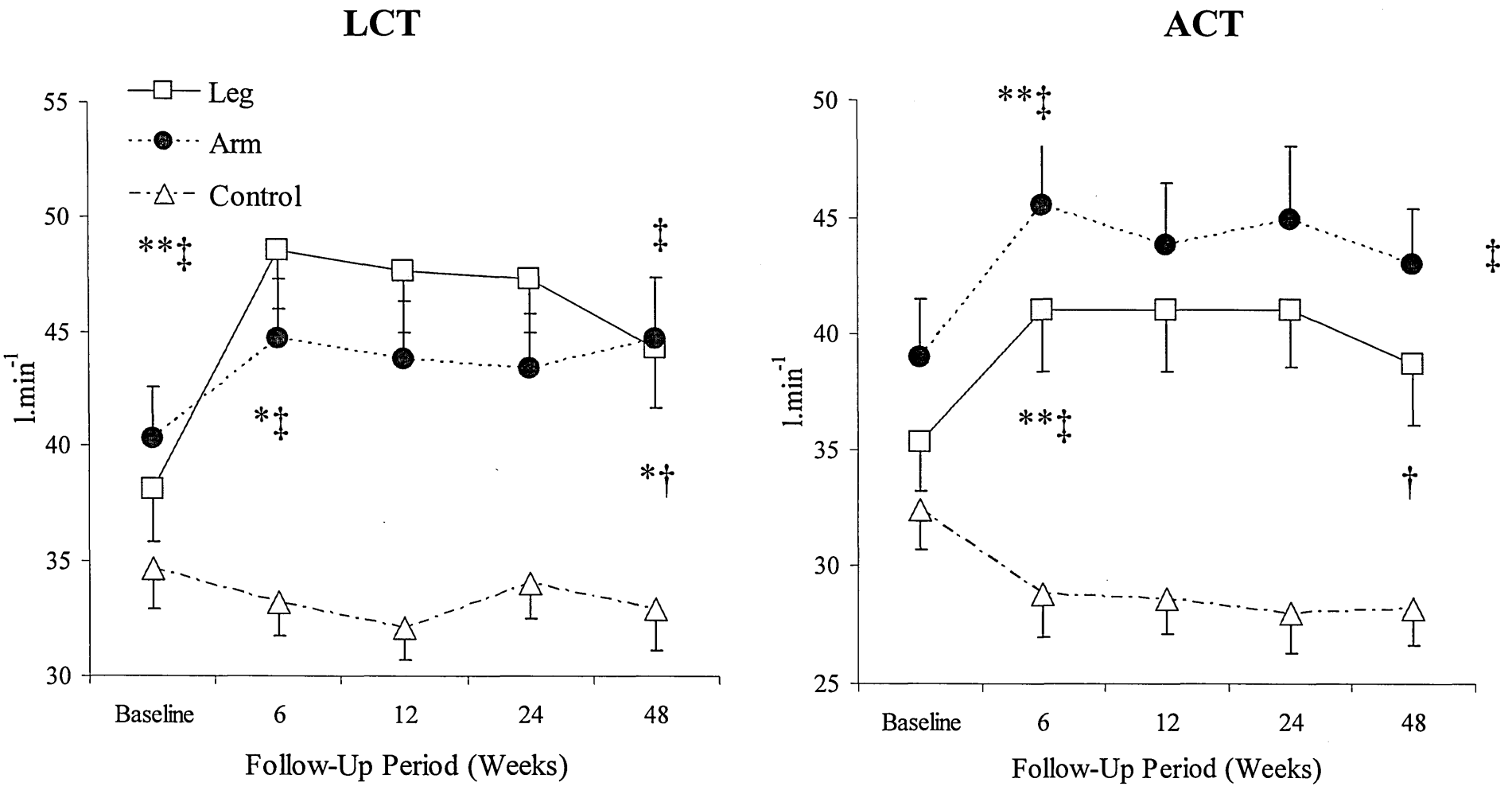


Figure 40. Changes in peak $\dot{V}E$ during the leg- and arm-cranking assessments during the follow-up period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the follow-up period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

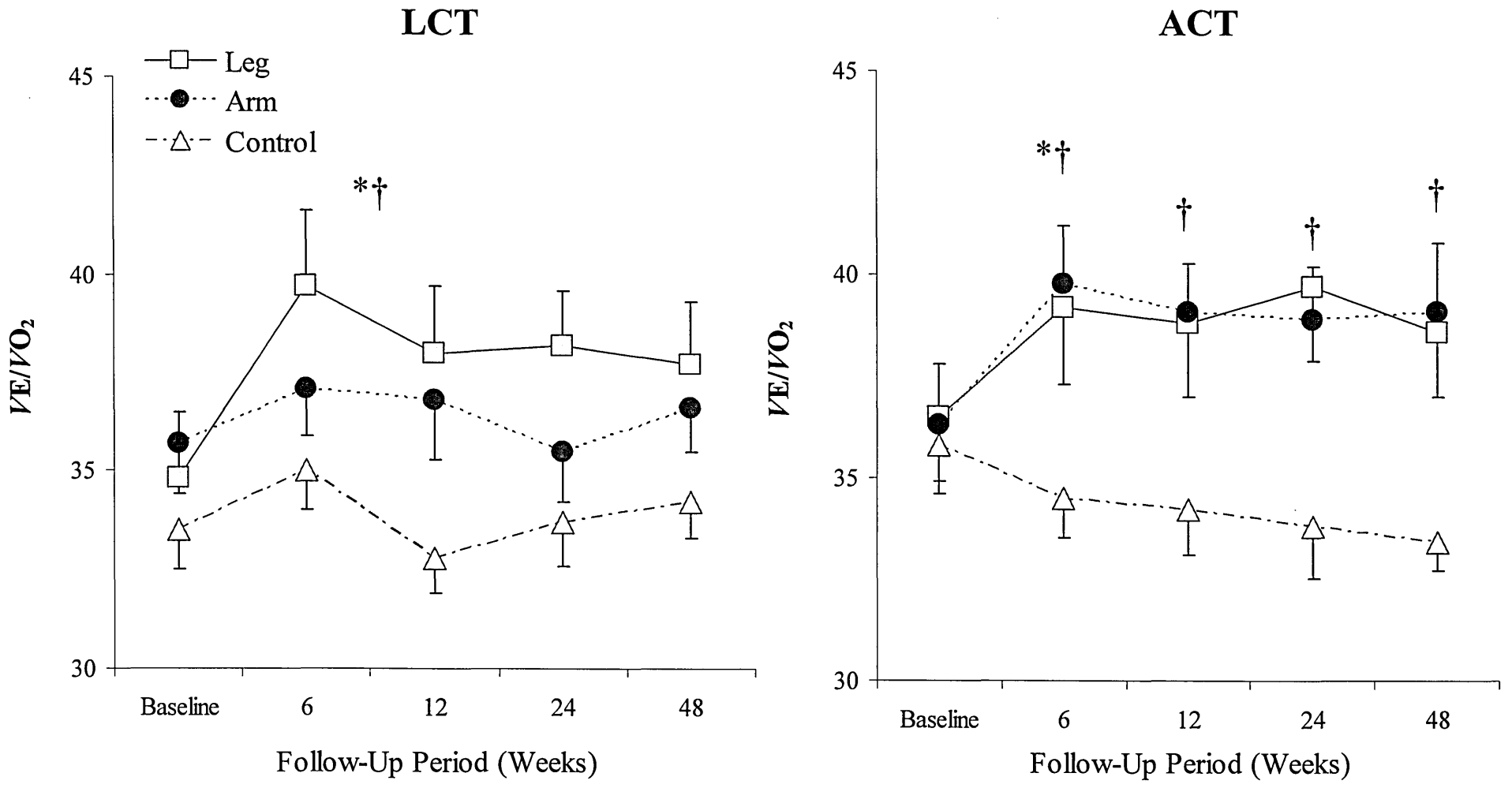


Figure 41. Changes in peak $\dot{V}E/\dot{V}O_2$ during the leg- and arm-cranking assessments during the follow-up period. Data are presented as mean ± S.E.M at maximum exercise tolerance, at each assessment stage during the follow-up period. * $P < 0.05$ compared to baseline. † $P < 0.05$ between the leg- or arm-training group and the control group of patients.

6.7.7 Peak breath frequency (Bf)

Peak breath frequency at maximum exercise tolerance remained higher during both the LCT and ACT in both exercise groups at 6-weeks follow-up, compared to baseline measures (P at least < 0.05), but was unchanged at the 48-week follow-up time-point. No change in peak breath frequency was observed in the control group throughout the follow-up period (Figure 42).

6.7.8 Peak tidal volume (Vt)

At 6-weeks follow-up peak tidal volume during the LCT remained higher compared to baseline measures in patients who were lower-limb trained ($P < 0.01$), but at the 48-week follow-up time-point no change from baseline was observed (Figure 43). Compared to baseline measures peak tidal volume was unchanged in both exercise trained groups during the ACT throughout the follow-up period. However at 6-weeks follow-up, tidal volume was greater in patients who who had undertaken upper-limb exercise training, compared to control patients ($P < 0.01$), and greater in both exercise groups at 48-weeks follow-up, compared to control patients (P at least < 0.05). Peak tidal volume was unchaged in the control patients during both the LCT and ACT throughout the follow-up period (Figure 43).

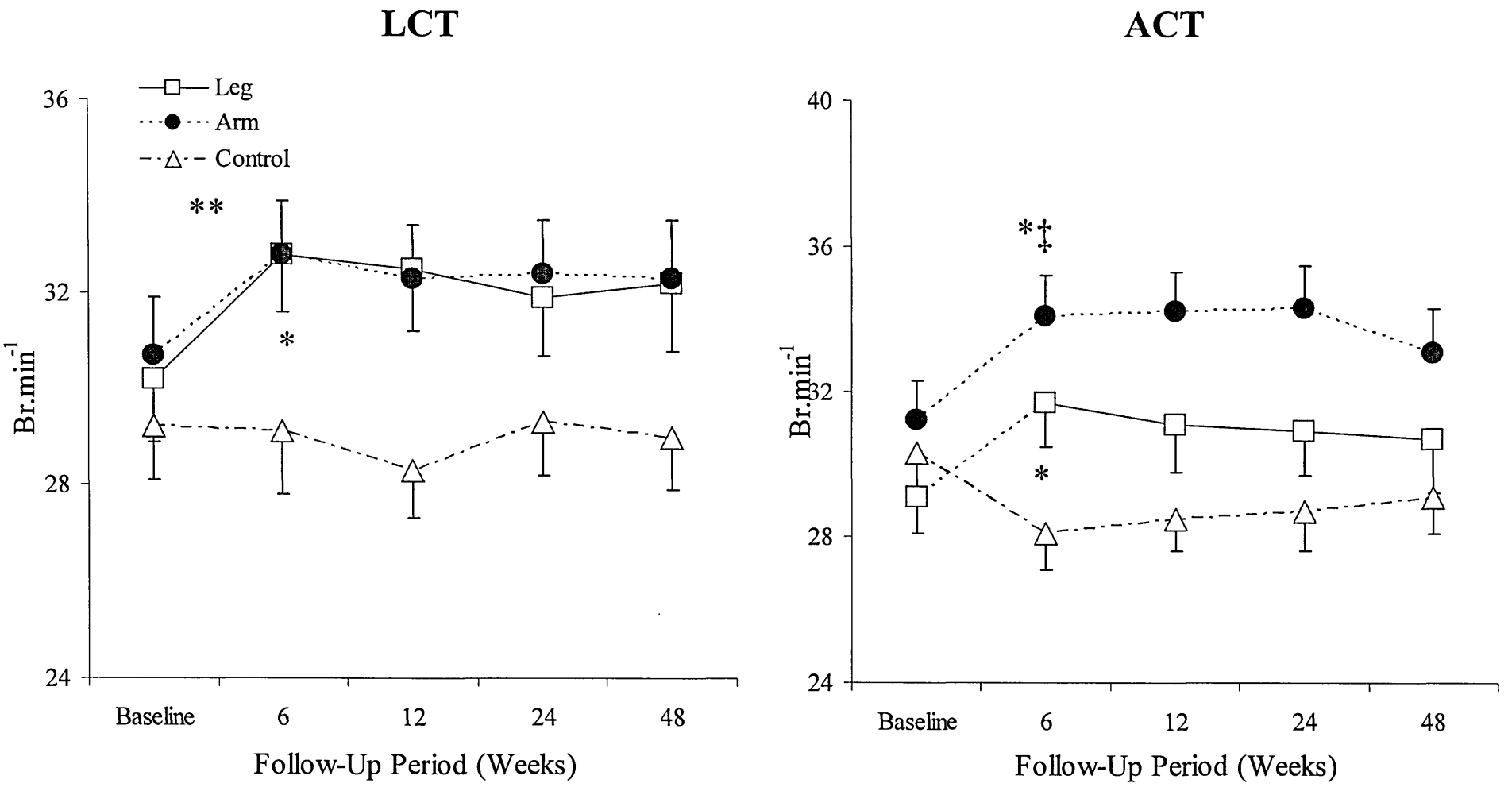


Figure 42. Changes in Peak Breath Frequency during the leg- and arm-cranking assessments during the follow-up period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the follow-up period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

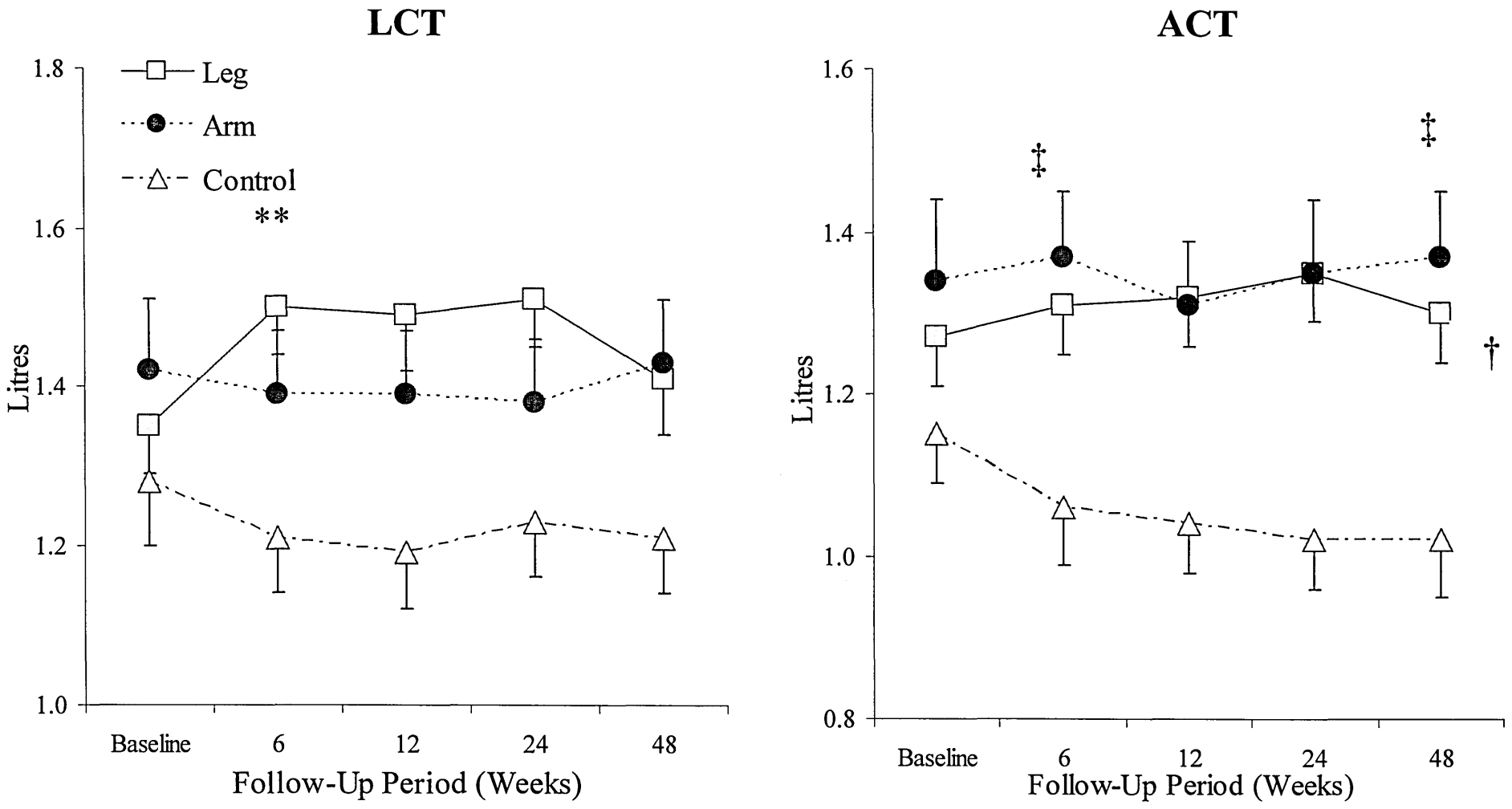


Figure 43. Changes in Peak Tidal Volume during the leg and arm cranking assessments during the follow-up period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the follow-up period.. ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg or arm-training group and the control group of patients.

6.8 Peak cardiovascular responses throughout the follow-up period

6.8.1 Peak systolic blood pressure (SBP)

Peak SBP during both the LCT and ACT assessment remained unchanged from baseline in both groups of exercise trained patients, throughout the course of the follow-up period. However, compared to control patients, at the 6-weeks follow-up time-point SBP was greater in the upper-limb trained group during the LCT ($P < 0.05$; Figure 44). During the ACT, at all follow-up time-points SBP was higher in the group of patients who had performed upper-limb exercise training, compared to control patients (P at least < 0.05). At all follow-up assessment time-points, peak SBP during the ACT was significantly lower in the control group of patients, as compared to baseline ($P < 0.01$; Figure 44).

6.8.2 Peak diastolic blood pressure (DBP)

Peak DBP during the LCT remained unchanged from baseline in both groups of exercise trained patients, throughout the course of the follow-up period. At the 6-week follow-up time-point, peak DBP during the LCT was lower than that at baseline in the control group of patients ($P < 0.05$) and was also lower than baseline during the ACT at all follow-up assessment time-points ($P < 0.01$). Similarly, peak DBP during the ACT was lower than that at baseline at 12-, 24- and 48-weeks follow-up in patients who had undertaken lower-limb exercise training (P at least < 0.05; Figure 45).

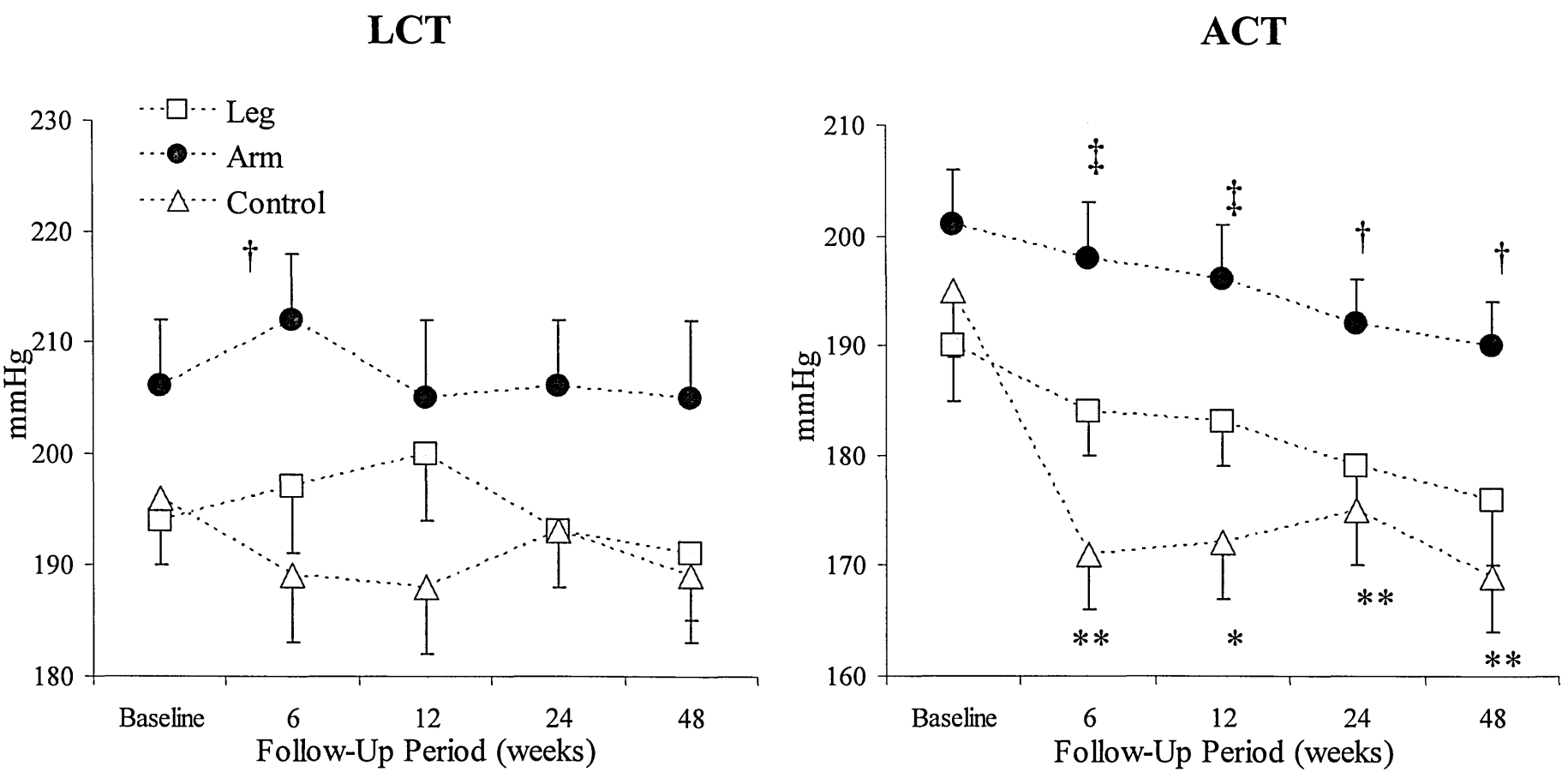


Figure 44. Changes in Peak Systolic Blood Pressure during the leg- and arm-cranking assessments throughout the follow-up period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the follow-up period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

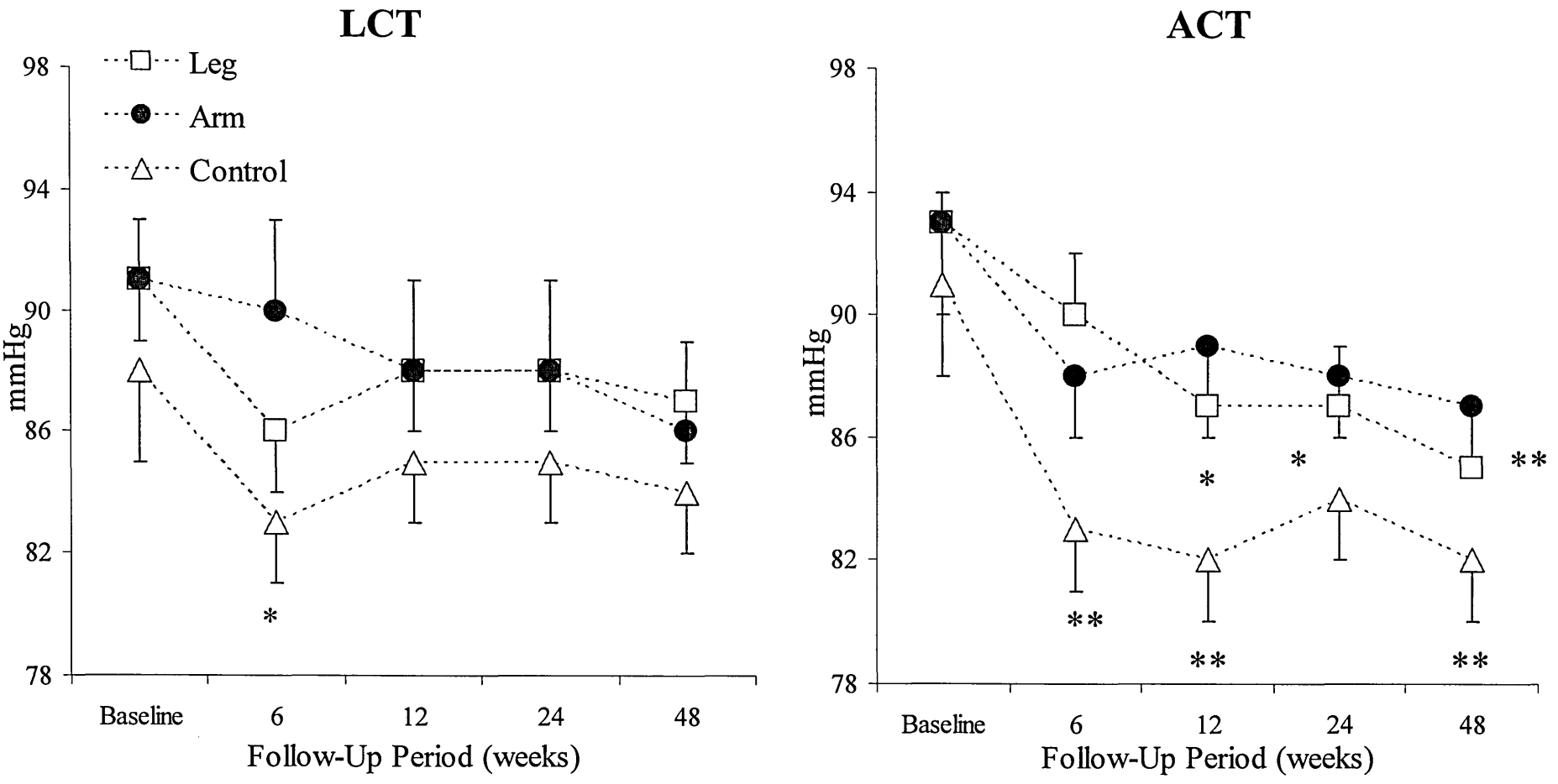


Figure 45. Changes in Peak Diastolic Blood Pressure during the leg- and arm-cranking assessments throughout the follow-up period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the follow-up period * $P < 0.05$; ** $P < 0.01$ compared to baseline.

6.8.3 Peak heart rate (HR)

Peak HR during the LCT and ACT remained unchanged from baseline in both groups of exercise trained patients, throughout the follow-up period. However, higher HR's during LCT and ACT were observed in these patients, as compared to the control group, during all follow-up time-points (P at least < 0.05). During the ACT, lower peak HR's were observed in the control group of patients at the 6- and 12-week follow-up time-points (P at least < 0.01; Figure 46).

6.8.4 Peak rate pressure product (RPP)

A similar pattern of response was observed in peak RPP. During the LCT and ACT peak RPP remained unchanged from baseline in both groups of exercise trained patients, throughout the follow-up period. However, compared to the control group, at the 6- and 12-week follow-up time-points RPP remained increased in both exercise trained patient groups during the LCT ($P < 0.01$) and at all follow-up time-points during the ACT (P at least < 0.05). During the LCT, at 48-weeks follow-up RPP remained increased in the upper-limb trained group of patients only, compared to the control group ($P < 0.01$). Lower RPP during the ACT was observed throughout the follow-up period in the control patients ($P < 0.01$; Figure 47).

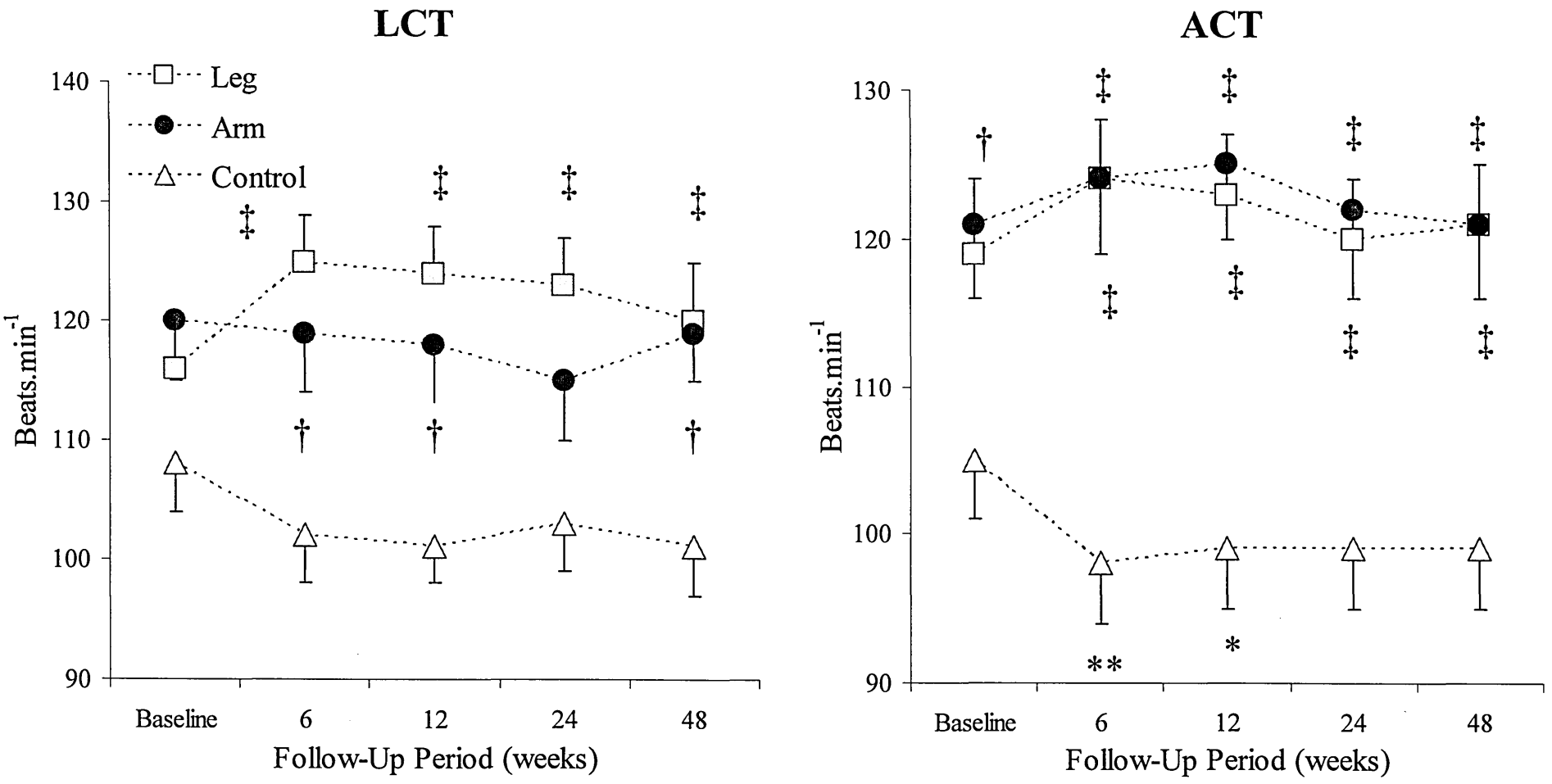


Figure 46. Changes in Peak Heart Rate during the leg- and arm-cranking assessments throughout the follow-up period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the follow-up period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

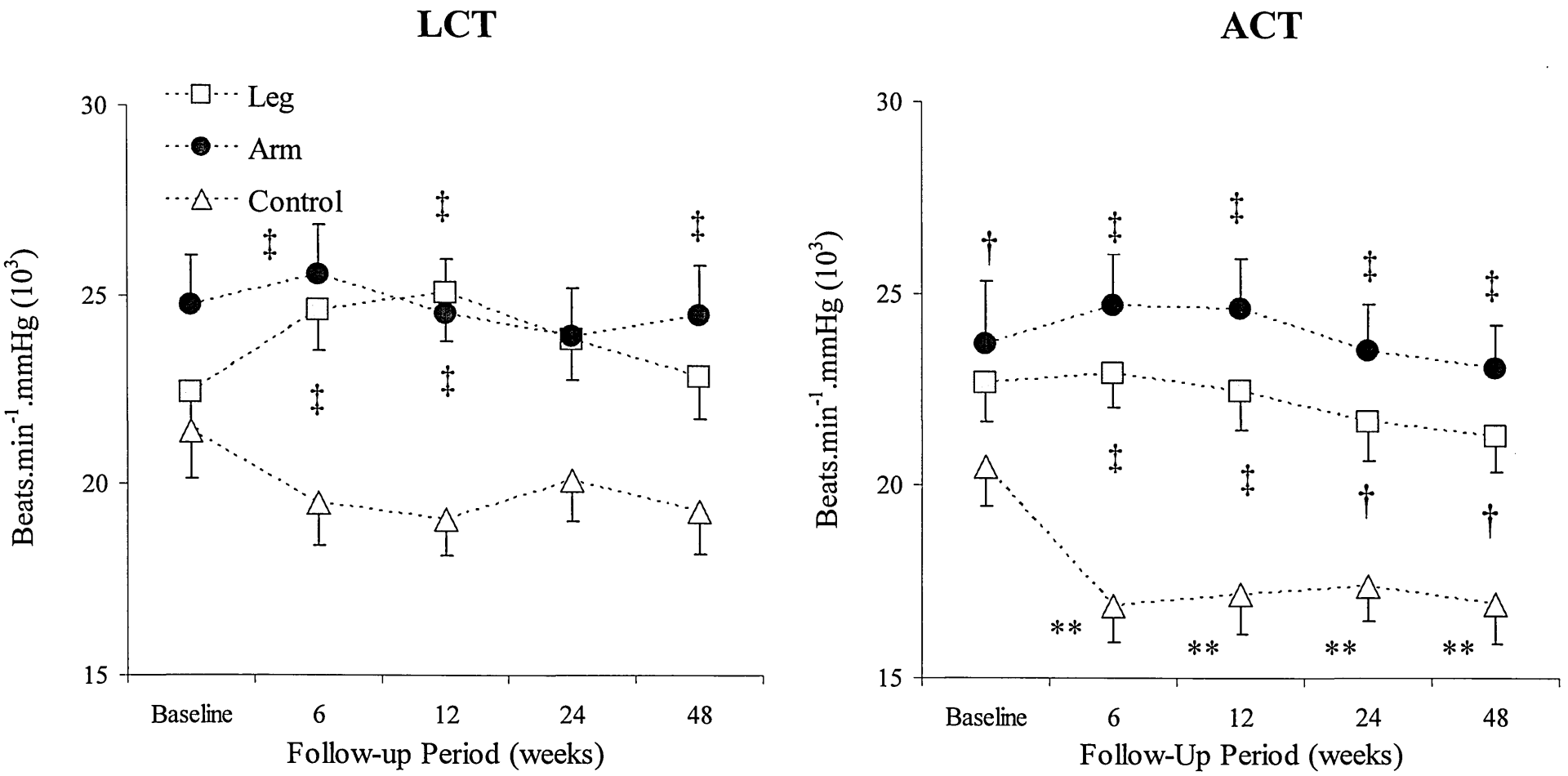


Figure 47. Changes in Peak Rate Pressure Product during the leg- and arm-cranking assessments throughout the follow-up period. Data are presented as mean ± SEM at maximum exercise tolerance, at each assessment stage during the follow-up period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg or arm-training group and the control group of patients.

6.8.5 Peak blood lactate responses throughout the follow-up period

The higher peak HR's observed during the LCT and ACT in both exercise trained groups were accompanied by higher peak blood lactate measures at each assessment time-point of the follow-up period, as compared to the control group of patients (P at least < 0.05). These increases in blood lactate concentration during the LCT over baseline were only of statistical significance at the 6-weeks follow-up time-point in patients who were upper-limb trained, and at the 12-weeks follow-up time-point in patients who were lower-limb trained (P at least < 0.05; Figure 48).

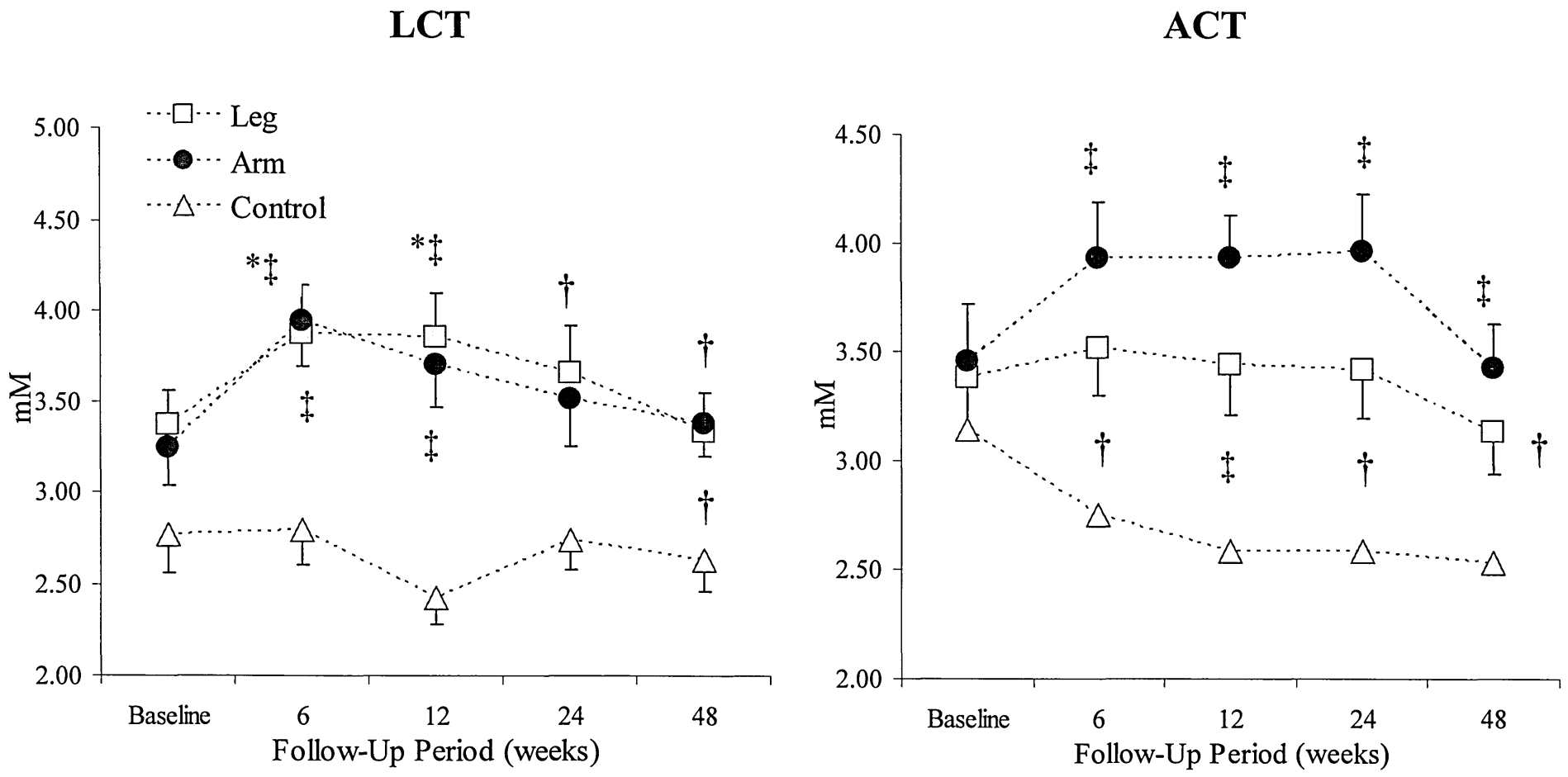


Figure 48. Changes in Peak Blood Lactate during the leg- and arm-cranking assessments throughout the follow-up period. Data are presented as mean ± S.E.M at maximum exercise tolerance, at each assessment stage during the follow-up period. * $P < 0.05$; ** $P < 0.01$ compared to baseline. † $P < 0.05$; ‡ $P < 0.01$ between the leg- or arm-training group and the control group of patients.

6.9 Peak psycho-physiological responses throughout the follow-up period

Peak RPE responses during both the LCT and ACT were unchanged throughout the course of the follow-up period, in all study groups (Table 39). Similarly there was no difference in peak pain perception during the LCT either between or within study groups. However, an increase in peak perceived pain perception during the ACT compared to baseline measures was observed at each follow-up assessment time-point in the patients who had undertaken upper-limb exercise training ($P < 0.01$; Table 39).

Table 39. Changes in perceived exertion and perceived pain at each assessment stage of the follow-up period.

	Follow-Up Period (Weeks)	Leg-Cranking Assessment			Arm-Cranking Assessment		
		Lower-Limb Training	Upper-Limb Training	Control Group	Lower-Limb Training	Upper-Limb Training	Control Group
Peak Exertion (RPE Scale)	Baseline	18 (13-20)	17 (13-20)	16 (13-20)	18 (13-20)	16 (10-20)	18 (13-20)
	6	17 (13-20)	15 (11-20)	17 (12-20)	17 (13-20)	17 (12-20)	17 (13-20)
	12	17 (13-20)	16 (11-20)	17 (6-20)	17 (13-20)	17 (13-20)	17 (11-20)
	24	17 (13-20)	16 (12-20)	16 (13-20)	17 (13-20)	17 (11-20)	17 (13-20)
	48	17 (13-20)	17 (12-20)	17 (12-20)	17 (14-20)	17 (13-20)	17 (13-20)
Peak Pain (CR-10 Scale)	Baseline	8 (5-11)	7 (3-11)	5 (0-11)	5 (0-10)	4 (0-10)	5 (0-11)
	6	8 (4-11)	7 (2-11)	7 (2-11)	7 (2-10)	7** (0-11)	7 (0-10)
	12	9 (4-11)	7 (0-11)	7 (0-10)	7 (2-11)	6** (0-11)	7 (0-11)
	24	8 (4-11)	7 (3-11)	7 (2-10)	7 (0-11)	7** (0-11)	7 (0-11)
	48	9 (3-11)	9 (5-11)	7 (4-10)	7 (3-11)	7** (0-11)	6 (0-10)

Data are presented as the median (ranges). * $P < 0.05$; ** $P < 0.01$ compared to baseline.

6.10 Changes in Haematocrit

No changes in haematocrit were observed either between or within groups, at any time-point throughout the follow-up period (Figure 49).

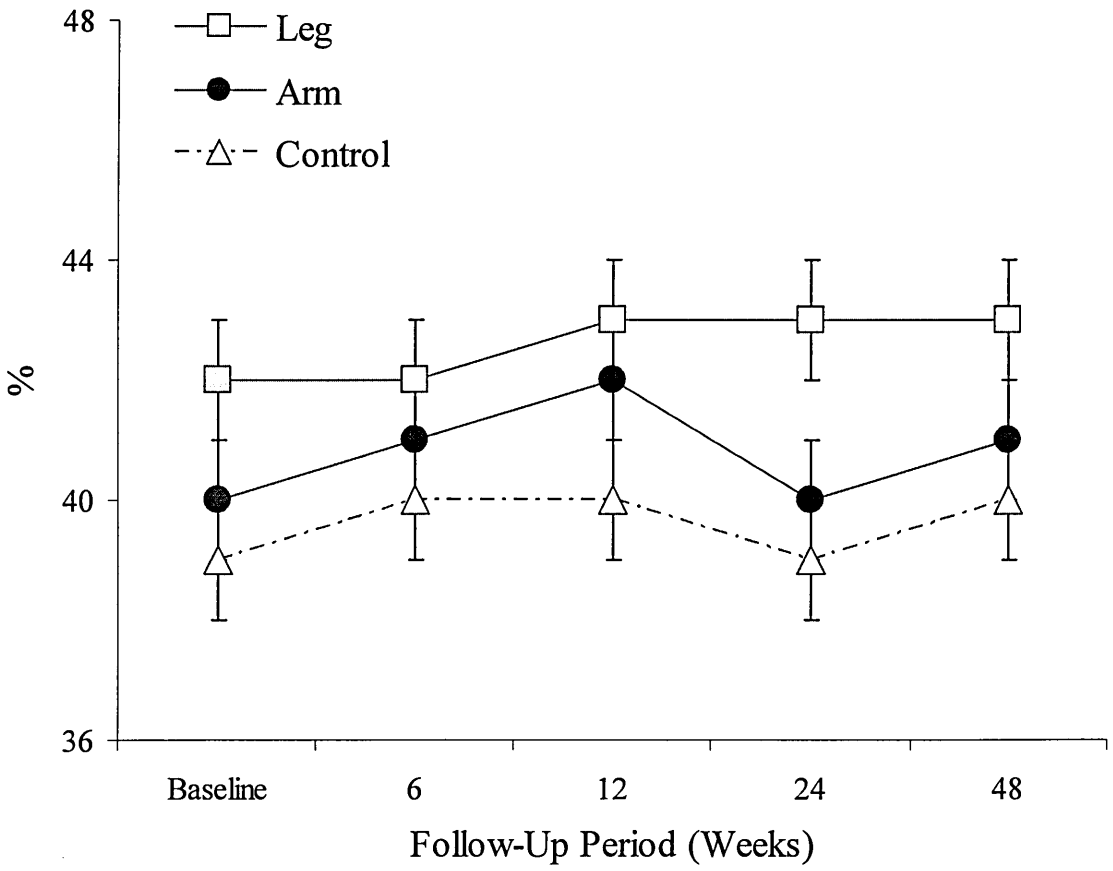


Figure 49. Changes in haematocrit during the follow-up period. Data are presented as mean ± SEM at each assessment stage during the follow-up period.

6.11 Changes in BMI

No changes in BMI within any of the study groups were observed at any time-point during the follow-up period (Figure 50).

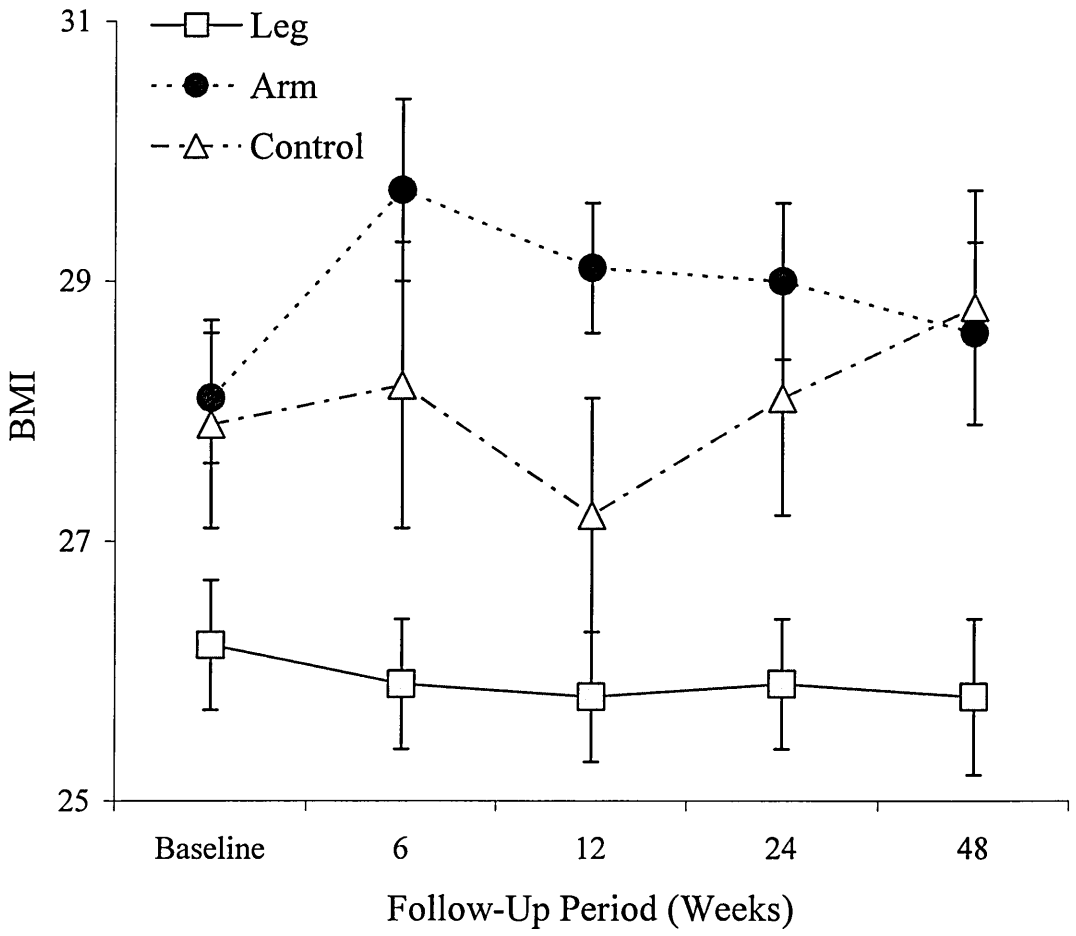


Figure 50. Changes in BMI during the follow-up period. Data are presented as mean ± SEM at each assessment stage during the follow-up period.

Chapter 7 – Follow-Up Study Discussion

Overview

Although the long-term success of an exercise programme has been defined as the ability to continue walking, with good functional status in the community setting and a maintained improvement of claudication symptoms (Menard *et al.* 2004), few studies have monitored the long-term benefits of exercise training following the cessation of the supervised classes and the long-term durability of results has not been fully established (Cheetham *et al.* 2004; Menard *et al.* 2004; Patterson *et al.* 1997). The logistics of keeping in touch and retaining patients following an exercise intervention can be problematic, and advancing years and a further deterioration in health can also contribute to a patient's unwillingness to attend. This study also monitored the persistence of any beneficial effects elicited by a 24-week programme of twice weekly upper- and lower-limb aerobic exercise training over a subsequent 48-week period. A great deal of effort was made to schedule return visits for the follow-up assessments for every patient who completed the 24-week intervention period.

All appointments were made in advance upon completing the intervention period. One week prior to the 6- and 12-week follow-up assessment sessions, patients were contacted to remind them of their appointment. Availability was also confirmed the day before the scheduled visit. Patients unable to attend were offered a similar day of day appointment on a mutually convenient day. Prior to the 24- and 48-week follow-up assessments, all patients were contacted approximately a fortnight in advance. This was important, since due to the advancing years and other medical complaints which these patients have, and considering that personal situations could change, patients might be unable to attend. Similarly, at these time-points patients were also contacted the day before the scheduled visit to confirm attendance. Out of the 94 patients who completed the 24-week intervention period, only 16% were unable to attend at the 48-week follow-up time-point. Inabilities to attend the follow-up assessments were primarily due to medical reasons, which included sustained M.I, stroke and, in some instances, death.

During the follow-up study the degree of retention of improvement in both CD and MWD over a period of 48-weeks was assessed. Changes in walking confidence, pain tolerance, functional capacity, physical activity status and quality of life were also investigated during this period. The follow-up analysis indicates that improvements in

walking performance persisted up to 48-weeks post-intervention, with MWD remaining improved by 26% and 18% in patients who had undertaken upper- and lower-limb aerobic exercise training, respectively. The persisting improvement in walking performance in these patients was associated with a continued improvement in walking confidence.

In both the groups of patients who had performed exercise training during the intervention period, HR at CD remained unchanged at each follow-up assessment time-point. Perceived pain at CD was lower in the group of patients who had undertaken lower-limb exercise training up to 48-weeks post-intervention, compared to baseline measures, a finding that was similar to that observed during the 24-week intervention period. This further suggests that an enhanced pain perception response was retained in this group of patients at least up to the 48-week follow-up time-point.

At the 48-week follow-up time-point, peak blood lactate concentration at MWD was higher in the group of patients who had undertaken lower-limb exercise training, in relation to the control group of patients. This suggests a possible alteration in exercise tolerance in these patients which continued after supervised exercise training. However, this observation was not apparent at all follow-up time-points. Peak HR at MWD was higher in both groups of patients who had performed exercise training relative to the control group, but was only higher in the group of patients who had performed lower-limb exercise training relative to baseline measures. This retained increase in peak HR suggests that these patients continued to push themselves further beyond the 'pain barrier' up to 48-weeks after undertaking the 24-week programme of exercise training.

Alternatively, the need for a greater exercise stimulus to elicit a claudication response could equally account for this observation. Peak perceived pain was higher at MWD at 48-weeks follow-up in the group of patients who had undertaken upper-limb exercise training, in relation to baseline measures, suggesting that an alteration in exercise pain tolerance accounted for more of the change in MWD than it did in patients who had undertaken lower-limb exercise training. In all study groups, resting ABPI was unchanged throughout the follow-up period. The lack of change in ABPI is supported by previous studies (Gardner *et al.* 2004b; McLafferty *et al.* 1997), and indicates that PAD, as defined by ABPI, did not worsen in any group during the follow-up study.

In both exercise training groups, improvements in community based walking distance remained improved up to 48-weeks follow-up, as compared to baseline. This finding is consistent with the persisting improvement in both CD and MWD in these patients. Up to the 24-week follow-up time point, walking speed and stair climbing ability were also perceived to be improved in both exercise training groups, as compared with the control group. Patients who had undertaken upper-limb exercise training perceived that their stair-climbing ability was improved up to the 48-week follow-up time-point, in relation to the control group of patients. All WIQ domains were unchanged in the control group of patients at all follow-up assessment time-points, in relation to baseline measures.

Disappointingly, global physical activity was unchanged at each follow-up assessment time-point in relation to baseline measures in patients who had undertaken exercise training. Nevertheless, trends indicating an increase in physical activity were observed up to the 24-week follow-up time point in both exercise groups. An increase in the leisure-time domain of the PAD-PAR questionnaire was only observed at the 24-week follow-up time-point in patients who had undertaken upper-limb exercise training. This suggests that patients with intermittent claudication need motivation, encouragement and perhaps supervision in order to routinely participate in exercise and to increase their physical activity status. There was no difference in the level of work activities or in the household chores domain of the PAD-PAR questionnaire throughout the post-intervention period in any of the study groups. These observations are typical of elderly patients who, in the main, routinely perform household work with little change in pattern observed over time.

Although a perceived improvement in general health in patients who had undertaken exercise training was not persistent during the follow-up period, the upper-limb exercise trained group did perceive their general health, as assessed using the SF-36 *v2* questionnaire to be better at the 12- and 48-week follow-up time-points, in relation to the control group of patients. Energy and vitality remained improved up to the 48-week follow-up time-point in these patients. The degree of bodily pain experienced by patients following the intervention period was no different to that present at baseline, although compared to the control patients, an improvement at the 12-week follow-up time-point was perceived in the upper-limb exercise training group only. There was no difference in any of the study groups, in the physical function, role limitation physical,

mental health, social functioning or role limitation emotional domains of the SF-36 *v2*, during the follow-up period.

Upon comparing quality of life using the EQ-5D questionnaire, general health remained improved up to the 24-week follow-up time-point in patients who had undertaken lower-limb exercise training, in relation to baseline measures. Patients who had undertaken upper-limb exercise training also perceived an improvement in general health and ability to perform usual activities at the 12-week follow-up time-point, compared to control patients. However, the difference from baseline measures in these domains, in these patients, was not significant. No changes in the domains of mobility, self care, bodily pain and discomfort, and anxiety and depression were observed at any follow-up assessment time-point, in any study group.

In order to further understand the effect of the two training regimens on upper- and lower-limb exercise tolerance, the physiological responses to incremental arm- and leg-cranking exercise were also studied following the intervention period. Peak power output remained improved up to the 48-week follow-up time-point for both the trained and untrained skeletal muscle groups in patients who had undertaken exercise training during the 24-week intervention period. The post-intervention training effect continued to be most apparent for the specific training apparatus, with some cross over improvement for the other exercise modality.

In both the groups who had undertaken exercise training, the retained improvement in walking performance was accompanied by the sustained increase in lower-limb peak aerobic power and blood lactate concentration during the LCT, compared to baseline measures and control patients, respectively. At the 6-week follow-up time-point peak $\dot{V}O_2$ remained increased in both exercise trained groups, compared to baseline measures, but was unchanged at 48-week's follow-up. However, compared to control, peak $\dot{V}O_2$ remained improved in the upper-limb training group of patients only at this time-point. At the 6- and 12-week follow-ups, peak lactate concentration, HR and RPP were higher during the LCT in both exercise groups of patients, in relation to baseline measures. At 48-weeks, these variables were higher in both exercise groups of patients, compared to the control group of patients, however higher values were not persistent throughout the follow-up period. RPE and perceived pain were unchanged in all groups throughout the follow-up period during the LCT.

During the ACT at maximum exercise tolerance, peak power output was higher in both groups who had undertaken exercise training, in relation to baseline measures. Peak blood lactate concentration, HR and RPP were all higher in these patients' at all follow-up assessment time-points, in relation to the control group of patients. Peak $\dot{V}O_2$ was unchanged from baseline measures in patients who had undertaken exercise training, however compared to control patients' peak $\dot{V}O_2$ remained improved in the upper-limb training group of patients throughout the follow-up period. RPE was unchanged in all groups, however perceived pain was higher in the group of patients who had undertaken upper-limb exercise training at all follow-up assessment time-points compared to baseline measures. In the control group of patients, during the ACT lower peak SBP, DBP and RPP values were observed at all follow-up assessment time-points.

Outcome Measures - Walking Performance

The benefits of supervised exercise are recognised and well documented. A structured, supervised exercise programme is more effective at improving CD compared to a less formal home-based exercise programme (Savage *et al.* 2001), and provides superior increased walking ability (Patterson *et al.* 1997). However, it is equally important to observe for how long such improvements can be retained. This study aimed to observe patients walking ability up to 48-weeks following the 24-week intervention period. The follow-up period in this present study was considered lengthy, however it was not as comprehensive as other studies (Menard *et al.* 2004; Perkins *et al.* 1996) which have assessed patients at up to approximately 6 years follow-up.

An improvement in walking performance following a short 12-week exercise programme has been sustained for a subsequent 24-weeks in patients with intermittent claudication (Savage *et al.* 2001; Patterson *et al.* 1997). Walking performance has also been shown to be improved 9- and 12-months following the cessation of a 6-month supervised exercise and motivation class involving exercise three times per week (Cheetham *et al.* 2004). However, the improvements in walking performance and walking economy were sustained for such a long period in this latter study due to the fact that patients undertook a less frequent exercise maintenance programme involving twice weekly exercise during the follow-up period (Cheetham *et al.* 2004). Patients who continue to exercise can potentially maintain the benefits obtained through supervised exercise rehabilitation (Menard *et al.* 2004). Similarly a 12-week home exercise programme, incorporating weekly lectures and exercise instruction can also

sustain improvements in walking performance for up to 6-months after its conclusion (Patterson *et al.* 1997).

In contrast, a study of the long-term effects of exercise training has found that the initial improvements in walking performance are not sustained, since the majority of patients do not continue to take regular exercise (Perkins *et al.* 1996). This present study has found that improved walking ability obtained as a direct result of exercise rehabilitation can be sustained for up to 48-weeks following the cessation of supervised exercise, although this is much reduced compared to that observed immediately following the 24-week intervention period. Furthermore, a gradual reduction in improved walking performance was observed at each follow-up time-point. Although the sustained improvements in walking performance demonstrated in the present study were lower than those reported by others (Gardner *et al.* 2002), the less frequent formal maintenance programme might account for these differences. Although increases in CD and MWD over baseline measures induced by an exercise rehabilitation programme can be maintained for up to 80-months in patients who continue exercising for a minimum of 60 $min.wk^{-1}$, both CD and MWD return to baseline values over such a time period in patients who do not continue with exercise (Menard *et al.* 2004).

For many patients even a small actual improvement in walking ability obtained during the intervention period could make a considerable difference to what they can cope with in everyday life and also to their attitude to their disability (Binnie *et al.* 1999). Therefore, an exercise rehabilitation programme which can sustain walking performance for a considerable time following exercise attendance might be considered to be of value to these patients. Some patients also learn to accept their disability, to live within its limits and to feel less fearful about their symptoms (Binnie *et al.* 1999).

An 18-month follow-up study observing the natural history of physical function in older men with intermittent claudication reported CD and MWD to decrease by 22% and 9%, respectively in these patients (Gardner *et al.* 2004b). A non-statistically significant trend towards a decline in walking performance was observed in the control group of patients at each follow-up assessment time-point in this present study. The method used to assess walking performance might explain these observed differences, since the Gardner *et al.* (2004) study used the 6-minute walk test to assess walking ability. Other studies using the 6-minute walk test from the same investigator have also indicated that

there is little change in CD in a non-exercise control group over an 18-month period (Gardner *et al.* 2002). Differences in these findings could be due to differences in the patient selection process (Gardner *et al.* 2004b).

A longer follow-up period (mean 45-months) of patients with intermittent claudication has indicated that walking distance in patients with intermittent claudication does decline at an average of 9.2 yards per year, with an average rate of ABPI decline of 0.014 per year (Aquino *et al.* 2001). It is thus believed that incorporating appropriate regular exercise into the lives of patients in a way that is sustainable indefinitely will improve long-term results (Binnie *et al.* 1999).

Physical Activity Status Following Exercise Rehabilitation

Having built up patients' confidence during the supervised exercise intervention period, it was essential to advise patients of the importance of continuity to exercise in the home setting. Finding realistic, practical strategies for participating in physical activity was necessary in the hope that it would be perceived as an enjoyable, long-term element of their lives (Binnie *et al.* 1999). Upon completing the 24-week intervention period, each patient who had undertaken supervised exercise was informed of the necessity of continuing exercising, in the hope of retaining the improvement in walking ability as a result of the study. Those patients assigned to the control group, were equally provided with identical physical activity advice.

Indeed the final assessment session upon completing the 24-week intervention period also focused on a consultation theme, feeding back to the patient on an individual basis their reported walking ability in terms of both CD and MWD which they had achieved as a result of the 24-week intervention period, compared to baseline values in terms of actual walking distance and percentage improvement. This information was provided on an individual basis for each patient. This provided a dual focus. In the majority of individuals, this feedback provided the patient with the satisfaction that their hard work had paid off. Secondly, it provided further motivation that patients need to continue with physical activity to sustain improvements. It can be argued that regular follow-up assessments can provide an important motivating function, since seeing a formal record of their improving walking performance reassures many patients that their efforts to exercise are worthwhile and encourages them to persevere (Binnie *et al.* 1999). It has been suggested that experience and skills in counselling and the use of the therapeutic

relationship (Binnie *et al.* 1999) can be particularly beneficial in motivating patients to continue exercising.

Some patients established that they enjoyed the exercise routine and they felt confident about maintaining an exercise programme following the intervention period. Indeed, the need for structure and routine for elderly patients is important, since regarding work or household chore activities, no difference between or within study groups was observed throughout the follow-up period. These observations are typical of elderly patients who routinely perform household chores with little change in pattern observed over time. Advice which was given to the patients regarding the continuation of exercise in the home setting included the advice of taking regular walks. A 'keep walking' regime of combined community-based intervention of cessation of smoking and increased physical activity has been shown to improve MWD attributed to increased physical activity through recreation walking (Fowler *et al.* 2002).

Patients were informed that going for a walk, ideally every day, but at least three or four times per week would be a key element to keeping active (Binnie *et al.* 1999). The advice that was given regarding walking included encouraging the use of local landmarks, in order for patients to mark stopping points and then to try to increase the distance between stops, since such an incremental approach further builds the patients confidence (Binnie *et al.* 1999). However, similar problems with encouraging patients to take up this advice to those experienced at the beginning of the intervention period were encountered, as much resistance and many anxieties have to be overcome before patients will adopt it, including the fear of pain, as patients fear that walking with pain will do some damage to the affected artery (Binnie *et al.* 1999). Patients were also encouraged to consider sports and hobbies of potential therapeutic value, including golf and dancing (Binnie *et al.* 1999). Attending a local gym was a further option considered for those patients requiring the need for structure and discipline.

A small proportion of patients heeded the advice to keep active. Patients who had undertaken lower-limb exercise training quickly associated the feasibility of continuing exercising from a practical perspective. Some patients already had exercise bikes in the home setting, although these had not been used for some time. Some patients purchased an exercise bike or other suitable aerobic equipment (arm crankers, and rowing machines in a few cases) upon completing the intervention study. These patients

continued the regimen that they were prescribed during the 24-week intervention period, with advice provided to exercise within safe limits in the home setting, with RPE and CR-10 scales provided for self-evaluation of exertion and pain. Patients who had undertaken upper-limb exercise initially reported a feeling of reluctance associated with other forms of exercise such as cycle exercise, since by comparison these patients had been exercising relatively pain-free during the 24-week intervention period. Some patients did indicate that they would consider purchasing arm-cranking equipment.

Disappointingly however, despite the in depth advice and encouragement given to patients upon completing the intervention study, the global physical activity status of patients who had undertaken exercise training during the intervention period was unchanged throughout the follow-up period. Nevertheless, trends indicating an increase in physical activity were observed up to the 24-week follow-up time-point in both exercise groups, and this most likely resulted from the fact that some patients heeded the keep active advice during the 6-, 12- and 24-week follow-up assessments. Orthopaedic and arthritic complaints, as well as general health concerns have been stated as being primary reasons for patients to discontinue with exercise (Menard *et al.* 2004). Also, the advice 'to take more exercise' is rarely an adequate or effective means of helping patients with intermittent claudication (Binnie *et al.* 1999). Ultimately, it would be beneficial to identify characteristics of patients with PAD who are likely to continue with an exercise programme (Menard *et al.* 2004).

In this study, the reluctance of patients to continue exercising might possibility result from the fact that a large proportion of patients were satisfied with their walking ability following the intervention period, as observed in previous studies (Andriessen *et al.* 1989). As a result they thought it unnecessary to engage in further exercise, believing it to be surplus and needless. Patients believed that improving walking ability was sufficient and that this would be endlessly retained, despite being informed that the retention of improved walking ability required continued exercise. Certainly, up to 12-weeks post-intervention leisure-time physical activity status was unchanged in all of the study groups, in relation to baseline measures.

A decrease in monitored physical activity in a previous 18-month follow-up study has suggested that this was related to a decline in walking performance in these patients (Gardner *et al.* 2004b). In the present study walking performance in patients who had

undertaken exercise training remained improved during the follow-up assessments compared to baseline measures in the absence of increased physical activity status, although it did decline. The retained confidence in walking in patients who were exercise trained could possibly contribute to the feeling that these patients were able to push themselves further when walking, and this in itself could help in part to account for the retained walking performance observed throughout the follow-up period. Nevertheless, this study also observed a progressive dwindling of enthusiasm for exercise in the home setting throughout the follow-up period.

Patients who initially felt enthusiastic about exercising in the home setting upon completing the intervention study soon lost interest, indicating that exercise in the home setting for patients with intermittent claudication is short-lived, since patients lacked motivation. A lack of motivation has previously been stated as a reason for discontinuation with exercise (Menard *et al.* 2004). It has been suggested that follow-up assessments provide the opportunity to discuss difficulties, to revise exercise strategies or to set new targets at follow-up visits, since these can revive waning enthusiasm (Binnie *et al.* 1999). In the present study, motivational advice was given to all patients at each follow-up assessment time-point. It has been suggested that a great deal of patient listening and careful exploration of sensitive issues is required to identify the right motivational triggers or to expose the real stumbling blocks (Binnie *et al.* 1999). During the follow-up assessments patients frequently commented on the need to attend and exercise in a group setting. Others felt less comfortable to exercise due to the safety issue and reluctant in the event of experiencing difficulty. The supervised intervention programme provides motivation, encouragement and feedback as well as instruction and supervision (Binnie *et al.* 1999).

A lack of enthusiasm could account for the differences in leisure-time physical activity at the 24-week follow-up time-point between both groups who had undertaken exercise training during the intervention period. It is possible that after the 12-week follow-up time-point, patients who had undertaken upper-limb exercise training heeded the advice regarding keeping active. Some of these patients reported that they enjoyed bowling and as such undertook this as a pastime. This could account for the overall increase in this domain of the PAD-PAR questionnaire in this patient group. Patients commented that the improved upper-body strength obtained during the intervention period resulted in an improvement in their bowling performance. It is also possible that these patients took

extra leisure-time walks, and that a mixture of activities cumulatively resulted in an increase in leisure-time physical activity at 24-week's follow-up. However, whatever the reason, the increase in physical activity was short-lived since leisure-time physical activity was unchanged from baseline measures in all groups at the 48-week follow-up time-point.

It has also been suggested that if patients are screened properly and simply receive advice and instruction, then a home-based programme can be a safe, low-cost alternative to a supervised exercise programme, providing similar long term (24-weeks) exercise benefits in MWD (Savage *et al.* 2001). The findings of the present study do not support this. At 48-weeks post-intervention, the physical activity status of all patients was unchanged from baseline measures. The long duration from the 24-week follow-up assessment to the 48-week follow-up assessment involved no patient-investigator contact, apart from the fact that each patient received a phone call approximately 2 weeks and the day before the 48-week assessment session to confirm attendance. Had weekly or fortnightly phone calls been maintained, then perhaps this could have motivated patients sufficiently to continue exercising in the home setting. Future studies should take this into account.

Functional Status Measures Following Exercise Rehabilitation

As in previous studies, the WIQ was administered in order to assess the functional status of the population (Menard *et al.* 2004). The findings of this study indicate that claudication pain severity was unchanged during the follow-up period. However, community-based walking distance, as assessed using the WIQ, continued to be perceived to be improved up to 48-weeks after the intervention in exercise trained patients. This is consistent with the retained improvement in walking performance which was observed throughout the follow-up period, as assessed using the incremental shuttle-walk test. However, an improvement in walking speed and stair-climbing ability was only perceived in both exercise trained groups of patients up to the 24-week follow-up time-point. The absence of sustained improvement in these WIQ domains at the 48-week follow-up time-point in both exercise groups could be explained by the fact that the retained improvement in walking performance at this time-point was less than that at 24-weeks follow-up. Differences between measured walking performance and WIQ perception might also account for the observed differences, since the WIQ is a subjective instrument to assess claudication pain, and therefore may be less sensitive to

detect change in claudication pain than the more objective measure of walking ability (Gardner *et al.* 2004b), as assessed using the incremental shuttle-walk test. Furthermore, the lack of continuation of exercise undoubtedly is a contributory factor, since higher WIQ distance, speed and stair climbing ability scores have been reported by patients who continue to exercise after exercise rehabilitation programmes (Menard *et al.* 2004).

By comparison, studies which have included a follow-up period of 18-months duration have found no significant change in self-reported ability to ambulate at various distances, speeds or stair climbing ability, as assessed using the WIQ (Gardner *et al.* 2004b). This indicates that if exercise is not maintained, patients perceived ability to ambulate in the community setting returns to baseline measures. Similarly, no changes at the end of the 48-week follow-up period were observed in the control group of patients in this present study. The lack of change in perceived claudication symptoms and walking distance, speed and stair-climbing ability, as measured by the WIQ, in the control group of patients supports previous investigations that report stabilisation in symptoms over time (Gardner *et al.* 2004b; Jelnes *et al.* 1986; Imparato *et al.* 1975; Bloor, 1961).

The psychological and quality of life improvement from participation in an exercise programme cannot be underestimated, nor can the contribution of this to the overall well-being of patients with intermittent claudication, who have to cope with chronic, handicapping symptoms (Binnie *et al.* 1999). Regarding quality of life, a persistent improvement in general health was not observed in either group of patients who had undertaken exercise training during the intervention period. Again, the lack of continuation of exercise undoubtedly contributed to this observation. Patients who continue to exercise for 60 $min.wk^{-1}$ following rehabilitation programmes will potentially experience improved health-related quality of life compared to patients who cease exercising after a period of supervised exercise (Menard *et al.* 2004). Such improvements have been reported to be in the domains of physical function, role-limitation physical function and bodily pain, yet no differences in general health, energy and vitality, social function, role-limitation emotional and mental health have been observed between patients who do and do not continue to exercise following a programme of supervised exercise (Menard *et al.* 2004). However, it is equally

important to note that general medical concerns and co-morbid disease can also limit functional status (Menard *et al.* 2004).

In the present study, patients who had undertaken upper-limb exercise training during the intervention period perceived their general health, as assessed using the SF-36 *v2* questionnaire to be better at the 12- and 48-week follow-up time-point, in relation to the control group of patients. The degree of bodily pain was improved at the 12-week follow-up time-point, in these patients compared to the control group. However, the differences were not significant compared to baseline measures. Energy and vitality remained improved up to the 48-week follow-up time-points in these patients. The design of the SF-36 *v2* questionnaire and types of questions, which relate to each domain could possibly account for the fact why patients who had undertaken lower-limb exercise training did not report an improvement in this domain throughout the follow-up period. No difference in the physical function, role limitation physical, mental health, social functioning or role limitation emotional domains of the SF-36 *v2* were observed in any study group throughout the follow-up period.

When comparing quality of life using the EQ-5D questionnaire, the general health of patients who had undertaken lower-limb exercise training continued to be improved up to the 24-week follow-up time-point, in relation to baseline measures. This indicates that lower-limb exercise training had a greater long-term impact following the cessation of supervised exercise rehabilitation, as compared to upper-limb exercise training. Equally, the withdrawal of the supervised exercise classes could have had a greater impact on patients who were upper-limb exercise trained, which was apparent 6-weeks after the intervention. Nevertheless, this finding again highlights the fact that improvements in general health are not retained indefinitely after undertaking such a programme, since at the 48-week follow-up time-point the general health of patients who were lower-limb trained also returned to baseline levels. The long-duration between the 24- and 48-week follow-up assessments, during which the contact with the investigator was minimal, could also of been a contributory factor, since at each follow-up assessment time-point general health concerns were also discussed with all patients, regardless of grouping.

An improvement in both general health and ability to perform usual activities at the 12-week follow-up time-point was observed in the patients who had undertaken upper-limb

exercise training, compared to control patients. It could be that a small, yet statistically insignificant increase in physical activity following the 6-week follow-up time-point contributed to this observation. However, the difference in both these domains was not significant from baseline measures in these patients. No changes in the domains of mobility, self care, bodily pain and discomfort, and anxiety and depression were observed at any follow-up assessment time-point, either between or within study groups.

Exercise Tolerance Following Exercise Rehabilitation

Regarding aerobic exercise capacity, the determination of peak $\dot{V}O_2$ is considered to be important for assessing a patient's functional capacity (Womack *et al.* 1998). Patients limited by intermittent claudication have previously been shown to experience a decline in physical function during 18-months of follow-up despite there being no change in ABPI (Gardner *et al.* 2004b). At the 6-week follow-up time-point, peak $\dot{V}O_2$ remained increased during the LCT in both groups of trained patients. However, a gradual decline in peak $\dot{V}O_2$ during the LCT was observed in both trained groups, which was unchanged from baseline measures at the 48-week follow-up time-point.

Peak $\dot{V}O_2$ during the ACT remained increased compared to control patients up to the 48-week follow-up time-point in the group of patients that were upper-limb trained. However, compared to baseline, at the 6- and 48-week follow-ups, peak $\dot{V}O_2$ during the ACT was unchanged in both exercise groups. The decline in physical activity during the follow-up study are more plausible explanations for the decline in physical function (Gardner *et al.* 2004b) and aerobic exercise capacity during the LCT and ACT throughout the follow-up period. Patients advancing years and general frailty also meant that patients were unlikely to increase their exercise tolerance further (Binnie *et al.* 1999). The eldest patient recruited onto this study was 85 years of age. The lack of change in ABPI during this study suggests that progression of disease is an unlikely explanation for the observed decline in physical function, as suggested in previous studies (Gardner *et al.* 2004b).

Chapter 8 – Follow-Up Study Conclusions

The main findings of the follow-up study indicates that although walking performance remained improved in both exercise trained patients at 48-week's follow-up, as compared to baseline measures, a progressive dwindling of improvement was observed over this time period. Reluctance for the continuation of exercise in the home-setting was observed. This study supports previous findings, which have indicated that patients with intermittent claudication need to continue with an exercise programme, either supervised or at home, and that this is necessary for the maintenance of the positive effects obtained from a supervised exercise programme (Menard *et al.* 2004). The need for continued motivation to exercise was also highlighted in this study.

If obstacles to continued exercise, such as lack of motivation were overcome, perhaps more patients would benefit (Menard *et al.* 2004) and this could have a direct impact on the retention of improved walking ability. Indeed, it has been estimated that in spite of the relatively high level of supervisor support, the cost of putting a patient through the first year of a conservative therapy programme is less than a quarter of the cost of an angiogram followed by angioplasty (Binnie *et al.* 1999). The referral of older patients with intermittent claudication to established physiotherapy programmes in the community can increase their levels of physical activity and thereby reduce disability related to PAD (Fowler *et al.* 2002). Perhaps a less frequent exercise maintenance programme during the follow-up period could have sustained the benefits that were induced during the intervention period, as has been observed in previous studies which have continued with such a strategy after exercise rehabilitation (Gardner *et al.* 2002).

Study Limitations and Strengths

Randomised controlled trials of supervised exercise therapy for the treatment of claudication have relatively small study populations and limited follow-up (Nehler and Hiatt, 1999a). This study included a large cohort of patients, with by comparison, a lengthy intervention and follow-up period. The 24-week intervention period consisted of 6-weekly assessments throughout this period, and the follow-up assessments comprised of four time-points at which both short and longer-term effects of the cessation of such a programme on patients walking performance, as well as other parameters of interest were observed. The excellent attendance and compliance during

this study undoubtedly allows detailed conclusions to be drawn regarding not only upper- and lower-limb exercise rehabilitation programmes, but also the duration in terms of improvement and patient's general health and well-being following such an intervention, in a large cohort of patients with intermittent claudication.

The major strength of this study is the integrated examination of the effects of exercise rehabilitation across the domains of walking performance, functional capacity, physical activity status and quality of life in a large well characterised cohort of older patients with a well-described stage of intermittent claudication. The intermittent protocol utilised in this study allowed such collection of detailed data. Furthermore, such a protocol also minimised the effects of accumulated localised fatigue and thus enabled improved maximal performance to be achieved especially during arm-crank exercise (Sawka, 1986). However, one drawback of such a protocol was the substantial length of time that each assessment took to administer.

A further limitation of this randomised controlled trial was that the main investigator was not blinded to training group assignment due to the volume of assessment sessions which had to be undertaken during the 24-week intervention period (1,410 assessments). A further 1,128 assessments were undertaken during the 48-week follow-up period. This could be interpreted as a study weakness, not only from the point of view of study duration, but also it could be suggested that those patients in the exercise training groups were provided with extra motivation to perform well during the training and assessment sessions. However, this was not the case, as all patients were provided with an equal level of encouragement and were pushed to their maximum exercise tolerance regardless of their grouping. Furthermore, consideration of the peak HR, RPE and CR-10 responses during the assessment sessions suggest that patients in both exercise groups were equally motivated to perform well on tests of physical function.

Although, physical activity levels were well balanced across both exercise training cohorts during the 24-week intervention period, it is conceivable that additional physical activity may have consisted primarily of unstructured types of activity, such as walking in and around the home, which is difficult to discern using standardised physical activity questionnaires because they focus more on structured activities (Gardner *et al.* 2001). As in previous studies (Gardner *et al.* 2001; Gardner *et al.* 2004a), a further limitation of this study was the select nature of the participants and the

high percentage of men enrolled despite extensive efforts to recruit women. This has also been found to be a weakness in previous studies and suggests that the natural history of female patients with claudication might be different from that of male patients (Aquino *et al.* 2001).

A further limitation is one which has previously been encountered in exercise rehabilitation studies i.e. that patients who participated in this study were volunteers and therefore that they might represent patients who were more interested in exercise, who had better access to transportation to the programme, and who were in relatively better health than patients with PAD who did not volunteer (Gardner *et al.* 2004a).

Future Research

We have shown that upper-limb aerobic exercise is as effective as lower-limb exercise in improving walking ability in patients with intermittent claudication. Individuals with increased disease severity might derive more benefit from an upper-limb exercise strategy compared to lower-limb exercise rehabilitation, especially in the early stages of an exercise regimen. It would be interesting to undertake a study in which patients undertake upper-limb exercise in the early stages and progress to lower-limb exercise (either cycle or walking) in order to observe whether such a programme further enhances walking ability in these patients. Such a programme could have direct clinical implications and the effectiveness of this pragmatic approach could be evaluated using intention to treat analysis. Furthermore, on the basis of the follow-up findings of this study, in order to sustain improvements achieved following exercise rehabilitation, regular motivational advice at least should be included in all future studies following the cessation of formal exercise classes. Also, the use of pole-striding as an alternative form of upper-limb exercise needs further evaluation.

Blood samples were taken at each assessment time-point throughout this study. It is proposed to study cardiovascular risk markers following upper- and lower-limb aerobic exercise training in this patient group as very little work has been reported in this area. Furthermore, some studies have found changes in blood rheology through training whereas others have not. Analysis for plasma viscosity and packed cell volume could also be performed, since it has been hypothesised that a decrease in PCV can lead to a reduction of blood viscosity, and consequently an improvement in blood flow in these patients (Tan *et al.* 2000a).

It would also be interesting to provide further insight into the mechanisms which contribute to improved walking performance and lower-limb circulatory function as a consequence of upper-limb aerobic exercise training. In particular, the cross-transfer effects of upper-limb aerobic exercise training on lower-limb circulatory function in patients with PAD should be investigated in more detail. This could be achieved by undertaking a shorter programme of upper-limb aerobic exercise training, for example of 12-weeks duration. In order to assess the effect of aerobic upper-limb exercise, techniques such as near-infrared sprectroscopy (NIRS) could be used to look at muscle oxygenation during exercise. This technique is non-invasive and completely painless and harmless to the patient, and has for many years been used in the clinical setting. The use of oxygen uptake kinetics in these patients could also provide further insight.

Patients in whom PAD progresses develop rest pain which leads to chronic critical limb ischaemia. These patients are severely disabled and have extremely low levels of physical activity. The usefulness of this type of exercise modality has yet to be established in this patient group. A possibility could be to take arm-ergometers to these patients and to supervise exercise in the home setting. Such a strategy might improve cardiovascular function in these patients. The influence of exercise in these patients could be observed using both generic (SF-36 *v2* and EQ-5D) and disease specific (WIQ) questionnaires in these patients.

Appendix 1

Prospective Patients for the BHF Claudication Study

(Study conducted at the Centre for Sport & Exercise Science, Sheffield Hallam University)

Inclusion Criteria	Exclusion Criteria
• Patients must present symptoms for > 12 months i.e. condition must be stable • No surgical intervention (i.e. to the lower-limbs) within the last 12 months • Able to undertake exercise • No severe exercise limiting arthritis • No exercise limiting angina • No reports of shortness of breath	• Presenting symptoms for < 12 months • Surgical intervention (i.e. to the lower-limbs) within the last 12 months • Unable to undertake exercise • Severe exercise limiting arthritis • Exercise limiting angina • Reports of shortness of breath

Appendix 2

Letter sent to patients

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Sheffield Hallam University

Dear .....

We are undertaking a British Heart Foundation sponsored study, to compare the effects of a 26-week training programme of both arm- and leg-exercise on the symptoms of claudication.

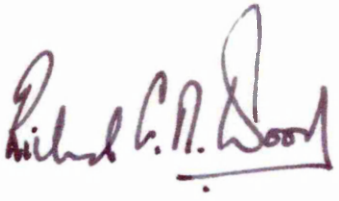
We have recently shown that a 6-week programme of either arm- or leg-exercise can improve walking distances in claudicant patients. We now need to show which is the more efficient way of exercising and whether there are long-term benefits over a home-based programme of walking.

You may have been selected as being a suitable patient from attending the Vascular Clinic or because you have been involved in a previous study.

Please find enclosed a patient information sheet, which describes the study in detail and answers the most frequently asked questions.

One of my staff (Miss Irena Zwierska), will be phoning you shortly to see if you would be interested in participating in this study and will gladly answer any further questions you may have. It is important to note that there is no pressure to participate in this study and if you do not wish to be contacted please phone 0114 225 5690 before (insert date).

Yours sincerely,



Professor R. F. M. Wood, M.D., F.R.C.S.

Appendix 3

Patient Information Sheet

University of Sheffield

THE SHEFFIELD CLAUDICATION STUDY

PATIENT INFORMATION SHEET

Sheffield Hallam University

This study is sponsored by the **British Heart Foundation** and the **Sheffield Vascular Institute**

Q: Why has my doctor asked me to take part in this study?

A: We are currently proposing to undertake a study, in order to compare the effects of a 26-week training programme of both arm- and leg-exercise on the symptoms of claudication. You may have been selected as being a suitable patient from your medical notes or because you have been involved in a previous study.

Exercising the legs can improve your walking distance, however this can be painful. We have recently shown that a 6-week programme of arm-exercise improved walking distances in claudicant patients. The improvements were equivalent to those in patients undertaking leg-exercise. However, the main advantage of undertaking arm-exercise is that patients are able to exercise without experiencing the pain associated with leg-exercise.

Q: What will I have to do?

A: All patients entering the study will have a medical examination and will be randomly allocated to one of three groups. Two groups will be required to undertake either an arm-exercise programme or a leg-exercise programme at the ***Centre for Sport and Exercise Science***, of Sheffield Hallam University, Collegiate Hall, Collegiate Crescent (off Ecclesall Road). The third group will not be required to undertake formal exercise training, but will be actively encouraged to exercise, with monitoring of physical activity using an activity diary.

Q: How long will the study last?

A: The programme will last for a total of 26-weeks. We will monitor everyone's progress with assessments at 6-week intervals and also at 6-, 12-, 24- and 48-weeks after the programme period has ended.

Q: How long will I have to exercise for?

A: If allocated to one of the exercise groups you will be required to exercise twice per week, for a total of 20 minutes during a 40-minute training session – i.e. 2 minutes exercise, 2 minutes rest, 2 minutes exercise, 2 minutes rest etc. All exercise will be carefully supervised and you will be shown how to use the equipment.

Q: Are there side-effects?

A: No side effects have been observed in our previous study and therefore none are expected.

Q: What will the assessment visits entail?

A: During the assessment visits we will:-

1. ask you to perform both arm- and leg-exercise (on two separate days). During these sessions we will monitor your heart rate and take your blood pressure. We will also take a small finger-prick blood sample and measure your oxygen consumption whilst you are exercising.
2. assess the distance that you can walk and take your blood pressure and a small finger-prick blood sample before and after walking.
3. take a small blood sample from you.

You will also be asked to complete a brief questionnaire at the start of the study, at the end of the training period and again when the study has ended. Two additional brief questionnaires will be completed during the training period and also during the assessment sessions.

Q: What if I do not wish to take part?

A: This will in no way affect your treatment.

Q: What if I change my mind during the study?

A: You are free to withdraw from the study at any time without affecting your treatment.

Q: What will happen to the information from the study?

A: The overall conclusions of the study will be available to you, however it will not be possible to produce an individualised report of your performance.

Q: What if I have further questions?

A: If you have any further questions with regards to this study you may phone:-

IF YOUR QUERY IS REGARDING ...	CONTACT	AT THE	TELEPHONE NUMBER
Participating in this study or the arrangements for the training and assessment sessions, at the:- CENTRE FOR SPORT & EXERCISE SCIENCE	**Miss IRENA ZWIERSKA OR DR JOHN SAXTON**	**CENTRE FOR SPORT & EXERCISE SCIENCE (SHEFFIELD HALLAM UNIVERSITY)**	**0114 225 5690 (DIRECT LINE)** / **0114 225 4414 (DIRECT LINE)**
Participating in this study	**DR GRAHAM POCKLEY**	**NORTHERN GENERAL HOSPITAL**	**0114 271 4450 (DIRECT LINE)**
Your health (i.e. medically related)	**MR SOHAIL CHOKSY**		**0114 271 4914 (DIRECT LINE)**

Appendix 4

PATIENT CONSENT FORM

To be completed by the patient:

Have you read the information sheet about this study?
YES/NO

Have you been able to ask questions about this study?
YES/NO

Have you received answers to all your questions?
YES/NO

Have you received enough information about this study?
YES/NO

Who have you spoken to about this study?

.....

Do you understand that you are free to withdraw from this study at any time?
YES/NO

Without giving a reason for withdrawing
YES/NO

Without affecting your future medical care
YES/NO

Do you agree to take part in this study?
YES/NO

Signed:

Name (Block Letters):
Date:
Witness:

Appendix 5

The PAR-Q Form

Physical Activity Readiness Questionnaire - PAR-Q (revised 1994)

PAR - Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO		
☐	☐	1.	Has you doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
☐	☐	2.	Do you feel pain in your chest when you do physical activity?
☐	☐	3.	In the past month, have you had chest pain when you were not doing physical activity?
☐	☐	4.	Do you lose your balance because of dizziness or do you ever lose consciousness?
☐	☐	5.	Do you have a bone or joint problem that could be made worse by a change in your physical activity?
☐	☐	6.	Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
☐	☐	7.	Do you know of any other reason why you should not do physical activity?

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want—as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active—begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal—this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever—wait until you feel better; or
- if you are or may be pregnant—talk to your doctor before you start becoming more active.

Please note: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

You are encouraged to copy the PAR-Q but only if you use the entire form

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction.

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT _____ WITNESS _____
or GUARDIAN (for participants under the age of majority)

Supported by: Health Canada Santé Canada

FIGURE 2-1. PAR-Q form. (Reprinted with permission from the Canadian Society for Exercise Physiology, Inc., 1994.)

Appendix 6

The Borg RPE scale

6	No exertion at all
7	
8	Extremely light
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Appendix 6. The Borg RPE (15-graded) scale (Gunnar Borg, 1998).

Appendix 7

The Borg CR10 scale

0	Nothing at all	"No P"
0.3		
0.5	Extremely weak	Just noticeable
1	Very weak	
1.5		
2	Weak	Light
2.5		
3	Moderate	
4		
5	Strong	Heavy
6		
7	Very strong	
8		
9		
10	**Extremely strong**	**"Max P"**
11		
•	Absolute maximum	Highest possible

Appendix 7. The Borg CR10 scale (Gunnar Borg, 1998).

Appendix 8

Borg's RPE scale instructions

While exercising I want you to rate your perception of exertion, i.e., how heavy and strenuous the exercise feels to you. The perception of exertion depends mainly on the strain and fatigue in your muscles and on your feeling of breathlessness or aches in the chest. Look at this rating scale; I want you to use this scale from 6 to 20, where

6 means "no exertion at all"

9 corresponds to "very light" exercise.
For a normal, healthy person it is like walking slowly at his or her own pace for some minutes.

13 on the scale is "somewhat hard" exercise, but it still feels OK to continue.

17 "very hard" is very strenuous.
A healthy person can still go on, but he or she really has to push him or herself. It feels very hard and the person is very tired.

19 on the scale is an "extremely strenuous" exercise level.
For most people this is the most strenuous exercise they have ever experienced.

20 means "maximal exertion".

Try to appraise your feeling of exertion as honestly as possible, without thinking about what the actual physical load is. **Don't underestimate it, but don't overestimate it either.** It's your own feeling of effort and exertion that's important, not how it compares to other people's. What other people think is not important either. Look at the scale and the expressions when performing exercise and then give a number.

Scaling perceived exertion

We want you to rate your perceived (P) exertion, that is, how heavy and strenuous the exercise feels to you. This depends mainly on the strain and fatigue in your muscles and on your feeling of breathlessness or aches in the chest. But you must only attend to your subjective feelings and not to the physiological cues or what the actual physical load is.

Appendix 9

Borg's CR-10 scale instructions

Basic instruction : 10, "Extremely strong – Max P", is the main anchor. It is the strongest perception (P) you have ever experienced. It may be possible, however, to experience or to imagine something even stronger. Therefore, "Absolute maximum" is placed somewhat further down the scale without a fixed number and marked with a dot "•". If you perceive an intensity stronger than 10, you may use a higher number.

Start with a *verbal expression* and then choose a *number*. If your perception is "Very weak", say 1; if "Moderate", say 3; and so on. You are welcome to use half values (such as 1.5, or 3.5 or decimals, for example, 0.3, 0.8, or 2.3). It is very important that you answer what *you* perceive and not what you believe you ought to answer. Be as honest as possible and try not to overestimate or underestimate the intensities.

Scaling pain

What are your worst experiences of pain? If you use 10 as the strongest exertion you have ever experienced or can think of, how strong would you say that your three worst pain experiences have been?

10 "Extremely strong – Max P" is your main point of reference. It is anchored in your previously experienced worst pain, which you just described, the "Max P".

- Your worst pain experienced, the "Max P" may not be the highest possible level. There may be pain that is still worst. If that feeling is somewhat stronger, you will say 11 or 12. If it is much stronger, 1.5 times "Max P", you will say 15.

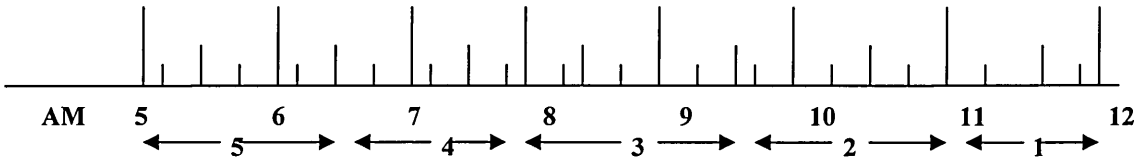
Appendix 10 - Modified Horne & Ostberg's (1976) Lark/Owl Questionnaire

Questionnaire Relating to an Individuals Time Preference to Perform Physical Activity

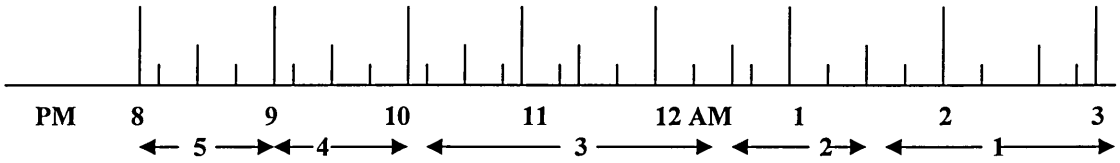
1. Please read each question very carefully before answering.
2. Answer ALL questions.
3. Answer questions in numerical order.
4. Each question should be answered independently of others. DO NOT go back and check your answers.
5. All questions have a selection of answers. For each question place a circle around ONE answer only. Some questions have a scale instead of a selection of answers. Place a cross at the appropriate point along the scale.
6. Please answer each question as honestly as possible. Both your answers and your results will be kept, in strict confidence.
7. Please feel free to make any comments in the section provided below each question.

The Questionnaire, with scores for each choice.

1. Considering only your own "feeling best" rhythm, at what time would you get up if you were entirely free to plan your day?



2. Considering only your own "feeling good" rhythm, at what time would you go to bed if you were entirely free to plan your evening?



3. If there is a specific time at which you have to get up in the morning, to what extent are you dependent on being woken up by an alarm clock?

Not at all dependent ...	4
Slightly dependent ...	3
Fairly dependent ...	2
Very dependent ...	1

4. Assuming adequate environmental conditions, how easy do you find getting up in the mornings?

Not at all easy ...	1
Not very easy ...	2
Fairly easy ...	3
Very easy ...	4

5. How alert do you feel during the first half hour after having woken in the mornings?

Not at all alert...	1
Slightly alert...	2
Fairly alert...	3
Very alert...	4

6. How is your appetite during the first half-hour after having woken in the mornings?

Very poor...	1
Fairly poor ...	2
Fairly good...	3
Very good...	4

7. During the first half-hour after having woken in the morning, how tired do you feel?

Very tired...	1
Fairly tired...	2
Fairly refreshed...	3
Very refreshed...	4

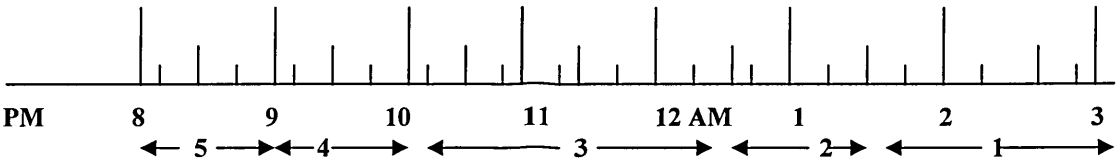
8. When you have no commitments the next day, at what time do you go to bed compared to your usual bedtime?

Seldom or never later...	4
Less than 1 hour later...	3
1-2 hours later...	2
More than 2 hours later...	1

9. You have decided to engage in some physical activity. A friend suggests that you do this 1 hour twice a week and the best time for him/her is between 7-8 AM. Bearing in mind nothing else but your own "feeling best" rhythm, how do you think you would perform?

Would be on good form...	4
Would be on reasonable form...	3
Would find it difficult...	2
Would find it very difficult...	1

10. At what time in the evening do you feel tired and as a result in need of sleep?



11. You wish to be at your peak performance for a test which you know is going to be mentally exhausting and lasting for two hours. You are entirely free to plan your day and considering only your own "feeling best" rhythm, which ONE of the four testing times would you choose?

8.00 - 10.00 AM...	6
11.00 AM - 1.00 PM...	4
3.00 PM - 5.00 PM...	2
7.00 PM - 9.00 PM...	0

12. If you went to bed at 11.00 PM, at what level of tiredness would you be?

Not at all tired...	0
A little tired...	2
Fairly tired...	3
Very tired...	5

13. For some reason you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which ONE of the following events are you most likely to experience?

Will wake up at usual time and will NOT fall asleep...	4
Will wake up at usual time and WILL dose thereafter...	3
Will wake up at usual time but will fall asleep again...	2
Will NOT wake up until later than usual...	1

14. One night you have to remain awake between 4.00 - 6.00 AM in order to carry out a night watch. You have no commitments the next day. Which ONE of the following alternatives will suit you best?

Would NOT go to bed until watch was over...	1
Would take a nap before and sleep after...	2
Would take a good sleep before and a nap after...	3
Would take ALL sleep before watch...	4

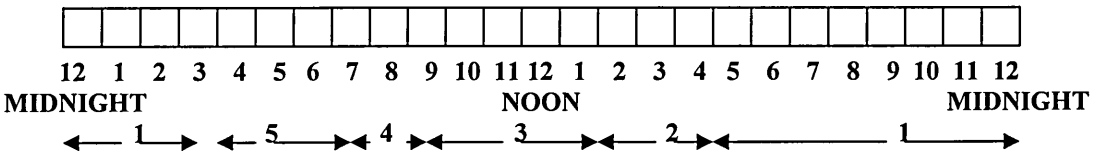
15. You have to do two hours of hard physical work. You are entirely free to plan your day and considering only your own "feeling best" rhythm, which ONE of the following times would you choose?

8.00 - 10.00 AM...	4
11.00 - 1.00 PM...	3
3.00 - 5.00 PM...	2
7.00- 9.00 PM...	1

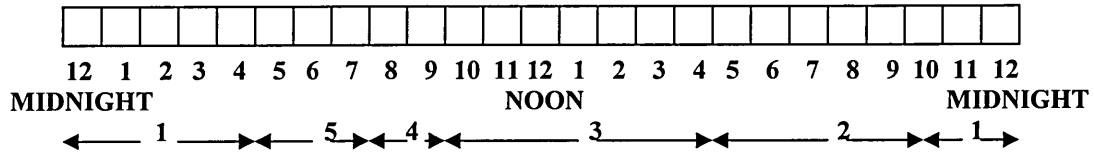
16. You have decided to engage in hard physical exercise. A friend suggests that you do this for one hour twice a week and the best time for him/her is between 10.00 - 11.00 PM. Bearing in mind nothing else but your own "feeling best" rhythm, how well do you think you would perform?

Would be on good form...	1
Would be on reasonable form...	2
Would find it difficult...	3
Would find it very difficult...	4

17. Suppose that you can choose your own work hours. Assume that you worked a FIVE-hour day (including breaks) and that your job was interesting and paid by results. Which FIVE CONSECUTIVE HOURS would you select ?



18. At what time of the day do you think that you reach your "feeling best" peak?



19. One hears about "morning" and "evening" types of people. Which ONE of these types do you consider yourself to be ?

Definitely a "morning" type...	6
Rather more a "morning" than an "evening" type...	4
Rather more an "evening" than a "morning" type...	2
Definitely an "evening" type...	0

Appendix 11

Demographics

Name:		
Address:		
Tel.		
Hospital No.		
D.O.B	**Age:**	**Male/Female**

INCLUSION CRITERIA

Symptoms > 12 months	☐	No Exercise limiting angina	☐
Able to undertake exercise	☐	No Shortness of breath	☐
No Interventional Procedure within the last 12 months	☐	No Severe Arthritis	☐

Past Medical History

Heart Attack	☐	High Cholesterol	☐	Chronic Airways Disease	☐
Stroke	☐	Dyspnoea	☐	Smoker	☐
Hypertension	☐	Alcohol	☐	Ex-Smoker	☐
Diabetes	☐	Angina	☐		

Presenting Complaint

Claudication Distance (m):	Maximum Walking Distance (m):

Operations

Date:	Operation:
Date:	Operation:
Date:	Operation:

Current Medication

Examination

Pulse		Popliteal	
Blood Pressure		Femoral	
		Posterior Tibial	
Ankle/Brachial Pressure Index		Dorsalis Pedis	

ECG	
Angiogram	
Duplex	

Any additional relevant information

-
-
-
-
-

Date of examination.....
Signed.....

Appendix 12

Letter sent to GP

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Sheffield Hallam University

Dear Dr.....

A comparison of upper- and lower-limb exercise training in patients with intermittent claudication

Re:.....

Your above named patient has consented to participate in a British Heart Foundation supported study, to determine the relative efficacy of a 6-month programme of upper-limb or lower-limb exercise training on walking distances in patients with intermittent claudication. The study, devised by the Sheffield Vascular Institute, will help to establish the mechanisms underlying exercise-induced symptomatic improvements with the aim of developing more effective strategies for the treatment of patients with peripheral vascular disease.

This is a controlled study and all participating patients will be randomised into one of three groups;- supervised upper-limb training, supervised lower-limb training or no-training (control) groups. Prior to entering this study all patients will have a full medical assessment at the Northern General Hospital.

Those patients randomised to the training groups will undertake 20 minutes of supervised exercise, twice a week for a period of 6 months. The study will be performed at the ***Centre for Sport and Exercise Science***, of Sheffield Hallam University (off Ecclesall Road). The control group will not be required to undertake formal exercise training, but will be actively encouraged to exercise and their physical activity will be monitored using an activity diary.

Every 6 weeks during the 6-month training period, all three patient groups will undergo walking distance assessments and incremental arm- and leg-ergometer assessments. During these assessment sessions blood pressure, blood lactate and peak oxygen consumption (peak VO_2) will be measured. A small blood sample will also be taken to measure systemic inflammatory responses to the exercise. Quality of life will be assessed by means of a questionnaire. Patients will also be assessed 6-, 12-, 24- and 48-weeks after the cessation of the 6-month training programme. The control group will be assessed at similar time points.

If you have any concerns or questions regarding your patient participating in this study please do not hesitate to contact me, my direct line telephone number is **0114 225 5690**.

Yours sincerely,

Miss Irena Zwierska, BSc, MSc,
Research Assistant, BHF Project

Appendix 13

Medical Outcomes Study SF-36 v2 Questionnaire

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
c. Lifting or carrying groceries	☐1	☐2	☐3
d. Climbing several flights of stairs	☐1	☐2	☐3
e. Climbing one flight of stairs	☐1	☐2	☐3
f. Bending, kneeling, or stooping	☐1	☐2	☐3
g. Walking more than a mile	☐1	☐2	☐3
h. Walking several hundred yards	☐1	☐2	☐3
i. Walking one hundred yards	☐1	☐2	☐3
j. Bathing or dressing yourself	☐1	☐2	☐3

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4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

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6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

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9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b. Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f. Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g. Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h. Have you been happy?	☐1	☐2	☐3	☐4	☐5
i. Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b. I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c. I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d. My health is excellent	☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!

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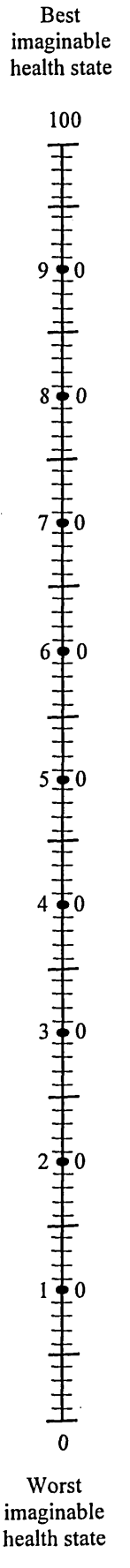
Appendix 14

EuroQoL EQ-5D

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

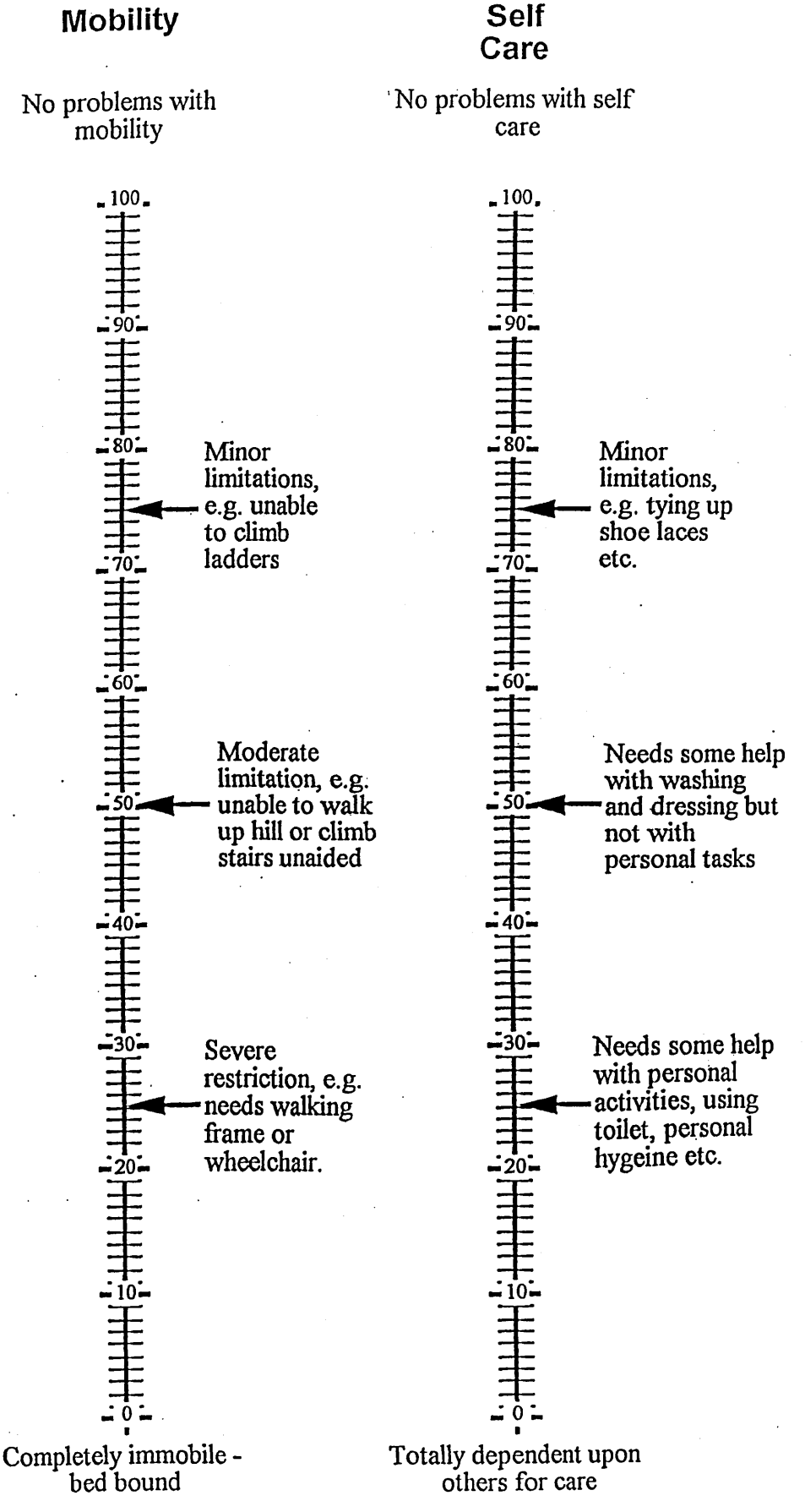
We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

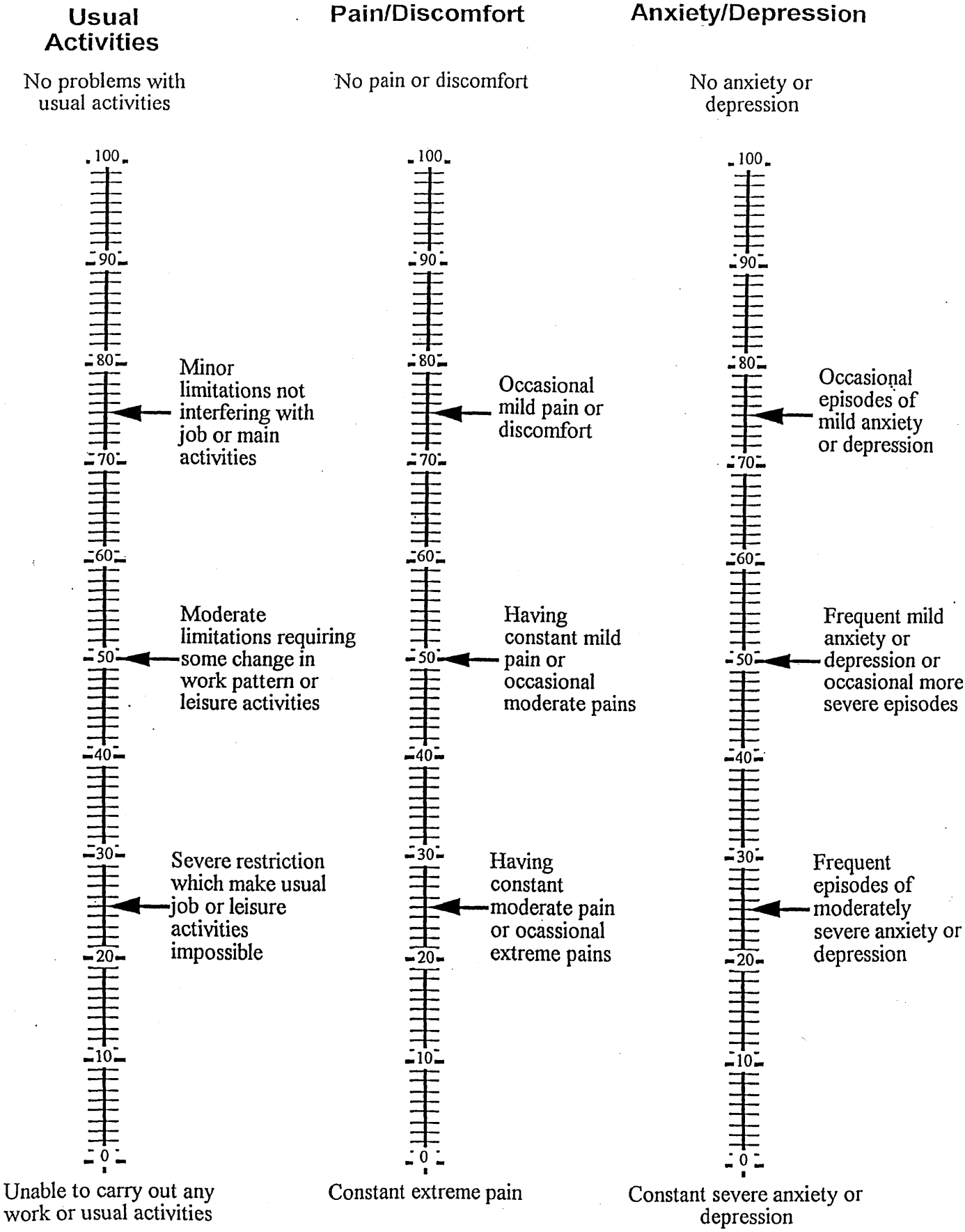
Your own health state today



Now could you mark the scales on this and the next page to show how you would rate your current state for each of the specific areas shown.

Some examples have been put on the scales to help you to identify where your own state should be but you are free to mark any point on the scale.




Usual Activities
No problems with usual activities
100
90
80
70
60
50
40
30
20
10
0
Minor limitations not interfering with job or main activities
Moderate limitations requiring some change in work pattern or leisure activities
Severe restriction which make usual job or leisure activities impossible
Unable to carry out any work or usual activities
Pain/Discomfort
No pain or discomfort
Occasional mild pain or discomfort
Having constant mild pain or occasional moderate pains
Having constant moderate pain or ocassional extreme pains
Constant extreme pain
Anxiety/Depression
No anxiety or depression
Occasional episodes of mild anxiety or depression
Frequent mild anxiety or depression or occasional more severe episodes
Frequent episodes of moderately severe anxiety or depression
Constant severe anxiety or depression

Walking Impairment Questionnaire (WIQ)

1. Walking impairment. These questions ask about the reasons why you had difficulty walking. We would like to know how much difficulty you had walking because of each of these problems during the last week. By difficulty, we mean how hard it was or how much physical effort it took to walk because of each of these problems.

A. PAD-Specific Questions	Leg (Right / Left / Both)	Degree of Difficulty: None	Slight	Some	Much	Very	Score
1. Pain, aching or cramps in your calves (or buttocks) % Score = (Individual Score/4) x 100		4	3	2	1	0	

B. Differential Diagnosis	None	Slight	Some	Much	Very	Score
1. Pain, stiffness, or aching in your joints (ankles, knees, or hips)?	4	3	2	1	0	
2. Weakness in one or both your legs?	4	3	2	1	0	
3. Pain or discomfort in your chest?	4	3	2	1	0	
4. Shortness of breath?	4	3	2	1	0	
5. Heart palpitations?	4	3	2	1	0	
6. Other problems? (Please list)	4	3	2	1	0	

2. Walking distance: Report the degree of physical difficulty that best describes how hard it was for you to walk on level ground without stopping to rest for each of the following distances during the last week:

Distance	Degree of Difficulty: None	Slight	Some	Much	Unable	Weight: Feet	Score
1. Walking indoors such as around your home?	4	3	2	1	0	x 20 =	
2. Walking 50 feet?	4	3	2	1	0	x 50 =	
3. Walking 150 feet (½ block)?	4	3	2	1	0	x 150 =	
4. Walking 300 feet (1 block)?	4	3	2	1	0	x 300 =	
5. Walking 600 feet (2 blocks)?	4	3	2	1	0	x 600 =	
6. Walking 900 feet (3 blocks)?						x 900 =	
7. Walking 1500 feet (5 blocks)?	4	3	2	1	0	x1500=	
% Score = (Sum Individual Score/14080) x 100							

3. Walking speed: Report the degree of physical difficulty that best describes how hard it was for you to walk one city block (300 feet) on level ground at each of these speeds without stopping to rest during the last week:

Speed	Degree of Difficulty: None	Slight	Some	Much	Unable	Weight: Mph	Score
1. Walking 1 block slowly?	4	3	2	1	0	x 1.5 =	
2. Walking 1 block at an average speed?	4	3	2	1	0	x 2.0 =	
3. Walking 1 block quickly?	4	3	2	1	0	x 3.0 =	
6. Running or jogging 1 block?	4	3	2	1	0	x 5.0 =	
% Score = (Sum Individual Score/ 46) x 100							

4. Stair climbing: For each of these questions, report the degree of physical difficulty that best describes how hard it was for you to climb stairs without stopping to rest during the past week:

Stairs	Degree of Difficulty: None	Slight	Some	Much	Unable	Weight	Score
1. Climbing 1 flight of stairs?	4	3	2	1	0	x 12 =	
2. Climbing 2 flights of stairs?	4	3	2	1	0	x 24 =	
3. Climbing 3 flights of stairs?	4	3	2	1	0	x 36 =	
% Score = (Sum Individual Score/ 288) x 100							

Appendix 16

Self perceived walking ability

As a result of the 24-week intervention period, do you feel that your walking ability has changed?

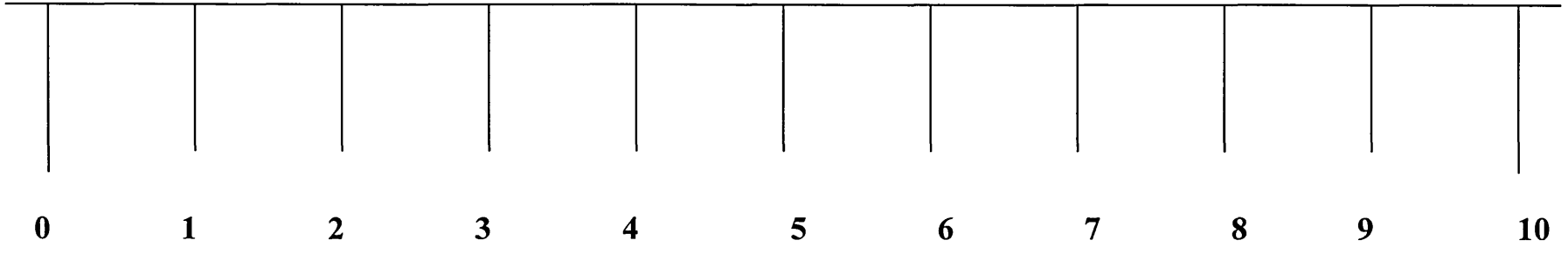
Please answer this question as honestly as possible, giving one response only, by circling the correct response.

Do you feel that your walking ability has now:-		
Improved	Remains Unchanged	Deteriorated

Appendix 17

Confidence in walking

Do you feel that your confidence in walking has changed? Please circle the number, which best describes your general confidence in walking (0-10 scale, 0 denoting no confidence and 10 denoting total confidence in walking). Please answer this question as honestly as possible.



No Confidence **Total Confidence**

Appendix 18

Peripheral Arterial Disease Physical Activity Recall (PAD-PAR)

Patient ID No.....
Week No.....
Date.....

1. How many hours do you sleep a night, on average?
   Hours x 7 =
   Sleep hours per week =

2. Explain to patient that you are going to ask about typical work activities performed during the past week (includes work for pay or regular volunteer activities).
   If patient is not employed, go to question 3.
   How many total hours did you work per week on average?
   Work hours per week?

   Here is a listing of typical work activities (show participant CARD A).
   Activities are classified as heavy, moderate, light and very light, depending on their average energy demands.
   With your job, time may be spent in more than one category of activity. Let's start with heavy activities and then go on to moderate, light and then very light activities.

   a) **Please tell me the average number of days during the last week you performed heavy activities at work**
   b) **Please tell me the average length of time you performed heavy activities in a day.**

Then, repeat above directions for all intensities of activity.

Intensity of Activity	Days per Week (0.5 to 7.0)	Hours per Day (nearest 0.5 h)	Hours per Week	MET Hours per Week
Heavy (5.1 - 7.0 METs)				
Moderate (3.1 - 5.0 METs)				
Light (2.1 - 3.0 METs)				
Very Light (0.9 - 2.0 METs)				
TOTAL				

3. **Did you perform household chores or yard work around the home during the past week? (Follow instructions given above, except refer to CARD B). If yes, how many total hours did you spend in household chores?**

Household or yard hours per week =

Intensity of Activity	Days per Week (0.5 to 7.0)	Hours per Day (nearest 0.5 h)	Hours per Week	MET Hours per Week
Heavy (5.1 - 7.0 METs)				
Moderate (3.1 - 5.0 METs)				
Light (2.1 - 3.0 METs)				
Very Light (0.9 - 2.0 METs)				
TOTAL				

4. Did you perform recreational or leisure-time activities during the past week (Refer to CARD C). If yes, how many total hours did you spend in leisure activities?

Recreation or leisure hours per week =

Intensity of Activity	Days per Week (0.5 to 7.0)	Hours per Day (nearest 0.5 h)	Hours per Week	MET Hours per Week
Heavy (5.1 - 7.0 METs)				
Moderate (3.1 - 5.0 METs)				
Light (2.1 - 3.0 METs)				
Very Light (0.9 - 2.0 METs)				
TOTAL				

Appendix 19

A Range of Physical Activities

Selected list of activities with MET Values (in Parentheses)*

Card A	**Physical Activities at Wok**		
Heavy	**Moderate**	**Light**	**Very Light**
Heavy power tools (6.0)	Locksmith (3.5)	Cashier (2.5)	Sitting (1.5)
Coal mining (7.0)	Carrying < 20 lbs (5.0)	Light assembly (2.5)	Standing (2.0)
Loading truck (6.5)	Farming (4.5)	Physician (2.5)	Typing (1.5)
Shovelling (7.0)	Machine tooling (4.0)	Teacher (2.5)	Computer work (1.5)
Heavy carpentry (7.0)	Forestry, chain saw (4.5)	Tailoring, machine (2.5)	Receptionist (1.5)

Card B	**Household Chores and Yard Work**		
Heavy	**Moderate**	**Light**	**Very Light**
Roofing (6.0)	Food shopping (3.5)	Preparing meals (2.5)	Sitting (1.5)
Digging (5.0)	Heavy cleaning (4.5)	Sweeping (2.5)	Standing/laundry (1.5)
Chopping wood (6.0)	Laying carpet (4.5)	Making bed (2.5)	Fold, hang clothes (1.5)
Shoveling snow (6.0)	Weeding (4.5)	Fertilising (2.5)	Sewing (1.5)
Manual lawn mowing (6.0)	Power lawn mowing (4.5)	Ironing (2.3)	

Card C	**Recreational Activities**		
Heavy	**Moderate**	**Light**	**Very Light**
Walking/hiking uphill (6.0)	Walking, level (4.0)	Walking (< 3 mph) (2.5)	Playing flute (2.0)
Moderate canoeing (7.0)	Easy bicycling (5.0)	Bowling, billiards (2.5)	Playing cards (1.5)
Bicycling 10-12 mph (6.0)	Frisbee, ultimate (3.5)	Walking down stairs (3.0)	Television/radio (1.0)
Light stationary cycle (5.5)	Ping pong (4.0)	Modern jazz (3.0)	Reading (1.0)
Aerobic dance (7.0)	Weight lifting (3.5)	Croquet (2.5)	Music listening (1.0)
Leisurely swimming (6.0)	Light rowing (3.5)	Golf with cart (2.5)	Socialising (2.0)

*MET values for many activities can be obtained from Ainsworth BE, *et al.* Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc.* 1993; 25: 71-80.

Appendix 20

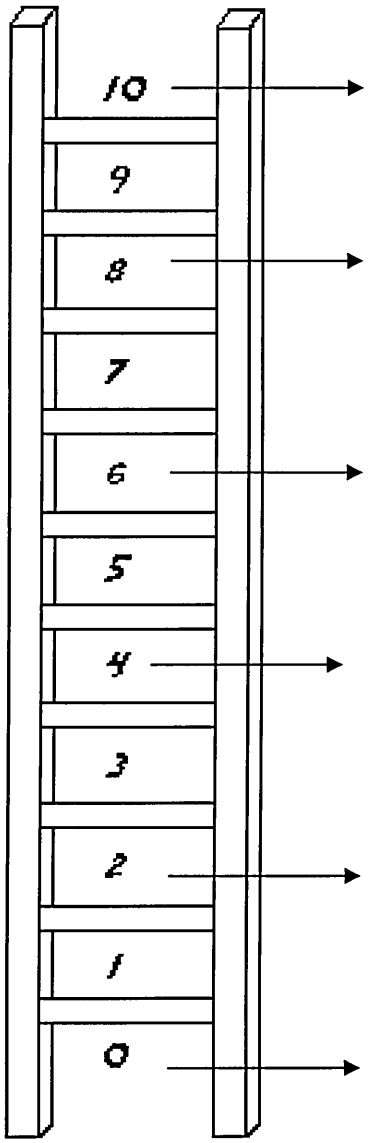
Self perception of changes in physical activity status

Please circle the **number on the ladder** that best describes your level of physical activity.

Please answer this question as honestly as you can.

*Regular exercise =

three or more times per week for 20 minutes or longer of moderate exercise e.g. walking briskly or cycling, swimming.



I exercise regularly* and have done so for longer than 6 months.

I exercise regularly* but have done so for less than 6 months.

I currently exercise some, but not regularly*

I have exercised in the past 6 months but have not done so recently

I currently don't exercise but I am thinking about starting in the next 6 months

I currently don't exercise and I do not intend to start in the next 6 months

Appendix 21

Incentive to perform physical activity

Do you feel that the 24-week intervention period has provided you with an incentive to perform physical activity? Please answer this question as honestly as possible, by circling the correct response.

Do you feel that this study has provided you with an incentive to perform physical activity?	
Incentive	No Incentive

Appendix 22

RISK ASSESSMENT PROFORMA

SHEFFIELD HALLAM UNIVERSITY

SCHOOL OF SPORT LEISURE AND MANAGEMENT

PROCEDURE: British Heart Foundation Funded Study: A comparison of upper- and lower-limb exercise training in patients with intermittent claudication.

ASSESSMENT No:- IZ/BHF/Out-line

DATE ASSESSED:- 23rd March 2001

ASSESSED BY:- Mr Graham Jarman and Dr John M. Saxton

SIGNED:- **POSITION:-**

HAZARDS	RISKS AND SPECIFIC CONTROL MEASURES
1. Cardio-vascular complications	**Medium** (C3xL2=R6). All patients to have a full clinical assessment prior to enrolment onto the study. Vascular Surgeon to be present at initial assessment session.
2. Venepuncture	**Medium** (C3xL1=R4). Reference should be made to CSES/SLM specific risk assessment.
3. Capillary blood sampling	**Low** (C2xL1=R2). Reference should be made to CSES/SLM specific risk assessment.
4. Use of ergometers	**Medium** (C3xL2=R6). Reference should be made to CSES/SLM assessment on maximal oxygen consumption on a friction braked ergometer.

RISK EVALUATION (OVERALL): MEDIUM

GENERAL CONTROL MEASURES

Medical pre-screening must be carried out on **all** patients prior to enrolment onto the study. Medical supervision should be arranged for each initial assessment session. In addition, at least one first aider should be present at each assessment and each training session. When there is in attendance a qualified medical practitioner or person trained in advanced life support, an automated external defibrillator should be available. All of the risk assessments referred to above must be adhered to.

EMERGENCY PROCEDURES

Initiate first aid response in accordance with training and agreed CSES procedures.

MONITORING PROCEDURES

All safety procedures to be monitored throughout the assessment and training sessions.

REVIEW PERIOD

Annually.

REVIEWED BY:

Mr Graham Jarman / Dr John M. Saxton **Date:** 23 March 2001

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