

Research article

The impact of short term supervised and home-based walking programmes on heart rate variability in patients with peripheral arterial disease

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Abstract

The aims of the study were to determine whether heart rate variability (HRV) measured at rest and during exercise could be altered by an exercise training programme designed to increase walking performance in patients with peripheral arterial disease. Forty-four volunteers were randomised into 12 weeks of either: supervised walking training twice weekly for 30 min at 75% $\dot{V}O_{2peak}$ (SU), home-based walking training sessions: twice weekly, 30 min per week (HB) or no exercise (CT). HRV measures were calculated from a 5-min resting ECG. Each patient then underwent maximal, graded exercise treadmill testing. All measures were repeated after 12 weeks. The SU group showed significantly ($p < 0.001$) increased maximal walking time (MWT) but no change in $\dot{V}O_{2peak}$. There were no statistically significant changes in any of the measures of HRV in any group. Effect sizes for change in HRV measures were all very small and in some cases negative. Improved walking performance was not accompanied by central cardiorespiratory or neuroregulatory adaptations in the present study. The lack of any change in HRV was possibly due to either the low intensity or discontinuous nature of exercise undertaken.

Key words: Exercise, ischemia, autonomic nervous system.

Introduction

Peripheral arterial disease (PAD) has an age-adjusted prevalence of 12% (Criqui 2001). Although only a quarter of PAD patients are symptomatic (Stewart et al., 2002) treatment is of great importance as sufferers have increased risk of coronary and cerebrovascular events similar to coronary artery disease (CAD) patients (Dormandy et al., 1999). The most commonly reported symptom of PAD is exercise-induced, ischemic leg pain or intermittent claudication (IC) (Zatina et al., 1986). Patients commonly have greatly reduced levels of physical activity and display low functional capacities (Hiatt et al., 1994).

Heart rate variability (HRV) is a non-invasive measure of autonomic modulation. Attenuated HRV has been reported in patients with CAD (Bigger et al., 1995; Hayano et al., 2001; Kuo and Chen 1998) and is predictive of future cardiac event in this population (van Boven et al., 1998). Aerobic exercise training can increase selected HRV measures in patients with CAD (Lucini et al., 2002) and other cardiovascular diseases (Tygesen et al., 2001; Sandercock et al., 2007). Commonly, exercise in-

intensities of 50 – 75% $\dot{V}O_{2peak}$ for durations of 25 to 60 min are used and evidence of a threshold for improved HRV due to exercise training exists (Pardo et al., 2000).

Walking is the most commonly used rehabilitative exercise modality in PAD patients and commonly produces large increases in walking capacity, often accompanied by more modest alterations in cardiopulmonary function (Hiatt et al., 1994). Supervised exercise remains the gold standard for rehabilitation in PAD patients (Degischer et al., 2002) but more economical, home-based exercise training can also increase exercise capacity (Imfeld et al., 2006).

Exercise-induced IC limits the duration of any continuous walking exercise in PAD patients who commonly require frequent rest periods during exercise to recover from leg pain. The effects that such a discontinuous exercise regimen may exert on the autonomic nervous system remain unclear.

The aims of the present study were to determine whether a supervised treadmill walking protocol and a home-based walking programme could alter autonomic function in PAD patients. It was hypothesised that improvements in walking performance from home-based and supervised exercise would be accompanied by increased global and particularly vagal measures of HRV.

Methods

Subjects

Subjects were 52 consecutive patients referred by a single practitioner from the vascular outpatient clinic in a UK district general hospital. Patients were referred to the investigators by a single practitioner. Participants were provided with oral and written information regarding the study. Volunteers gave written, informed consent to participate in the study. All procedures were approved by the local research ethics committee and carried out in accordance with the Declaration of Helsinki (World Medical Association 1997)

Subjects' body mass (Seca 880 Scales, Seca Ltd., Hamburg, Germany) and stature (Seca 202 Stadiometer, Seca Ltd., Hamburg, Germany) were measured. The presence of PAD was then confirmed by measurement of an ankle-to-brachial index < 0.94 at rest. This measurement was made by a trained technician using a Mini Dopplex, (Model 2000, Huntleigh Diagnostics, Cardiff, UK).

Measurements were made at the vascular outpatients clinic on the morning prior to initial exercise testing. All measurements were made in accordance with the recommendations of the Society of Cardiovascular and Interventional Radiology.

All patients were confirmed as having symptomatic IC during walking, using the Leg Pain Scale (ACSM 2000). Exclusion criteria included inability to perform a familiarisation test, poorly controlled hypertension, poorly controlled diabetes, severe coronary artery disease (angina at rest), valvular heart disease, limb ischemia and debilitating pulmonary disease.

Heart rate variability analysis

Subjects were advised to avoid caffeine-containing beverages and asked not to smoke on the morning of testing. Five-minute ECG recordings were made using a standard 12-lead ECG (CardioPerfect ST 2001, Cardio Control, Delft, The Netherlands) while each patient rested in the semi-recumbent position in a quiet room. This commercially available system is designed to measure HRV indices in accordance with recommended standards (Taskforce 1996). Briefly, each tachogram was first filtered using an automated beat rejection and interpolation algorithm. Beats were rejected if they differed by a default value of > 20% from previous interval and interpolated based on neighbouring intervals. The resultant time series was transformed into the frequency domain using a fast Fourier transformation and the following HRV indices calculated: low frequency spectral power (LF, 0.04 - 0.15 Hz) high frequency power (HF, 0.15-0.40 Hz). LF was assumed to be a measure of mixed sympathovagal modulation, HF was used as a marker of cardiac vagal modulation, and the ratio of LF to HF power (LF:HF) was calculated as a marker of sympathovagal interaction.

After initial ECG recordings were made, subjects remained seated while brachial blood pressure was measured using a hand-held aneroid sphygmomanometer to ensure that blood pressure was within the acceptable limits to perform exercise. Each patient then received a short familiarisation session on the treadmill (Marquette 2000, Marquette Electronics, Milwaukee, WI, USA). During this time the speed was gradually increased to that required for the treadmill testing protocol (2 mile·hr⁻¹). A 12-lead ECG was recorded during the familiarisation period, monitored in real time by one researcher and recorded and stored on hard disk. Patients then rested in the seated position until heart rate had returned to within ± 10% of baseline.

Exercise testing

Each patient completed a graded treadmill test recommended for use in PAD patients (Labs et al., 1999). All tests were carried out in the same laboratory between 9.00 and 11.00 am. To reduce potential fatigue, subjects were advised not to undertake strenuous activity on the day of testing and all subjects arrived at the hospital by motor vehicle. Subjects walked on the treadmill at an initial speed of 2 mile·h⁻¹ for 2 min. The gradient of the treadmill was then increased by 2% every 2 min until test termination. Good reliability of treadmill test scores and clinical measurements taking during and after this test

have been demonstrated previously (Labs et al., 1999). During exercise, heart rate was measured and recorded via a 12-lead ECG; oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were measured breath-by-breath, using an online analysis system (Medical Graphics Cardio₂, Medical Graphics Corporation, St. Paul, Minnesota). Blood pressure and ratings of perceived exertion (RPE) were measured during the last minute of each stage. The onset and change in severity of claudication pain was assessed using the Leg Pain Scale (ACSM, 2000) which rates claudication pain from 1 (mild discomfort) to 4 (excruciating and unbearable pain). The following exercise termination criteria were employed: volitional exhaustion, achievement of $\dot{V}O_{2max}$ according to recognised criteria (ACSM 2000), heart rate within 10% of age related maximum, sustained ST segment depression > 2 mm, acute chest pain, acute leg pain other than that of ischemic origin. Maximal walking time (MWT), peak oxygen uptake achieved ($\dot{V}O_{2peak}$, mL·kg⁻¹·min⁻¹), and peak heart rate (HR_{peak}) were recorded. All testing procedures were then repeated at the same time of day at 6 and 12 weeks.

Randomisation and intervention

Following initial treadmill testing, subjects were randomly allocated to 12 weeks of either: supervised exercise (SU), home-based exercise (HB) or no exercise (CT) using random number tables. Researchers and patients remained blind to group allocation until after initial testing procedures were completed. The SU group attended the hospital twice a week to complete a total of 30 min treadmill walking per visit, at a work rate equivalent to 70 - 75% of $\dot{V}O_{2peak}$. The intensity of exercise was adjusted by the researchers to account for improvements in exercise tolerance and performance using the RPE scale. This training protocol was similar to those used previously that have been associated with significant increases in walking performance (Stewart et al., 2002). The SU group were given an exercise diary to complete and instructed to undertake one additional weekly 30 min walking session. The HB group were given an exercise diary to complete and instructed to undertake three 30 min walking sessions per week at an RPE of 12 - 14. This group was also contacted weekly by telephone and given support and encouragement in adhering to the protocol. The CT group were given verbal information regarding the safety and efficacy of walking exercise but no specific instructions regarding exercise duration, intensity or frequency.

Due to the nature of the interventions being compared, no reasonable effort to blind either subjects or experimenters to group allocation was possible after initial group allocation. Patients were given minimal feedback relating to changes in any measures until the end of the study. Following each exercise testing session, data were filed for analysis until completion of the trial, in an attempt to reduce experimenter bias.

Statistical analyses

An 'intention to treat' analysis was performed and where data were missing, most recent recorded values were carried forward. All data were visually checked for nor-

mality of distribution. Frequency domain measures (LF, HF) were log transformed (ln) to facilitate parametric analysis. HRV measures and treadmill testing data (MWT, $\dot{V}O_{2peak}$) were analysed using 2 x 3 (time x group) mixed analysis of variance (ANOVA) with repeated measures. Between-group differences were assessed by *post hoc* testing (Scheffé). An alpha value of $p < 0.05$ was used to indicate statistical significance.

Due to between-group differences in HRV measures at baseline, change in these measures was analysed using analysis of covariance (ANCOVA) controlling for baseline values. This analysis creates an estimated marginal mean and the difference between this measure and the mean 12-week value for each group is assessed.

All assumptions underlying use of parametric statistics were checked prior to analysis. Due to the relatively small sample size and the novel nature of this research no correction for alpha was employed. All statistical tests were carried out using SPSS 11.0 (SPSS Inc. Chicago, IL.)

Table 1. Pharmacological and comorbidity data for all subjects at baseline (n=50).

| Prescribed drug | Frequency in initial 50 volunteers (%) |
|--------------------------------------|--|
| Beta Blocker | 7 (14%) |
| Statin | 29 (58%) |
| ACE Inhibitor | 22 (44%) |
| Ca ⁺ channel blocker | 10 (20%) |
| PPI | 11 (22%) |
| Diuretic | 12 (24%) |
| Inotrope | 4 (8%) |
| Biguinide | 11 (22%) |
| Anteplatelet therapy | 37 (74%) |
| Sulphonylureas | 5 (10%) |
| Insulin | 4 (8%) |
| Comorbidities/Previous interventions | |
| Diabetes | 5 (10%) |
| Current coronary artery disease | 7 (14%) |
| Hypertension (controlled) | 22 (44%) |
| Previous PTCA (>12 months) | 1 (2%) |
| Previous CABG (>12 months) | 2 (4%) |
| Previous MI | 1 (2%) |

PTCA – Percutaneous transluminal coronary angioplasty
CABG – Coronary artery bypass graft

Results

Of the 52 patients who volunteered for the study, two were rejected prior to initial treadmill testing. One male had recently undergone coronary angioplasty and one refused to take part in exercise testing. During familiarisation and initial testing one male was excluded due to acute chest pain on exertion and another due to persistent ST

segment depression (> 2 mm); a further male was excluded due to a suspected previous myocardial infarction and one due to possible left bundle branch block. One male was rejected after exercise testing due to no evidence of IC. One SU group patient and one HB patient failed to return at week 12 and values testing week six carried forward to week 12. One SU group patient was retested at week 6 of the study due to upcoming elective angioplasty. This value was also carried forward. Table 1 gives the descriptive characteristics and pharmacologic status at baseline for the 50 patients who underwent initial evaluation (Table 1).

Table 2 provides the physiological characteristics of the patients who entered the study by group. No between-group differences were evident at baseline. The HB patient group was slightly younger with a more widely distributed age range ($p > 0.05$). No changes in anthropometric, pharmacologic or ABI measures were detected over the 12-week period. Chi-squared analysis showed no differences between groups in terms of the numbers of females, smokers and frequencies for use of prescribed drugs.

Table 3 shows peak exercise data values from incremental treadmill testing at baseline and week 12. There were no significant, between-group differences at baseline. As expected, the SU group showed a large and statistically significant increase in maximal walking time ($p < 0.001$). ANOVA revealed no main effect and no group interactions for any other measure. The HRV data for all groups at baseline and week 12 are shown in Table 4. ANCOVA revealed no between-group differences in change baseline values for any measures of HRV and no effect on RR interval.

Discussion

Patient values for $\dot{V}O_{2peak}$ were greatly attenuated and equal to approximately half those expected in age-matched, healthy controls. These data concur with those from previous studies in PAD patients (Eldridge and Hossack 1987). Our data also agree with previous findings (Gardner 2002; Hiatt et al., 1994) that walking distance and exercise response to graded treadmill testing is severely attenuated in PAD patients. High RPE scores and high ratings of leg pain during moderate-to-low absolute intensity walking exercise suggest that IC and associated ischemic leg pain are largely responsible for poor exercise performance in this patient population.

Baseline measures of heart rate variability

The present data regarding HRV measures demonstrate

Table 2. Descriptive characteristics for subjects at baseline by group. Data are means (±SD).

| Group | Number | Current smokers | Age (yrs) | Height (m) | Mass (kg) | BMI | ABI | Age (yrs) |
|------------------------|------------|-----------------|-----------|------------|-------------|------------|-----------|-----------|
| Supervised (n = 13) | Males– 10 | Yes – 5 | 66 (8) | 1.70 (.12) | 76.9 (18.3) | 26.3 (4.5) | .59 (.01) | 66 (8) |
| | Females– 4 | No – 9 | | | | | | |
| Home Based (n = 15) | Males– 12 | Yes – 6 | 62 (14) | 1.69 (.11) | 79.3 (13.0) | 27.1 (4.2) | .57 (.01) | 62 (14) |
| | Females– 3 | No – 9 | | | | | | |
| Control (n = 15) | Males– 10 | Yes – 7 | 67 (6) | 1.71 (.08) | 81.3 (22.5) | 27.7 (6.7) | .57 (.12) | 67 (6) |
| | Females– 5 | No – 8 | | | | | | |

BMI = body mass index ($\text{kg}\cdot\text{m}^{-2}$). ABI = ankle to brachial index: ratio of systolic blood pressure at the ankle to systolic blood pressure at the brachial artery.

Table 3. Exercise test data at baseline, week six and week twelve. Data are means (\pm SD).

| Week | Supervised | | | Home based | | | Control | | |
|--------------------|------------|-------------|-------------|------------|------------|------------|------------|------------|------------|
| | 1 | 6 | 12 | 1 | 6 | 12 | 1 | 6 | 12 |
| MWT(min) | 6.5 (4.0) | 12.0 (5.6)* | 12.1 (6.3)* | 6.1 (3.3) | 7.1 (4.7) | 7.2 (5.2) | 6.4 (4.4) | 6.3 (5.2) | 7.1 (7.1) |
| $\dot{V}O_{2peak}$ | 14.2 (3.8) | 14.3 (3.7) | 13.7 (4.2) | 14.3 (4.1) | 14.0 (4.4) | 13.7 (4.1) | 14.8 (4.7) | 14.5 (3.9) | 14.3 (5.1) |
| RER | .96 (.10) | 1.00 (.10) | .99 (.12) | 1.03 (.08) | 1.01 (.10) | 1.03 (.99) | 1.00 (.13) | .99 (.07) | .99 (.09) |
| RPE | 16.0 (2.0) | 15.0 (2.5) | 15.1 (2.4) | 16.0 (2.0) | 16.0 (2.5) | 16.1 (2.5) | 15.0 (2.0) | 14.7 (2.5) | 14.3 (5.1) |
| Pain rating | 3.0 (.5) | 3.0 (1.0) | 2.8 (.9) | 3.0 (1.0) | 3.0 (1.0) | 2.8 (.9) | 3.0 (.5) | 3.0 (1.0) | 2.6 (.7) |

* Significant ($p < 0.001$) change from baseline. MWT = Maximal walking time (min), $\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) = maximal oxygen uptake attained during incremental exercise testing, RER = Respiratory exchange ratio, RPE = Rating of perceived exertion.

low values of the vagally mediated HRV measure HF power. Such low levels and a propensity toward sympathetic predominance or low levels of vagal modulation at rest (high LF:HF ratio) are present in similar clinical populations and known to be indicative of poor prognosis (van Boven et al., 1998; Weber et al., 1999). Values for short-term HRV measures in the present study are similar to those reported under similar conditions in patients with severe coronary artery disease (Hayano et al., 2001; Kuo et al., 1999).

The effects of exercise training on heart rate variability.

Healthy subjects of a similar age to subjects in the present study have shown desirable changes in HRV due to aerobic exercise training programs (Jurca et al., 2004) and exercise is known to improve the HRV profiles in clinical populations (La Rovere et al., 2003). Animal data suggest that as little as six weeks of aerobic training infers anticipatory benefit against arrhythmic event via increased vagal modulation which manifests as increased HRV (Hull et al., 1994).

In the present study, no significant changes in resting HRV measures were found. The lack of change in the CT group demonstrates that HRV measures remain relatively stable over a 12-week period in this population. The similarities in HRV measures over the 12-week intervention in the HB group, accompanied by no change in MWT, suggest solely home-based walking interventions may be ineffectual as a form of rehabilitation in this population. In agreement with previous data, (Gardner 2002) there was evidence of significantly improved walking performance ($p < 0.001$) in the SU group. There was, however, no concomitant improvement in $\dot{V}O_{2peak}$. Where exercise training has favourably altered HRV previously, concomitant changes in exercise capacity and $\dot{V}O_{2peak}$ have also been shown (Stahle et al., 1999). Evidence of a

threshold effect for the link between improved exercise capacity and autonomic adaptation also exists (Pardo et al., 2000). These authors stratified patients according to improvement in exercise capacity (METs) after a 12-week rehabilitative aerobic exercised regime. They found that vagal modulation measured by total (HF) and relative (HFnu) high frequency power, was only increased significantly in those patients displaying the greatest increases in exercise capacity. The failure of the present exercise regimen to significantly increase HRV requires further explanation.

A likely explanation lies in the nature of exercise undertaken by PAD patients in the present study. Previous studies report varied durations, intensities and modalities of aerobic exercise training that have brought about favorable alterations in HRV. One feature common to all these studies is that exercise bouts are continuous, usually lasting 30 - 60 min. In the present study, although the intensity, exercise session time and frequency of sessions were similar to previous studies, the walking exercise was largely discontinuous. No patient was able to complete 30 min of continuous walking at the prescribed exercise intensity (70 - 75% $\dot{V}O_{2peak}$) during week one. Many patients required an hour of supervised exercise to accomplish the required 30 min total walk time. Such a regimen created a work to rest ratio of 1:1 and although this ratio improved in all cases during the program, only two patients were able to walk continuously for 30 min by week six and three by week 12. It may be, therefore, that intermittent exercise is less able to promote cardio-neuroregulatory adaptation as proposed previously in cross-sectional data from healthy subjects (Aubert et al., 2001). Alternatively, the low absolute exercise intensity used in the present study may have been insufficient to promote central adaptations.

Peripheral arterial disease causes alterations in gait (Crowther et al., 2007) and improvements in walking

Table 4. Heart rate variability measures at baseline, week six and week twelve. Data are means (\pm SD).

| Week | Supervised | | | Home based | | | Control | | |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| | 1 | 6 | 12 | 1 | 6 | 12 | 1 | 6 | 12 |
| HF(ln) | 4.10 (1.28) | 4.39 (1.58) | 3.98 (1.18) | 3.61 (1.34) | 3.30 (1.40) | 3.88 (1.30) | 4.02 (1.35) | 4.40 (1.43) | 4.17 (1.28) |
| LF(nu) | 64.4 (22.0) | 70.3 (21.2) | 68.4 (14.3) | 67.7 (21.2) | 75.9 (15.3) | 66.3 (14.3) | 79.6 (20.0) | 72.5 (18.8) | 68.7 (24.8) |
| LF(ln):HF(ln) | 1.33 (.45) | 1.33 (.34) | 1.22 (.28) | 1.22 (.32) | 1.54 (.43) | 1.25 (.24) | 1.48 (.43) | 1.44 (.44) | 1.38 (.28) |
| Mean RR-interval | 756.6 (154.3) | 766.3 (114.5) | 799.8 (144.6) | 773.0 (213.0) | 748.1 (201.8) | 808.4 (177.0) | 840.5 (118.2) | 824.4 (136.7) | 836.6 (146.7) |

HF(ln) = Natural logarithm of high frequency spectral power. LF(nu) = Low frequency spectral power in normalised units. LF(ln):HF(ln) = Ratio of natural logarithm of high frequency spectral power to natural logarithm of low frequency spectral power. RR = mean R-R interval from filtered ECG data.

performance without changes in $\dot{V}O_{2peak}$ provide evidence of an improved walking economy as noted elsewhere (Womack et al., 1997). Better walking economy may have reduced the physiological demands placed up the cardiorespiratory system during the walking exercise in spite of increases in absolute workloads. Ideally, adjusting exercise intensity by RPE should avoid this but without constant measurement of gas exchange data during all exercise session, this cannot be guaranteed.

Walking exercise was used in the present study, as it is a functional exercise modality known to be effective in increasing exercise performance and enhancing quality of life in PAD patients. The pain associated with claudication in PAD limits exercise intensity and the duration of continuous walking exercise. It is known that untrained patients with PAD are able to tolerate cycling exercise for significantly longer periods than walking at the same relative intensity (Askew et al., 2002). Such alternative exercise modalities may be superior in promoting cardiopulmonary and cardioneuroregulatory adaptation to exercise. Walking exercise creates large changes in time to onset of claudication and maximal claudication (Hiatt et al., 1994) concomitant with improved quality of life in PAD patients (Nehler et al., 2003). The benefits of walking cannot, therefore, be ignored but the role of alternative exercise modalities warrants further investigation.

Study limitations

Statistically, power analysis was only carried out for changes in walking performance to determine sample sizes. This was because estimates for effect sizes for HRV indices in this population were not possible. It must be recognised that the sample sizes used may be insufficient show a significant effect for HRV. However, observation of the group means shows that exercise exerted: no effect (LFnu) or only very small effects (LF:HF, RR interval). These changes are undoubtedly below the level required to suggest any clinical significance.

It may, therefore, be argued that the 12-week period was inadequate in the present study. It is perhaps the case that the time course of central cardiovascular and neuroregulatory adaptation differ from those associated with increases in walking performance and that a longer intervention would demonstrate changes in these measures.

Conclusion

Twelve weeks of supervised or home-based walking training did not significantly heart rate variability measures in patients with peripheral arterial disease. This was probably due to the low intensity and intermittent nature of exercise undertaken despite the relatively high intensity and close monitoring of the exercise undertaken in the SU group. Mixed-modality exercise training may be more beneficial than walking training alone in promoting change in autonomic function in PAD patients. Such an intervention programme has not yet been investigated.

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Key points

- It is known that exercise can positively influence heart rate variability in some cardiac patients.
- It is known that exercise can increase walking performance in peripheral vascular disease patients.
- Exercise training improved walking performance in peripheral vascular disease patients but HRV was unaltered.
- This may be due to low overall physiological demands on the cardiovascular system or the intermittent nature of the exercise.