



Factors predicting walking intolerance in patients with peripheral arterial disease and intermittent claudication

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Objective. To determine which physiological variables conduce to walking intolerance in patients with peripheral arterial disease (PAD).

Design. The physiological response to a graded treadmill exercise test (GTT) in patients with PAD was characterised.

Setting. Patients were recruited from the Department of Vascular Surgery, Groote Schuur Hospital, Cape Town.

Subjects. Thirty-one patients diagnosed with PAD were included in the study.

Outcome measures. During a GTT, peak oxygen consumption (VO_{2peak}), peak minute ventilation (VE_{peak}), peak heart rate and peak venous lactate concentrations were measured and compared with those from a comparison group. Ankle-brachial index (ABI) was measured at rest and after exercise. During the GTT, maximum walking distance (MWD) and pain-free walking distance (PFWD) were measured to determine walking tolerance.

Results. Peak venous lactate concentrations did not correlate significantly with either PFWD ($r=-0.08$; $p=0.3$) or MWD ($r=-0.03$; $p=0.4$). Resting ABI did not correlate with either MWD ($r=0.09$; $p=0.64$) or PFWD ($r=-0.19$; $p=0.29$). Subjects terminated exercise at significantly ($p<0.05$) lower levels of cardiorespiratory effort and venous lactate concentrations than did a sedentary but otherwise healthy comparison group: peak heart rate 156 ± 11 v. 114 ± 22 beats per minute (BPM); $p=0.001$; and peak venous lactate concentration 9.7 ± 2.7 mmol/l v. 3.28 ± 1.39 mmol/l; $p=0.001$.

Conclusion. Perceived discomfort in these patients is not caused by elevated blood lactate concentrations, a low ABI or limiting cardiorespiratory effort but by other factors not measured in this study.

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Peripheral arterial disease (PAD) is a complex disease with patients typically suffering from hypertension, diabetes and coronary artery disease (CAD). Risk factors for PAD include smoking, hypercholesterolaemia, male gender and age.¹ Patients with PAD are walking intolerant.

The cause of walking intolerance in patients with PAD is not clear. It has been suggested that a compromised oxidative metabolism accelerates lactate accumulation in the exercising skeletal muscles, inducing the pain of intermittent claudication.^{2,3} Studies have shown that improvements in walking tolerance with exercise training are associated with increases in the concentration of skeletal muscle oxidative enzymes^{2,4,5} and improved oxygen extraction by the trained skeletal muscles.^{6,7} These findings have served to reinforce the hypothesis that skeletal muscle anaerobiosis causing increased lactate production in the ischaemic exercising skeletal muscles causes the pain of claudication.

Other researchers have suggested that walking intolerance results primarily from decreased blood flow to the lower limb so that improvements in blood flow as a result of a training-induced increase in collateral circulation enhance walking tolerance in patients with PAD.⁸⁻¹⁰ Therefore the ankle brachial index (ABI) is a commonly used clinical measure to predict the functional capacity of patients with this complaint.

Our main objective was to examine the relationship between peak physiological parameters measured during symptom-limited maximal exercise and the walking tolerance of patients with PAD. We postulated that certain physiological parameters (in particular, high venous blood lactate concentrations and a low ABI, both indicating a reduced capacity for blood flow to the exercising skeletal muscles, thus causing an early onset of ischaemia) would predict their walking distance. A secondary objective was to report the demographical and medical characteristics of 31 patients with PAD.

Methods

Participants

Thirty-one patients with PAD were recruited from the Department of Vascular Surgery at Groote Schuur Hospital, and from Kingsbury Hospital, Claremont, Cape Town. All patients had PAD with intermittent claudication, as diagnosed by a vascular surgeon using duplex flow Doppler and/or segmental Doppler pressures. For inclusion, patients had to

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develop intermittent claudication during a screening treadmill test and to have an ABI at rest of less than 0.97 or a fall of the ABI to <0.85 during exercise. Patients were excluded if any of the following were present: absence of PAD; rest pain or tissue loss; limitations of exercise tolerance caused by conditions other than claudication (e.g. severe CAD, dyspnoea, severe arthritis); and active cancer, liver or renal disease. Patients gave their written informed consent. The study protocol was approved by the Ethics and Research Committee of the Faculty of Health Sciences of the University of Cape Town.

Measurements

On the first visit to the laboratory, a full anthropometric analysis was performed for determination of body composition, a full medical history was taken and medical records were obtained from the vascular surgeon and cardiologist. Patients were familiarised with the treadmill protocol.

Exercise test

On the second visit, patients performed a graded treadmill exercise test (GTT) to measure physiological variables during maximal exercise. During the GTT, the speed was held constant at 3.2 km/h with an initial 2% gradient.¹¹ The gradient was then increased by 2% every 2 minutes. If unable to walk at that speed, subjects were tested using the Modified Bruce protocol in which the treadmill speed was held constant at 1.7 km/h. Heart rate and brachial artery blood pressure were monitored every 2 minutes. Patients reported their level of perceived pain according to a perception of pain scale¹² that uses simple-to-understand verbal expressions which accurately describe sensations of perceived peripheral pain. Pain-free walking distance (PFWD) was recorded as the distance walked before the patient first reported calf pain during exercise. Maximum walking distance (MWD) was defined as the distance covered on the treadmill until the patient voluntarily terminated exercise as a result of severe claudication pain that could not be tolerated.

During exercise, inspiratory ventilation rate (VE), oxygen uptake (VO₂) and respiratory exchange ratio (RER) were measured over 15-second intervals by breath-by-breath Oxycon Alpha Analyzer (Oxycon Alpha, Enrich Jaeger, Wuertzburg, Germany). Before each test, the gas meter was calibrated with a Hans Rudolph 3-litre syringe (Vacumed, Ventura, California), and the analysers were calibrated with room air and a 4% CO₂ - 16% O₂ - 80% N₂ gas mixture. The reliability of the Oxycon Alpha Analyzer was tested weekly by burning ethanol (99% analytical reagent, Associated Chemical Enterprises, Glenvista, South Africa) as a reference. Heart rate during the GTT was recorded using an electrocardiogram monitor (Cardio Perfect 3.3, Rijswijk, the Netherlands) with self-adhering electrodes placed in a modified 10-electrode (Mason-Likar) configuration.⁸

Blood pressure

Before the treadmill test, subjects remained supine in a quiet environment for 15 minutes and the resting brachial blood pressure (Korotkoff phase I and IV) was measured and recorded by means of audible sphygmomanometry using a calibrated mercury column sphygmomanometer with an appropriately sized cuff. Simultaneously, another tester measured left and right ankle pressures consecutively with a Doppler (Huntleigh Technology PLC 1997 Dopplex Advanced Pocket Dopplers, UK) and blood pressure cuffs affixed just above the ankles. The Doppler probe was placed over the posterior tibial or dorsalis pedis artery. The cuff was inflated until the Doppler sound disappeared, and slowly deflated until the sound returned. The ankle systolic pressure was measured when the sound returned. ABI was calculated for each patient by dividing the ankle pressure reading by the brachial pressure reading. The procedure was repeated immediately after exercise.

Blood sample analysis

Before the start of the treadmill test, a resting venous blood sample was drawn from each patient; 2 ml of blood was drawn directly into a sodium oxalate-lined glass test tube and immediately placed on ice for later analysis of plasma lactate concentrations; and a 2 ml blood sample was collected 3 minutes after exercise when the blood lactate concentration peaks.¹³

The 2 ml blood samples in the sodium oxalate test tubes were centrifuged using a Sigam 302-K centrifuge (Munich, Germany) at 3 000 rpm for 10 minutes at 4°C. Blood lactate concentrations were measured in plasma by means of an enzymatic kit technique (bioMerieux SA, lactate PAP 69280, Marcy l'Etoile, France).

Statistical analysis

Data are presented as means \pm SD. Correlation coefficients within the patient population were calculated by means of Pearson's product moment correlation coefficient for continuous data using Statistica (StatSoft Inc., Tulsa, USA). Levels of significance were calculated at the 0.05 confidence levels. In the cases of correlations, correlation coefficients were denoted as *r* and the sample size as *N*. A dependent *t*-test was used to assess differences between pre-exercise venous lactate concentrations and post-exercise lactate concentrations. Ratings of pain taken every 2 minutes during the exercise tests were converted to a single variable for each patient by plotting an area under the curve for each patient. The data were normalised by expressing the pain measure (Y axis) relative to 100% of elapsed time (X axis). Independent *t*-tests were used to detect differences between means of this sample group and the comparison group from this laboratory.



Results

General and medical characteristics of patients are detailed in Tables I and II.

The mean MWD during the GTT was 317 m; pain-free walking distance was 98 m (Table I). Of significance is that 45% of patients with PVD also had clinical evidence for CAD, 81%

Table I. Patient characteristics on entry to the study (mean \pm SD)

Age (yrs)	63 \pm 13
BMI (kg/m ²)	27 \pm 5.0
Mass (kg)	78 \pm 15
Height (m)	1.7 \pm 0.1
BF (%)	32 \pm 7
DOD (months)	26 \pm 28
Smoking (pk yrs)	23 \pm 27
MWD (m)	317 \pm 166
PFWD (m)	98 \pm 53
ABI (rest)	0.6 \pm 0.4
ABI (after exercise)	0.4 \pm 0.4
Lactate (rest) mmol/l	2.1 \pm 1.6
Lactate (after exercise) mmol/l	3.3 \pm 1.4

Yrs = years; kg = kilograms; BMI = body mass index; BF = body fat; DOD = duration of disease; pk yrs = pack years; MWD = maximum walking distance; PFWD = pain-free walking distance; m = meters; ABI = ankle brachial index; SD = standard deviation.

Table II. Medical history and risk factor profile of patients with PAD on entry to the trial

	No. of patients (%)
Peripheral arterial disease	31 (100%)
PTA and stent	5 (16%)
Bypass graft	2 (6%)
Coronary artery disease	14 (45%)
History of heart failure	2 (6%)
History of MI	6 (19%)
History of angina pectoris	8 (26%)
CABG	8 (26%)
Pacemaker	1 (3%)
Stent	1 (3%)
PTA	1 (3%)
Cerebral vascular disease	5 (3%)
History of transient ischaemic attack	1 (3%)
History of stroke	1 (3%)
Carotid endarterectomy	2 (6%)
Hypercholesterolaemia	15 (48%)
Hypertension	25 (81%)
Sedentary lifestyle	31 (100%)
Obesity	22 (71%)
Diabetes	14 (40%)
Current smoker	5 (16%)
Former smoker	18 (58%)
Respiratory disease	3 (10%)
Rheumatoid arthritis	1 (3%)
Osteoarthritis	7 (23%)

MI = myocardial infarction; CABG = coronary artery bypass graft; PTA = percutaneous transluminal angioplasty.

had hypertension, 48% had hypercholesterolaemia and 40% had diabetes (Table II).

We were unable to develop an age-matched control group of apparently healthy individuals without PVD. The findings were therefore compared with data collected from a previous study in this laboratory of a sedentary but otherwise healthy middle-aged control group (CONT²³ – Table III). The CONT group had higher peak VO₂, VE, HR and RER values and peak lactate concentrations than patients with PVD (Table III).

There was no correlation between peak post-exercise venous lactate concentrations and PFWD ($r=-0.08$; $p=0.33$) or MWD ($r=-0.03$; $p=0.44$) during the GTT (Figs 1a and 1b).

There was a trend for ABI to drop after the GTT (0.6 \pm 0.4 v. 0.4 \pm 0.4 pre-exercise to post exercise, $p=0.056$) (Table I). However, resting ABI did not correlate with MWD ($r=0.08$; $p=0.3$) or pain-free walking distance ($r=-0.19$; $p=0.15$) (Figs 2a and 2b); nor was there any relationship between post-exercise ABI and walking tolerance during the GTT. Predictably, VO_{2peak} ($r=0.68$; $p=0.001$) and Ve_{peak} ($r=0.5$; $p=0.005$) correlated significantly with MWD during the treadmill exercise test.

No significant correlations were found between age, BMI, fat percentage, duration of disease, pack-years of cigarette smoking and total pain, and walking tolerance during the GTT; i.e. there was no relationship between these variables and walking tolerance. There was, however, a weak but significant correlation between mass and PFWD during the GTT ($r=0.39$; $p=0.03$).

A correlation analysis was performed between total pain perceived on the GTT and peak venous blood lactate concentration and total pain perceived on the GTT and ABI. There was no correlation between total pain perceived on the GTT and peak venous blood lactate or with ABI.

Table III. Peak oxygen consumption, peak heart rate, peak RER, peak venous lactate concentration and peak VE in patients with PAD and a control group during a maximal exercise test

	PVD (N=31)	Cont. (N=13)
Age (yrs)	63 \pm 13	55 \pm 7*
Mass (kg)	75 \pm 15	83 \pm 10
VE (l/min)	43.0 \pm 14.2	87.5 \pm 22.1*
VO ₂ (mlO ₂ /kg/min)	17.0 \pm 4.2	26.0 \pm 6*
HR (bpm)	114 \pm 22	156 \pm 11*
RER(units)	1.0 \pm 0.1	1.4 \pm 0.2*
[lactate] (mmol/l)	3.3 \pm 1.4	9.7 \pm 2.7*

All data are presented as mean \pm SD.

* $p<0.05$ significant difference to PVD group.

Yrs = years; kg = kilogram; VE = minute ventilation; VO₂ = oxygen consumption; HR = heart rate; bpm = beats per minute; RER = respiratory exchange ratio; PAD = peripheral arterial disease; Cont. = control group.

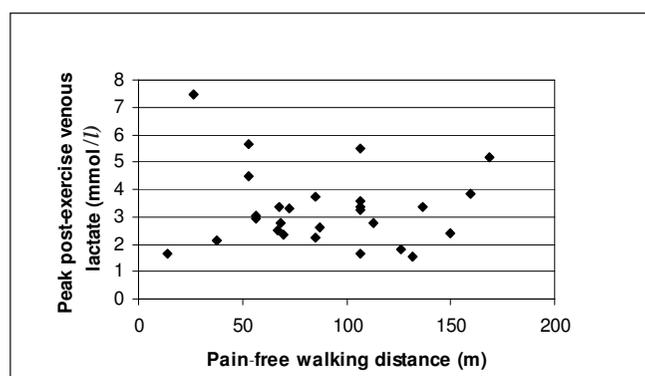


Fig. 1a. Lack of relationship between peak post-exercise venous lactate concentration and pain-free walking distance during the GTT (N=27; $r=-0.08$; $p=0.33$).

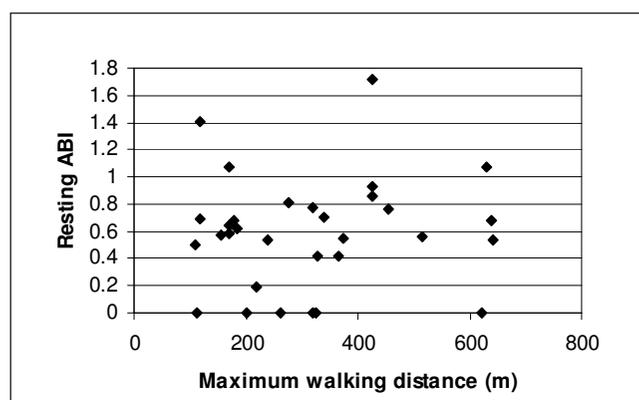


Fig. 2a. Lack of relationship between resting ABI and maximum walking distance during the GTT (N=31; $r=0.08$; $p=0.30$).

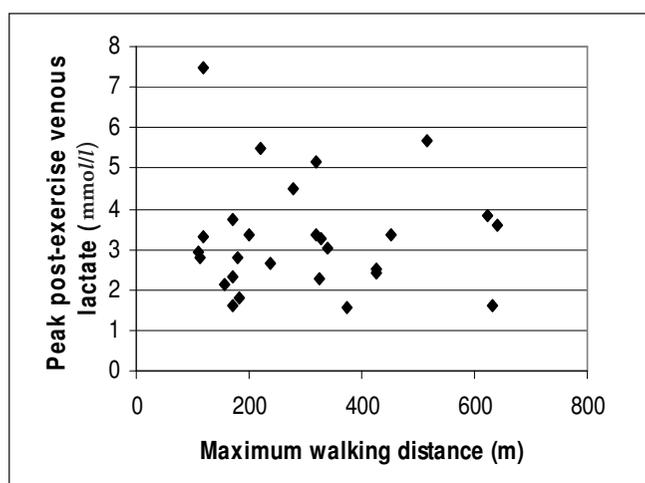


Fig. 1b. Lack of relationship between peak post-exercise venous lactate concentration and maximum walking distance during the GTT (N=27; $r=-0.03$; $p=0.44$).

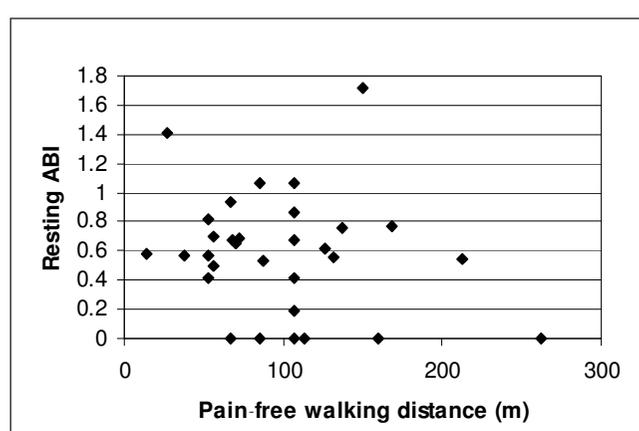


Fig. 2b. Lack of relationship between resting ABI and pain-free walking distance during the GTT (N=31; $r=-0.19$; $p=0.15$).

Discussion

We found that resting ABI did not predict PFWD or MWD or perception of pain during the GTT. Therefore, functional capacity was independent of ABI, suggesting that ABI should not be used to predict exercise tolerance or functional improvement in patients with PAD. This finding agrees with a report that improvements in walking performance in patients with PAD were not accompanied by improvements in ABI.¹⁴ If ABI cannot predict functional capacity, the use of a GTT to monitor functional capacity in patients with PAD may be more valuable than reliance on the ABI alone.

We also found that peak post-exercise venous lactate concentrations did not correlate with PFWD or MWD (Figs 1a and 1b). Therefore, patients with the highest post-exercise venous lactate concentrations did not have the shortest PFWD or MWD, as might be expected if venous lactate concentrations are related to the development of leg pain in this condition. Moreover, peak venous lactate concentrations of patients with

PAD in this study were lower (Table III) than in a control group. There was no correlation between total pain perceived on the GTT and peak venous blood lactate.

This finding is of interest as exercise physiologists and clinicians studying PVD commonly believe that anaerobic glycolysis and the resultant increase in lactate concentrations in the ischaemic muscles and blood explains why these patients develop the pain of intermittent claudication and why their exercise tolerance is so impaired.^{2,3,5} For example, Tan *et al.* stated: 'In patients with peripheral vascular disease, increasing the workload causes an inequality in the supply of and demand for oxygen. Aerobic generation of adenosine triphosphate (ATP) becomes inadequate and anaerobic metabolism predominates. The result (of exercise) is an increase in lactic acid production, and a depletion of ATP and creatine phosphate (CP), leading to pain.'³

This explanation stems from the popular theory suggesting that fatigue develops as a result of anaerobiosis in the exercising skeletal muscles and accelerates glycolysis.¹⁵ The by-product of anaerobic glycolysis is lactate accumulation in the skeletal muscles and blood. Therefore, many studies of



patients with PAD investigated peripheral adaptations that may delay the onset of anaerobic glycolysis and therefore delay the onset of claudication and increase walking tolerance. These adaptations include increases in the concentration of skeletal muscle oxidative enzymes^{2,4,5} and improved oxygen extraction by the skeletal muscles.^{6,8} Lundgren *et al.* reported that '... the results ... support the contention that an improved oxidative capacity is beneficial in improving PFWD. But as long as there is blood flow restriction, there will be a point when flow becomes the limiting factor producing hypoxia, lactate accumulation and pain.'²

It can be argued that low blood lactate concentrations could be associated with elevated muscle lactate concentrations in patients with PAD. If this is true, lactate accumulating in the skeletal muscle, and not in the blood, would be the direct cause of pain and should be measured rather than blood lactate concentrations to evaluate the role of lactate in the production of pain in this condition. However, Pernow *et al.* reported that peak muscle lactate concentrations in controls and in patients with PAD were equally high (13.7 ± 1.6 v. 12.1 ± 2.3 mmol/kg).¹⁶ While these data seem to differ from our own, since we would have expected muscle lactate concentrations to be low (in keeping with the low blood lactate concentrations in our patients), Pernow *et al.*'s data do not support the theory that lactate 'leads to pain' (Tan *et al.*) as their control group did not experience claudication during maximal exercise despite similar peak muscle lactate concentrations to patients with PAD.^{3,16}

In addition, our patients with PAD terminated exercise at lower heart rates, lower RER values and lower venous lactate concentrations than a sedentary control group. Patients with PAD also had lower VO_2 and VE values than a sedentary control group. Therefore, perceived discomfort in these patients was not caused by elevated blood lactate concentrations or by limiting cardiorespiratory effort, but must be caused by other factors not measured.

Lastly, patients with PAD in this study exhibited a variety of other co-morbid conditions, all of which can be positively influenced by participation in regular physical activity since this reduces all-cause mortality,¹⁷ reduces the risk of cardiovascular disease,^{18,19} lowers resting blood pressure²⁰ and favourably influences the blood lipid profile.^{21,22}

Conclusion

Patients with PAD terminated exercise at low venous blood lactate concentrations and low levels of cardiorespiratory demand compared with a control group. Furthermore, no

measured variable could predict walking distance in the PAD patients. Therefore, perceived discomfort and factors determining the walking distance of these subjects could not be explained on the basis of the traditional measurements used to predict exercise performance in healthy subjects or in patients with PAD. Future research should consider alternative explanations for this unexpected finding.

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