

Acute Exercise and Markers of Endothelial Injury in Peripheral Arterial Disease

K. R. Woodburn*¹, A. Rumley², A. Murtagh² and G. D. O. Lowe²

¹Unit for Peripheral Vascular Surgery and ²University Department of Medicine, Glasgow Royal Infirmary

Objectives: To determine the acute effects of exercise on plasma levels of markers of endothelial damage in patients with symptomatic peripheral arterial occlusive disease (PAOD).

Design: Prospective observational study of patients with angiographically proven PAOD undergoing treadmill exercise testing prior to surgical or radiological intervention.

Materials and methods: Ante-cubital venous blood sampling was performed in 20 patients with symptomatic PAOD prior to, and 2 min after, treadmill exercise testing. Samples were then assayed for von Willebrand factor (vWf), tissue-type plasminogen activator (tPa), and plasminogen activator inhibitor (PAI) levels.

Results: Despite a significant fall in median ankle-brachial pressure indices from 0.96 pre-exercise to 0.59 post-exercise on the right, and from 0.92 to 0.40 on the left (both $p < 0.005$), there were no significant changes in plasma levels of vWf, tPa, or PAI following claudication-inducing exercise.

Conclusions: Claudication-inducing exercise does not produce acute alterations in plasma markers of endothelial damage, and the results of this study do not support the belief that claudication-inducing exercise in PAOD is damaging to vascular endothelium.

Key Words: Claudication; Exercise; Endothelial damage.

Introduction

Most patients with peripheral vascular disease and intermittent claudication are initially managed with advice on lifestyle modification, including the recommendation that they continue to walk within the limits of their claudication.¹ Recent evidence, however, suggests that the ischaemia associated with intermittent claudication may result in potentially harmful systemic effects that promote endothelial injury.²

Plasma von Willebrand factor (vWf) is mainly derived from endothelium, and elevated levels of vWf are found in association with endothelial damage.³ There is evidence of a rise in vWf immediately following the acute endothelial injury that accompanies percutaneous angioplasty,⁴ and hence vWf is considered to be a marker of endothelial injury. Similarly, tissue plasminogen activator (tPa) and plasminogen activator inhibitor (PAI) are products of the endothelium,^{5,6} and there is some evidence that tPa levels fall acutely in association with endothelial injury.⁴ This

study therefore examined the effects of claudication-inducing exercise on plasma levels of three markers of endothelial damage: vWf, tPa and PAI.

Patients and Methods

Twenty patients with intermittent claudication and angiographic evidence of occlusive peripheral arterial disease underwent ante-cubital venous blood sampling prior to, and 2 min after, exercise. Subjects were exercised on a treadmill at 2 km/h with an incline of 10°, until unable to walk any further due to their claudication symptoms, or up to a maximum of 200 m, the walking distance being recorded for all patients. The ankle-brachial pressure index (ABPI) was recorded immediately before and after exercise using a standard sphygmomanometer and an SD1 super Dopplex bi-directional Doppler flow detector with an 8 MHz Doppler probe (Huntleigh Technology plc, Cardiff, U.K.). The ABPI was calculated for both limbs by dividing the highest systolic ankle pressure in each limb by the brachial systolic pressure. Informed consent was obtained from all patients participating in the study,

* Address correspondence to: Mr K. R. Woodburn, Consultant Vascular Surgeon, Royal Cornwall Hospital Trust, Treliske Hospital, Truro, TR1 3LJ, U.K.

Table 1. Pre- and post-exercise levels of endothelial products in ante-cubital venous blood samples. Values are median (interquartile range). Statistical analysis performed using Wilcoxon matched pairs testing.

Endothelial product	n	Pre-exercise	Post-exercise	p value
vWf (iu/dl)	20	159 (108–184)	149 (120–183)	p=0.5
tPa (ng/ml)	18	9.2 (4.1–12.5)	9.0 (5.9–11.2)	p=0.8
PAI (% pool)	15	130 (96–151)	103 (89–167)	p=0.2

which had been approved by the hospital ethical committee.

Venous blood samples were obtained with minimal venous stasis. Nine millilitres of blood from each sample were added to a plastic tube containing 1 ml of trisodium citrate (0.109M) and subsequently handled, stored, and assayed as previously described³ for plasma vWf (ELISA, Dako, High Wycombe, U.K.), PAI (chromogenic activity assay, KabiVitrum Ltd. Uxbridge, Middx., U.K.), and tPa antigen (ELISA, Biopool TintElize, Biopool AB, Umeå, Sweden). The pre- and post-exercise levels of these endothelial products and the ABPI in each limb were then compared using Wilcoxon matched pairs testing.

Results

Eleven male and nine female patients with a mean age of 64 years (range 46–71 years) were studied. The median walking distance (interquartile range) was 94m (76–116m), and the ABPI fell from a median of 0.96 (0.7–1.1) on the right and 0.92 (0.7–1.0) on the left, to 0.59 (0.38–0.84) and 0.40 (0.32–0.64), respectively (both $p < 0.0005$). Levels of vWf, tPa, and PAI in ante-cubital venous blood were not significantly altered following exercise (Table 1).

Discussion

Baseline levels of vWf, tPa and PAI in the patients studied were similar to the increased levels reported in patients with symptomatic occlusive arterial disease.³ This study failed to show any significant increase in levels of the endothelial product vWf following claudication-inducing exercise. Although some of the systemic effects of claudication-inducing exercise have been attributed to endothelial damage,² the absence of any rise in vWf levels in this study is not consistent with this hypothesis. This is reinforced by the observation that both tPa (a specific endothelial product) and PAI (which is released from both endothelial

cells and hepatocytes) remained unchanged following exercise.

The absence of systemic evidence of endothelial injury may be related to the short claudication distances of the patients studied, and the fact that samples were obtained from arm veins rather than the femoral vein draining the most affected leg. Previous studies in healthy volunteers have, however, shown an immediate post-exercise rise in vWf levels in ante-cubital venous blood samples,⁷ while cigarette smoking has been shown to raise systemic venous vWf and tPa levels acutely,^{8,9} presumably as a result of endothelial damage.

While elevated lipid peroxide levels and increased microalbuminuria have been found following exercise in claudicants,² this study suggests that these observations may not be related to increased capillary permeability following endothelial damage. There are, as yet, no significant contraindications to the advice to 'stop smoking and keep walking',¹ and a recent meta-analysis¹⁰ supports the benefits of an exercise programme in claudication.

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