Short communication

Effects of upper-limb exercise on lower-limb cutaneous microvascular function in post-surgical varicose-vein patients

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Abstract

Regular walking exercise attenuates lower-limb cutaneous microvascular endothelial dysfunction in post-surgical varicose-vein patients. This study assessed the effects of upper-limb exercise training on lower-limb cutaneous microvascular function in this patient group. Six post-surgical (4-5 weeks) varicose-vein patients completed an 8-week arm-crank exercise training programme. Changes in cutaneous microvascular function of the lower leg were assessed using laser Doppler flowmetry and iontophoretic administration of endothelial-dependent and -independent agonists (acetylcholine [ACh] and sodium nitroprusside [SNP], respectively). At eight weeks, median lower-limb cutaneous vasodilator responsives to ACh and SNP remained unchanged relative to baseline (e.g. 6 mC: 37 (interquartile range, 24-63) vs 40 (20-71) PU and 35 (23-48) vs 38 (21-64) PU respectively for the supine position). Upper-limb exercise appears ineffective for improving lower-limb cutaneous microvascular function in post-surgical varicose-vein patients. Therefore, limb specificity appears an important factor in optimal exercise prescription for these patients.

Introduction

Chronic venous disease is a common cause of lower-limb ulceration (Iabichella et al. 2006). Several factors might affect tissue viability and susceptibility to ulceration, but the structural and functional integrity of the microcirculation to maintain blood flow, tissue oxygenation, and nutrient delivery might be particularly important (Iabichella et al. 2006). Indeed, microcirculatory impairment is involved in all the hypotheses on ulcer pathophysiology (Iabichella et al. 2006), the trophic tissue damage caused by vein insufficiency is preceded by the development of microvascular abnormalities (Iabichella et al. 2006), and skin microvascular abnormalities are a risk factor for chronic ulceration in patients with varicose veins but no history of venous ulcer (Robertson et al. 2009). Therefore, assessment of cutaneous microvascular function in patients with mild-to-moderate venous disease might be useful for identifying those at high risk of venous ulceration. It might also be useful for assessing ulcer risk in patients who have recently had varicose-vein surgery, given that approximately 20% of patients with spontaneous ulcers have previously had varicose-vein surgery (Kulkarni et al. 2008).

In recent years, we studied lower-limb cutaneous microvascular function in patients being treated for lower-limb varicosities (Klonizakis et al. 2003, 2009a) using laser Doppler flowmetry

combined with incremental-dose iontophoretic administration of endothelial-dependent (acetylcholine [ACh]) and -independent (sodium nitroprusside [SNP]) vasodilators. A key finding was that varicose-vein patients had microvascular endothelial dysfunction (reduced ACh-responsiveness) compared to age-matched healthy controls (Klonizakis et al. 2003), which persisted after venous surgery (Klonizakis et al. 2009a). Therefore, it appears important to identify strategies to improve cutaneous microvascular endothelial function in post-surgical varicose-vein patients.

We recently investigated the effects of aerobic exercise training (brisk walking) on lower-limb cutaneous microvascular function in this patient group. We found that both acute (Klonizakis et al. 2009a) and chronic (Klonizakis et al. 2009b) walking exercise improved microvascular endothelial function (ACh-responsiveness), an adaptation that might be clinically meaningful with respect to risk of venous ulceration. As it was unclear if this adaptation can be induced by other modes of exercise, we investigated the effects of upper-limb exercise training (arm-cranking) on lower-limb cutaneous microvascular function in post-surgical varicose-vein patients. This exploratory study has practical implications because many of these patients have difficulty walking. We hypothesised that arm-cranking might be a useful alternative for improving lower-limb microvascular function in post-surgical varicose-vein patients, given that it has been shown to improve lower-limb haemodynamics in patients with intermittent claudication (Tew et al. 2009).

Methods

With Local Research Ethics Committee approval, six patients who had recently (within 4-5 weeks) received ligation and stripping of the great saphenous vein (for isolated venous incompetence) were recruited from the Sheffield Vascular Institute at the Northern General Hospital, Sheffield, UK. Patients with skin changes of the gaiter area (between the ankle and proximal calf), diabetes, cardiovascular disease, or those who were taking vasodilatory therapy were excluded from participation. Those who were non-ambulatory were also excluded. This research was carried out in accordance with the Declaration of Helsinki of the World Medical Association, and all volunteers provided written informed consent. No residual refluxing segments were reported post-operatively. Demographic data are shown in Table 1.

Outcome measures were assessed at baseline and 8 weeks. Cutaneous microvascular vasodilator function of the gaiter area was assessed in the supine and standing positions using laser

Doppler flowmetry combined with incremental-dose iontophoretic administration of ACh and SNP, as described in detail previously (Klonizakis et al. 2009a; Klonizakis et al. 2009b). After this, patients completed an incremental arm-cranking test to maximum exercise tolerance using an electronically-braked cycle ergometer (Lode Excalibur Sport) positioned specifically for arm cranking. Patients were asked to maintain a cadence of 50 rev·min^{-1}. Following a 2-min warm-up against no resistance (0 W), the work rate was increased by 7 W·min^{-1}.

Patients attended twice weekly arm-crank exercise training sessions for 8 weeks, with each session comprising 10 × 2-min bouts of exercise at 60-70% of peak work rate, separated by 2 min rest (Tew et al. 2009). The intensity of exercise was progressed gradually throughout the 8-week programme so that it remained "somewhat hard". The prescribed intensity, frequency, and duration of exercise were the same as described previously (Tew et al. 2009; Klonizakis et al. 2009b).

Wilcoxon signed-rank tests were used to detect changes in outcome measures with statistical significance set at $P \leq 0.05$. Data are presented as median (interquartile range).

Results

Compliance to the twice weekly exercise sessions was 100% and there were no drop-outs or exercise-related complications. The % predicted maximum heart rate towards the end of each training session was 74% (66-81%). Peak arm-crank work rate increased from 56 W (36-70 W) at baseline to 71 W (60-77 W) at 8 weeks ($P < 0.001$). At 8 weeks, baseline flux values and flux responses to ACh and SNP were unchanged in both body positions (Table 2; $P > 0.05$). There was also no effect of posture on cutaneous microvascular function ($P > 0.05$).

Discussion

The purpose of this study was to assess the effects of upper-limb exercise training on lower-limb cutaneous microvascular function in post-surgical varicose-vein patients. We observed that skin blood flow responses to ACh and SNP were unchanged after 8 weeks of exercise training, despite an improvement in fitness (peak work rate). Therefore, our data suggest that upper-limb exercise (at least in the form of moderate-intensity arm-cranking) does not improve lower-limb microvascular function in post-surgical varicose-vein patients.

The pre-training peak responses to ACh (Table 2) were similar to those observed previously for this patient group (45-48 PU) (Klonizakis et al. 2009a) and lower than those observed for age-matched healthy controls (63-96 PU) (Klonizakis et al. 2009a), suggesting that the patients had microvascular endothelial dysfunction at baseline. In contrast to lower-limb exercise training (Klonizakis et al. 2009b), upper-limb exercise training was ineffective for attenuating lower-limb cutaneous microvascular endothelial dysfunction in post-surgical varicose-vein patients. Previous studies have reported improvements in ACh-responsiveness of the forearm skin microvessels after lower-limb aerobic exercise training (Wang 2005; Hodges et al. in press). Therefore, the available evidence suggests that lower-limb aerobic exercise can improve upper-limb cutaneous microvascular endothelial function, but not *vice versa*. This is probably because arm-cranking activates a smaller muscle mass than cycling or treadmill exercise, and therefore provides a relatively small cardiovascular challenge. Exercise training-induced changes in skin microvascular function are thought to be the result of exercise engaging thermoregulatory mechanisms (Hodges et al. in press). With this in mind, lower-limb aerobic exercise probably induces significant thermoregulatory responses and changes in leg skin blood flow, whereas arm-cranking probably does not. We cannot exclude the possibility that a more intensive training regime would have induced favourable lower-limb microvascular adaptations; however, we believe that such a regime would have been poorly tolerated, given that our patients were older and untrained.

There are two main implications for clinical practice from our recent series of investigations. Firstly, vascular surgeons need to recognise that microvascular abnormalities often persist after varicose-vein surgery. Therefore, additional steps need to be implemented post-surgically to reduce a patients' risk of future venous ulceration. Secondly, upper-limb exercise cannot be considered as alternative to the effects of supervised walking in the improvement of microvascular dysfunction and thus limitation in mobilisation may be a bad prognostic factor in patients with chronic venous insufficiency even after varicose-vein surgery.

Limitations to this study include the small sample size and the fact that, despite careful probe positioning, it is likely our microvascular measures were taken from different areas of skin pre- and post-training. Our power calculation, which was based on previous data (Klonizakis et al. 2009b), suggested that we needed 6 patients to identify a 20-PU change in the peak response to ACh with an average standard deviation of 17.3 PU and $\beta = 80\%$. We accept that this is a small sample size, but

believe it is sufficient for an exploratory study. As there were no trends for altered microvascular responses, we are confident that our interpretation of the findings is not confounded by the small sample size.

In summary, our results suggest that upper-limb exercise training does not improve lower-limb skin microvascular function in post-surgical varicose-vein patients. Therefore, it appears that exercise modality and limb-specificity are important factors in optimal exercise prescription for this patient group. Future research is needed to identify the mechanisms by which cutaneous microvascular endothelial function is improved after lower-limb aerobic exercise training, as well as to explore the feasibility of more wide-spread exercise rehabilitation in the clinical setting for venous disease patients.

References

Hodges GJ, Sharp L, Stephenson C, Patwala AY, George KP, Goldspink DF, Cable TN (in press) The effect of 48 weeks of aerobic exercise training on cutaneous vasodilator function in post-menopausal females. Eur J Appl Physiol.

Iabichella ML, Melillo E, Mosti G (2006) A review of microvascular measurements in wound healing. Int J Low Extrem Wounds 5: 181-199.

Klonizakis M, Yeung JM, Nash JR, Lingam K, Manning G, Donnelly R (2003) Effects of posture and venous insufficiency on endothelial-dependent and -independent cutaneous vasodilation in the perimalleolar region. Eur J Vasc Endovasc Surg 26: 100-104.

Klonizakis M, Tew GA, Michaels JA, Saxton JM (2009a) Impaired microvascular endothelial function is restored by acute lower-limb exercise in post-surgical varicose vein patients. Microvasc Res 77: 158–162.

Klonizakis M, Tew GA, Michaels JA, Saxton (2009b) Exercise training improves cutaneous microvascular endothelial function in post-surgical varicose vein patients. Microvasc Res 78: 67-70.

Kulkarni SR, Gohel MS, Whyman MR, Poskitt KR (2008) Significance of limb trauma as an initiating factor in chronic leg ulceration. Phlebology 23: 130-136.

Robertson L, Lee AJ, Gallagher K, Carmichael SJ, Evans CJ, McKinstry BH, Fraser SC, Allan PL, Weller D, Ruckley CV, Fowkes FG (2009) Risk factors for chronic ulceration in patients with varicose veins: a case control study. J Vasc Surg 49: 1490-1498.

Tew GA, Nawaz S, Zwierska I, Saxton JM (2009) Limb-specific and cross-transfer effects of arm-crank exercise training in patients with symptomatic peripheral arterial disease. Clin Sci 117: 405-413.
Wang JS (2005) Effects of exercise training and detraining on cutaneous microvascular function in man: the regulatory role of endothelium-dependent dilation in skin vasculature. Eur J Appl Physiol 93: 429-434.

Table 1 Patient demographics

Sex	5 female, 1 male
Age (years)	57 (39-72)
Body mass (kg)	73.4 (67.0-82.5
Stature (cm)	163.2 (161.2-180.3)
Body mass index ($kg \cdot m^{-2}$)	26.0 (24.8-27.6)
Systolic blood pressure (mmHg)	134 (124-140)
Diastolic blood pressure (mmHg)	83 (77-86)

Data are presented as median (interquartile range).

Table 2 Cutaneous flux responses to ACh and SNP

	Arm-crank exercise group		Age-matched healthy controls*
Variable	**Baseline**	**8 weeks**	**Baseline**
ACh supine			
Basal flux (PU)	8 (6-10)	6 (3-8)	7 (5-9)
2 mC (PU)	12 (10-23)	9 (6-24)	12 (7-20)
3 mC (PU)	16 (11-35)	21 (11-41)	19 (12-41)
4 mC (PU)	31 (9-49)	35 (13-61)	43 (19-52)
6 mC (PU)	37 (24-63)	40 (20-71)	53 (32-76)
PK%BL (%)	648 (342-1294)	883 (598-1069)	691 (433-1076)
ACh standing			
Basal flux (PU)	6 (5-8)	9 (4-12)	6 (5-8)
2 mC (PU)	15 (8-24)	10 (4-20)	13 (7-23)
3 mC (PU)	18 (9-42)	12 (6-43)	28 (13-44)
4 mC (PU)	32 (15-51)	22 (12-66)	57 (33-71)
6 mC (PU)	49 (17-80)	43 (18-94)	65 (56-118)
PK%BL (%)	800 (311-1490)	698 (287-1093)	996 (460-1847)
SNP supine			
Basal flux (PU)	10 (7-15)	8 (5-11)	3 (2-5)
2 mC (PU)	11 (8-16)	10 (7-38)	6 (3-10)
3 mC (PU)	17 (7-37)	21 (12-43)	14 (8-20)
4 mC (PU)	28 (9-61)	32 (16-46)	20 (16-29)
6 mC (PU)	35 (23-48)	38 (21-64)	28 (18-35)
PK%BL (%)	306 (126-453)	408 (157-695)	736 (418-1290)
SNP standing			
Basal flux (PU)	9 (7-12)	11 (5-15)	4 (2-5)
2 mC (PU)	12 (8-20)	16 (7-21)	5 (3-10)
3 mC (PU)	14 (8-20)	17 (8-28)	7 (4-15)
4 mC (PU)	19 (15-24)	21 (14-32)	13 (7-16)
6 mC (PU)	27 (15-46)	29 (13-51)	19 (12-33)
PK%BL (%)	181 (50-386)	207 (67-417)	513 (364-616)

Data are presented as median values with the inter-quartile range in parentheses.

PK%BL, percentage increase between peak and baseline

*Data from Klonizakis et al. (2009a)