

Effect of functional electrostimulation on impaired skin vasodilator responses to local heating in spinal cord injury

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²Department of Physiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; ³Faculty of Human Movement Sciences, VU University, Amsterdam, The Netherlands; ⁴Duyvensz-Nagel Research Laboratory, Rehabilitation Center, Amsterdam, The Netherlands; ⁵School of Sport Science, Exercise and Health, The University of Western Australia, Crawley, Western Australia, Australia; and ⁶Department of Human Physiology, University of Oregon, Eugene, Oregon

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Van Duijnhoven NT, Janssen TW, Green DJ, Minson CT, Hopman MT, Thijssen DH. Effect of functional electrostimulation on impaired skin vasodilator responses to local heating in spinal cord injury. *J Appl Physiol* 106: 1065–1071, 2009. First published February 19, 2009; doi:10.1152/jappphysiol.91611.2008.—Spinal cord injury (SCI) induces vascular adaptations below the level of the lesion, such as impaired cutaneous vasodilation. However, the mechanisms underlying these differences are unclear. The aim of this study is to examine arm and leg cutaneous vascular conductance (CVC) responses to local heating in 17 able-bodied controls (39 ± 13 yr) and 18 SCI subjects (42 ± 8 yr). SCI subjects were counterbalanced for functional electrostimulation (FES) cycling exercise (SCI-EX, $n = 9$) or control (SCI-C, $n = 9$) and reanalyzed after 8 wk. Arm and leg skin blood flow were measured by laser-Doppler flowmetry during local heating (42°C), resulting in an axon-reflex mediated first peak, nadir, and a primarily nitric oxide-dependent plateau phase. Data were expressed as a percentage of maximal CVC (44°C). CVC responses to local heating in the paralyzed leg, but also in the forearm of SCI subjects, were lower than in able-bodied controls ($P < 0.05$ and 0.01 , respectively). The 8-wk intervention did not change forearm and leg CVC responses to local heating in SCI-C and SCI-EX, but increased femoral artery diameter in SCI-EX ($P < 0.05$). Interestingly, findings in skin microvessels contrast with conduit arteries, where physical (in)activity contributes to adaptations in SCI. The lower CVC responses in the paralyzed legs might suggest a role for inactivity in SCI, but the presence of impaired CVC responses in the normally active forearm suggests other mechanisms. This is supported by a lack of adaptation in skin microcirculation after FES cycle training. This might relate to the less frequent and smaller magnitude of skin blood flow responses to heat stimuli, compared with controls, than physical inactivity per se.

microcirculation; nitric oxide; inactivity; functional electrical stimulation

A SPINAL CORD INJURY (SCI) leads to dramatic central and peripheral cardiovascular adaptations. A decrease in cardiac mass and dimensions has been reported (13), while, below the level of the lesion, an increased peripheral vascular resistance (23), reduced peripheral capillarization (5, 27), and decreased conduit artery diameters (14, 24, 30) have been observed. These adaptations seem to be largely accomplished within 3 wk after the SCI (10, 11). In addition, an impaired skin microcirculation

below the level of the lesion has been reported (31, 33), which likely contributes to frequently reported pathologies in individuals with SCI, such as skin breakdown lesions (15) and poor wound healing. Apart from reports of impaired axon reflex-mediated vasodilation in SCI in the leg (26, 33), little is known about the mechanisms that may underlie the impaired skin microcirculation in SCI.

The nitric oxide (NO) pathway is of special interest to explain differences between subjects with SCI and able-bodied controls, given the antiatherogenic properties of this molecule and its proposed link with vascular health. Recent studies have examined the role of NO in conduit and resistance arteries, but, remarkably, subjects with SCI showed a preserved NO-mediated endothelium-dependent dilation in the femoral artery (12) and a preserved contribution of NO to baseline leg vascular tone (2). However, to date, no study has examined NO-dependent vasodilation in the skin above and below the lesion in subjects with SCI to assess whether the microcirculation follows the findings in the conduit arteries (2, 12).

Previous studies uniformly demonstrated that 2- to 8-wk functional electrostimulation (FES) cycling exercise in subjects with SCI reduces peripheral vascular resistance (23, 36), increases capillarization (5), enhances peak vasodilator capacity of resistance vessels (19, 38), and enlarges conduit artery diameters (19, 30, 37). These findings suggest that resistance and conduit artery vascular adaptations in the legs of SCI subjects relate primarily to the physical inactivity, rather than denervation. Accordingly, FES cycling exercise may improve skin microcirculation in SCI subjects, especially since exercise training preserves the attenuated skin vasodilation during bed rest (35) and improves the impaired skin microcirculatory function in older men (1) and individuals with diabetes (6). However, no studies have examined the impact of FES cycle training on microcirculatory function in SCI subjects.

The aim of the present study was to examine skin microcirculation in the upper and lower limbs of able-bodied controls and SCI individuals, while the SCI subjects were examined again after an 8-wk intervention (FES cycling or control). We utilized a local heating protocol to examine the axon reflex-mediated and NO-dependent vasodilation (29). We hypothesized that, compared with able-bodied controls, individuals with a SCI will exhibit impaired axon reflex and NO-dependent

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vasodilation in the paralyzed legs, but not in the forearm. In addition, we hypothesized that these microcirculatory adaptations in the paralyzed legs of SCI subjects would be partially reversible by 8 wk of FES cycling exercise.

METHODS

Subjects

Seventeen healthy, recreationally active men (38.6 ± 13.8 yr) and 18 individuals with SCI (41.5 ± 8.4 yr) were recruited from the community. While two of the individuals with SCI performed regular endurance exercise (5 h/wk), most SCI subjects were moderately active ($n = 5$, 1–3 h/wk) or sedentary ($n = 11$, <1 h/wk). The group SCI subjects were allocated to a group that participated in an 8-wk FES exercise training group (SCI-EX, $n = 9$, 38.8 ± 7.2 yr) or a control group (SCI-C, $n = 9$, 44.2 ± 9.0 yr). All SCI subjects, except one (C6, SCI-EX, excluded for analysis of forearm skin microvascular function) had a complete thoracic spinal cord lesion, varying between T₁ and T₁₂, which existed for at least 4 yr. In addition, three subjects reported to have (limited) sweating response below the lesion, suggestive of an incomplete lesion of the sympathetic ganglia. These subjects, however, demonstrated similar responses to local heating compared with those without a sweating response. No subject reported having been diagnosed with cardiovascular disease or risk factors such as hypercholesterolemia or hypertension. Subjects who were on medications influencing the cardiovascular system were excluded. Subjects participating in the exercise training part of this study were physically screened for cardiac abnormalities and cardiovascular disease before entering the study. The study procedures were approved by the Ethics Committee of the Radboud University Nijmegen Medical Center and adhered to the Declaration of Helsinki, and all subjects gave prior, written consent.

Experimental Design

Under standardized conditions, forearm and thigh skin microvascular function were examined in control subjects and SCI individuals, using laser-Doppler flowmetry. Subsequently, the SCI subjects were divided into a group that embarked upon an 8-wk FES cycling training program of the paralyzed legs to assess whether skin microvascular function could be altered by training. The other SCI subjects continued their normal daily activities during the same time frame. After 8 wk, SCI subjects were tested at the same time of day as during the first measurement to avoid diurnal variation.

Procedures

Microvascular function measurements. All measures were performed following a 6-h fast, 18 h of abstinence from caffeine and/or alcohol, and at least 24 h after strenuous physical activity. At least 1 h before the test, SCI subjects emptied their bladder to minimize the influence of any reflex sympathetic activation on peripheral vascular responses and central arterial pressure. The tests were performed in a quiet, temperature-controlled room ($23 \pm 1^\circ\text{C}$), with the subjects positioned comfortably on a bed in the supine position with a slight elevation of the head. The left arm was positioned ~5 cm above heart level, and the laser-Doppler probe was positioned on the volar side of the forearm, ~5 cm below the elbow crest. Both legs were elevated, and the lower legs rested on a 14-cm-high platform, while the laser-Doppler probe was placed ~10 cm above the left proximal patellar rim, ~5 cm above heart level. Positioning of the probes was registered to ensure comparable placement after the 8 wk in SCI subjects.

After an acclimatization period of 30 min, microvascular function was examined via recording of local skin blood flow (SkBF) responses to certain stimuli. To obtain an index of SkBF, cutaneous red blood cell (RBC) flux (in mV) was measured in the forearm and thigh

using a Moor laser-Doppler flowmetry system (DRT-4). Skin temperature was controlled at the two measuring sites with Moor local heating units (SH02), each covering ~100 mm² of tissue. To verify whether blood pressure was stable throughout the experimental protocol, blood pressure was measured at 10-min intervals by brachial auscultation in the right arm.

After instrumentation, RBC flux of both sites was monitored to examine baseline SkBF. The temperature of the local heating units at both sites was kept constant at 33°C during the baseline period. After recording baseline RBC flux for 10 min, the local heating protocol was performed simultaneously at both sites. Temperature of the local heating units was increased at a rate of 0.5°C every 5 s to a temperature of 42°C. This resulted in an increase in skin temperature to ~42°C at the heating probe-skin surface interface (29). Subjects did not feel any sensations of pain during the rise in temperature at this rate or with prolonged heating at this temperature. The local heating units were held constant at 42°C throughout the entire protocol. After RBC flux in both sites had reached a stable plateau (~30–40 min), the local heating units were further increased to 44°C, which will result in a maximal SkBF (29). Previous studies have shown that the SkBF response to this rapid heating protocol is NO dependent (29). Cutaneous vascular conductance (CVC) was calculated as laser-Doppler flow (mV) divided by mean arterial pressure (MAP; mmHg) to account for any differences in blood pressure between the groups. Data were expressed as a percentage of maximal CVC obtained during maximal heating (%CVC_{max}).

Effects of FES cycling. To evaluate the effect of FES cycling, leg cycling performance was assessed before and after the FES training using a computer-controlled leg cycling ergometer (Ergys2, Therapeutic Alliances, Fairborn, OH). Stimulation was increased to achieve a pedaling rate of 50 rpm. When maximal stimulation (140 mA) was reached and pedaling rate dropped below 35 rpm, the test was ended, and the average workload achieved in that session was taken as the leg cycling performance (19, 37).

The effect of FES cycling on the conduit vasculature was evaluated before and after the 8-wk exercise training. Baseline diameter of the femoral artery was recorded after 20 min of supine rest ~2 cm above the bifurcation into the deep and superficial femoral artery by echo ultrasound with a high-resolution 5- to 10-MHz linear array transducer (ART.LAB System, Pie Medical). From each artery, four measurements were obtained over the period of six heartbeats and stored for later offline analyses.

FES exercise training. Exercise training was performed using a stationary computer-controlled FES ergometer. The FES ergometer provides stimulation via surface electrodes (5 × 8 cm, Farmadomo, Nuland, The Netherlands) to the hamstrings, gluteal, and quadriceps muscles. Details regarding this training are described elsewhere (19, 20, 23). Each FES cycling training consisted of one to five sessions. During each session, electrostimulation was increased to maintain a stable pedaling rate of 50 rpm, until peak stimulation was reached. A session was terminated when pedaling rate dropped <35 rpm. We aimed for ~30-min stimulation per training. SCI individuals trained twice a week during the first 4 wk, while frequency was increased to three times a week during the last 4 wk.

Data Analysis

Laser-Doppler data were digitized at 100 Hz and stored on a computer. Data were analyzed offline with customized signal-processing software (MIDAC, Instrumental Department, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands). SkBF during baseline, plateau during local heating, and plateau during maximal heating were calculated by averaging values over a stable 10-min period. Initial peak and nadir CVC values were calculated over a stable 30-s period, with the initial peak identified as the highest values and the nadir as the bracket with the lowest values in the first 5–10 min of local heating. As is typical with the local heating experiment,

a clear nadir was not detected in all subjects. In those subjects (~10%), we included data from a 30-s period, 1 min after the initial peak. This value was always lower than the initial peak.

Statistics

Statistical analyses were performed using SPSS 14.0 (SPSS, Chicago, IL) software. All data are presented as means \pm SE, unless stated otherwise. Subject characteristics between groups at baseline and after the 8-wk intervention were compared using an unpaired *t*-test. The effect of the 8-wk intervention was examined using paired *t*-tests. CVC during baseline, initial peak, nadir, and plateau were analyzed by two-way ANOVA with repeated measures to examine differences between groups (group \times local heating protocol) and limb differences (limb \times local heating protocol) and study the effect of the 8-wk intervention on forearm and leg microcirculation (intervention \times local heating protocol). When a significant interaction effect was observed, least significant difference post hoc analysis was used to identify significant differences in the pairwise comparisons. The level of statistical significance was set at $P < 0.05$.

RESULTS

Able-Bodied Controls vs. SCI Subjects

Able-bodied controls and SCI subjects did not differ in MAP, while MAP did not change during the protocol in both groups (Table 1).

Forearm. Forearm RBC flux between controls and SCI subjects was not different at baseline (24 ± 24 and 15 ± 11 mV, respectively; *t*-test; $P = 0.46$), nor during maximal heating (220 ± 71 and 208 ± 224 mV, respectively; *t*-test; $P = 0.75$). Forearm baseline %CVC_{max} was not different between controls and SCI subjects. Local heating resulted in the typical pattern, characterized by the initial increase in %CVC_{max}, followed by a transient drop ("nadir") and a subsequent increase, leading to a plateau in %CVC_{max}. Responses to local heating were significantly higher in able-bodied controls compared with SCI subjects (Fig. 1A).

Leg. RBC flux in the leg between controls and SCI subjects was not different at baseline (28 ± 12 and 29 ± 21 mV, respectively; *t*-test; $P = 0.91$), nor during maximal heating (235 ± 66 and 210 ± 106 mV, respectively; *t*-test; $P = 0.43$). Baseline leg %CVC_{max} was not different between controls and SCI subjects, whereas leg responses to local heating in SCI subjects were significantly lower compared with that in able-bodied controls (Fig. 1B).

Limb differences. Able-bodied subjects, as well as subjects with SCI, demonstrated no differences between the forearm and leg %CVC_{max} during the local heating protocol (two-way ANOVA; $P = 0.13$ and 0.36 , respectively).

Table 1. Mean arterial blood pressure at baseline and during the local heating protocol (first peak, nadir, and plateau phase) in able-bodied controls and SCI subjects

	Baseline	Local Heating			ANOVA
		Peak	Nadir	Plateau	
Able-bodied controls	88 \pm 10	87 \pm 9	87 \pm 9	88 \pm 9	0.22
Subjects with SCI	90 \pm 12	90 \pm 13	89 \pm 13	89 \pm 12	0.70

Values are mean \pm SD in mmHg; $n = 17$ able-bodied controls and $n = 18$ spinal cord injury (SCI) subjects.

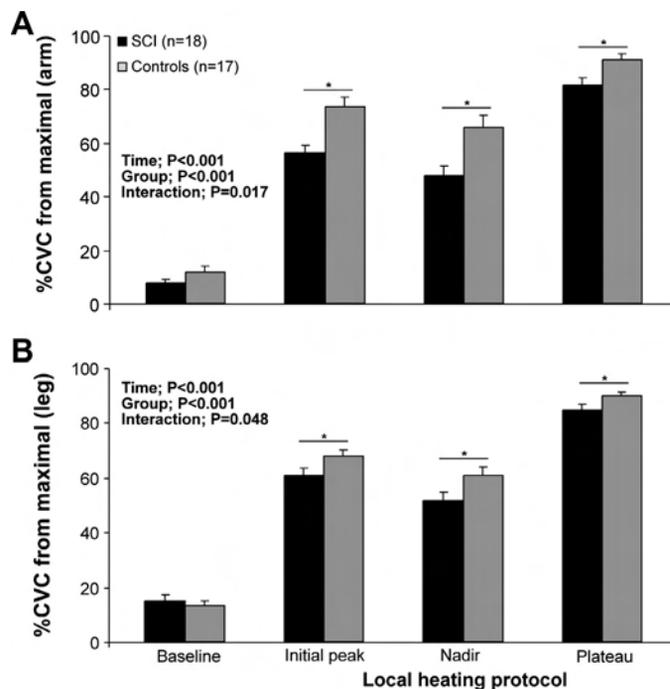


Fig. 1. Arm (A) and leg (B) cutaneous vascular conductance (CVC) is expressed as a percentage of maximal CVC during the local maximal heating protocol in able-bodied controls (shaded bars) and spinal cord-injured (SCI) subjects (solid bars). Values are presented at baseline and during the local heating protocol (initial peak, nadir, and plateau phase). A two-way repeated-measured ANOVA (heating protocol \times group) found a significant difference in microcirculation between able-bodied controls and subjects with SCI in the forearm as well as the leg. Values are means \pm SE.

Effect of 8-wk FES Cycling or Control Intervention in SCI Subjects

Two SCI subjects did not finish the FES cycling training and were, therefore, excluded from posttraining analysis. Power output during the leg cycling performance test increased after training (pretraining; 2.2 kJ, posttraining 16.9 kJ, *t*-test; $P = 0.006$). Femoral artery diameter significantly increased from 7.0 ± 0.8 mm to 7.5 ± 0.9 mm (*t*-test; $P = 0.04$). Systolic and diastolic blood pressures were not different after training (117 ± 20 and 112 ± 10 mmHg, $P = 0.65$; 76 ± 9 and 69 ± 6 mmHg, $P = 0.23$, respectively), while MAP did not change during the protocol (Table 2).

Forearm. There was no significant change in baseline (18 ± 8 and 22 ± 11 mV, respectively; *t*-test; $P = 0.39$) and peak (150 ± 40 and 184 ± 50 mV, respectively; *t*-test; $P = 0.09$) forearm RBC flux after FES cycling. FES cycling exercise training did not change %CVC_{max} in the arm at baseline or during the local heating protocol (Fig. 2A). SCI-C showed no differences in baseline (15 ± 13 and 14 ± 11 mV, respectively; *t*-test; $P = 0.58$) or peak (233 ± 146 and 203 ± 30 mV, respectively; *t*-test; $P = 0.54$) forearm RBC flux after 8 wk. In addition, SCI-C demonstrated no differences in %CVC_{max} responses between 0 and 8 wk at baseline and during local heating (Table 2).

Leg. Baseline (23 ± 4 and 22 ± 8 mV, respectively; *t*-test; $P = 0.88$) and peak leg RBC flux (176 ± 113 and 260 ± 24 mV, respectively; *t*-test; $P = 0.28$) did not change after 8 wk. Baseline leg %CVC_{max} and the %CVC_{max} responses to local

Table 2. Mean arterial blood pressure and cutaneous vascular conductance at baseline and during the local heating protocol (first peak, nadir, and plateau phase) in SCI subjects before (0 wk) and after an 8-wk intervention

	Baseline		Local Heating Protocol					
			Peak		Nadir		Plateau	
	0 wk	8 wk	0 wk	8 wk	0 wk	8 wk	0 wk	8 wk
SCI-EX								
MAP, mmHg	88±13	82±8	87±14	82±11	87±14	81±11	87±13	83±11
Arm %CVC _{max}	8±5	11±10	55±14	52±19	51±14	42±17	75±14	72±17
Leg %CVC _{max}	14±11	10±4	59±16	60±13	46±14	51±16	82±10	82±14
SCI-C								
MAP, mmHg	88±13	92±8	87±14	91±15	87±14	92±14	87±13	92±12
Arm %CVC _{max}	7±5	7±5	55±10	63±9	43±13	52±11	83±7	81±6
Leg %CVC _{max}	15±8	14±6	61±7	62±13	56±11	55±13	86±5	83±6

Values are mean ± SD. SCI-EX, SCI exercised subjects; SCI-C, SCI control subjects; MAP, mean arterial pressure; CVC_{max}, maximum cutaneous vascular conductance. The intervention consisted of functional electrostimulation cycling (before, $n = 9$, after training, $n = 7$, SCI-EX) or continuation of the subjects' normal activity (before and after, $n = 9$). There are no significant differences between both groups nor between 0 and 8 wk in SCI-EX and SCI-C.

heating were not different after 8-wk FEC cycling in SCI-EX (Fig. 2B). In SCI-C, baseline (33 ± 25 and 31 ± 13 mV, respectively; t -test; $P = 0.28$) and peak leg RBC flux (229 ± 117 and 226 ± 45 mV, respectively; t -test; $P = 0.29$) did not change after 8 wk. Also, baseline leg %CVC_{max} and responses during local heating were not altered after 8 wk in SCI-C (Table 2).

DISCUSSION

This is the first study that comprehensively examined SkBF responses to local heating below (leg) and above (arm) a spinal cord lesion, and whether possible differences between SCI

subjects and able-bodied controls can be altered by 8 wk of FES cycling training. SCI subjects demonstrated impaired CVC in the paralyzed legs during local heating compared with able-bodied controls. Interestingly, the forearm CVC responses (above the spinal cord lesion) were also impaired in SCI subjects compared with able-bodied controls. These unexpected findings suggest that a chronic spinal cord lesion results in a systemic adaptation of the skin microcirculation to local heating, rather than changes in the paralyzed region only. This hypothesis is supported by the lack of limb differences regarding skin microcirculatory responses to local heating in SCI subjects, despite the marked difference in activity level between the upper and lower limb in SCI subjects. While physical inactivity is the key factor for vascular adaptations in conduit and resistance vessels in the paralyzed legs of SCI subjects (10, 23, 36–38), our findings suggest that physical activity itself is not the key factor that affects skin microcirculation, but most likely it is the exercise-induced thermoregulation. This conclusion is supported by the finding that 8 wk of FES cycling in SCI subjects, which increases physical activity in the legs, did not alter the SkBF and CVC responses to local heating below (leg) or above (forearm) the spinal cord lesion, despite an increase in the femoral artery. These latter findings reinforce the evolving hypothesis that a change in physical activity level has a different effect on large and small arteries and that physical activity alone may not explain the impaired skin microcirculatory responses to local heating in SCI subjects.

Subjects With SCI vs. Able-Bodied Controls

The “initial peak” during the local heating protocol represents the axon-reflex mediated vasodilation (29). In our study, we found impaired leg CVC responses during this initial peak of the local heating protocol in SCI subjects. This finding is in line with a previous study examining this response in the foot (31), but contrasts with another paper that found a comparable CVC response to local heating below the level of the lesion (32). However, these previous studies did not normalize for individual differences in the maximal CVC, which may have impacted their results. Continuing the local heating protocol will result in a “plateau phase,” which is predominantly mediated through NO (1, 29). The leg %CVC_{max} responses during

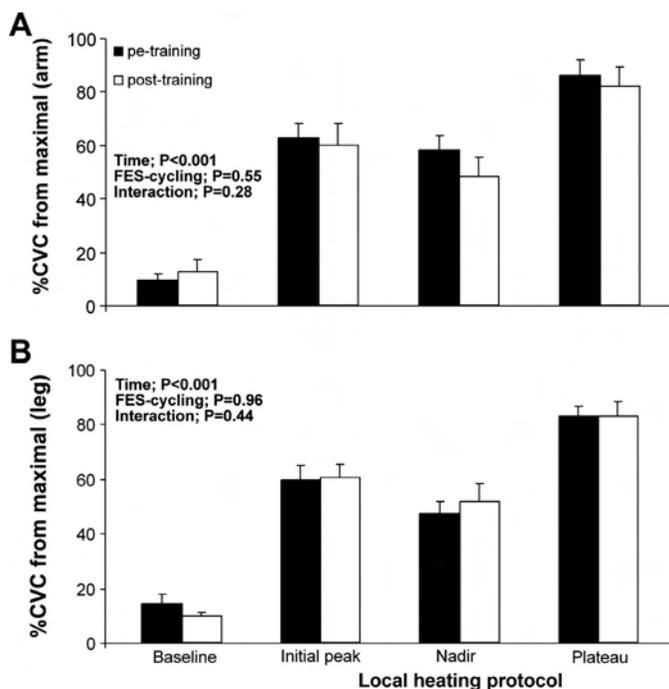


Fig. 2. Arm (A) and leg (B) CVC in SCI subjects is expressed as a percentage of maximal CVC during the local maximal heating protocol before (solid bars) and after 8-wk functional electrostimulation (FES) cycling exercise (open bars, $n = 7$). Data are presented at baseline and during the local heating protocol (initial peak, nadir, and plateau phase). A two-way repeated-measured ANOVA (heating protocol × intervention) found no impact of 8-wk FES cycling on arm or leg microcirculation. Values are means ± SE.

this plateau phase in SCI subjects were significantly lower than in able-bodied controls. Although we did not perform pharmacological NO blockade to verify the contribution of NO to this response, this finding provides the first evidence that leg microcirculation NO function in SCI subjects might be impaired. Interestingly, this impaired NO function in the microcirculation contrasts with previous studies reporting a preserved contribution of NO to leg muscular vascular tone (2) and preserved NO-mediated superficial femoral artery endothelial function (12). A recent study suggested that only a weak relation is present between measures of micro- and macrovessel reactivity (16). At least these previous findings suggest that adaptations of the NO pathway in conduit, resistance, or skin vessels to physical inactivity are not necessarily coupled. Taken together, our findings indicate an impaired axon- and NO-mediated response of the skin microcirculation to local heating in the paralyzed and extremely inactive legs of SCI subjects.

Physical inactivity in the paralyzed limb in SCI subjects is identified as a key stimulus for the dramatic adaptations found in the conduit and resistance arteries of the lower limb (9, 23, 30, 36). Short-term inactivity (e.g., 13–14 days of bed rest) is found to attenuate maximal cutaneous vasodilator responses (8, 28), while exercise can prevent this decline (35). Accordingly, we hypothesized that inactivity may also explain the impaired CVC responses to local heating in the leg of SCI subjects. However, in contrast to our hypothesis, SCI subjects also exhibited impaired CVC responses to local heating in the active forearm, suggesting the presence of a generalized, rather than a local, impairment in the skin microcirculation in SCI subjects. Interestingly, Freund et al. (17, 18) found attenuated SkBF responses in the forearm to whole body hyperthermia. Also Nicotra et al. found a generalized impairment in CVC responses to local heating (31), but they could not repeat these findings in a different study (32). These conflicting results may be explained by the lack of normalization for the peak CVC. As paraplegic subjects have normal, or even supranormal, upper arm function, physical inactivity cannot explain the impaired CVC responses observed in the arms of SCI subjects.

A possible explanation for impaired upper limb responses relates to the lack (or insufficient presence) of a heat stress stimulus in SCI subjects, as is present during exercise. A rise in core body temperature is a key stimulus for CVC to increase in an attempt to thermoregulate. Although the SCI subjects in our study frequently performed upper limb muscle activities in daily living, none performed regular strenuous exercise training. Moderate-to-strenuous exercise is required to produce a sufficient heat gain to increase core body temperature to the level where reflex CVC changes are induced. Low-intensity exercise will be sufficient to increase shear rate, e.g., the key stimuli for conduit and resistance vessels to adapt to exercise (3, 34), but will not substantially increase core body temperature. In addition, due to the smaller active muscle mass, it is more difficult for SCI to produce a large heat stress compared with controls. Finally, an increase in core body temperature in individuals with SCI is associated with smaller changes in SkBF (17, 18). This further limits the ability to sufficiently increase SkBF during exercise. While repeated heat exposure is found to improve endothelial function of conduit arteries (25), but not the sweating response (4), to date no study has assessed the impact of heat exposure alone on the skin micro-

circulation. This knowledge is important to assess the significance of heat exchange to the potential changes in skin microcirculatory function. Hence, the less frequent exposure of chronic SCI subjects to heat stress stimuli (for example, through exercise), combined with attenuated SkBF responses to whole body heating, may explain the impaired CVC responses to local heating in both the arms and legs, rather than physical inactivity per se.

Effect of FES Cycling Exercise

Since FES cycling involves activation of leg muscles only, adaptations in the forearm skin microcirculation were not expected. Indeed, we found no adaptation in forearm skin microcirculation function. Regarding leg muscle activation, several previous studies have reported a partial reversibility of leg conduit and resistance artery function and structure after FES cycling training (10, 23, 36–38), supporting the idea that physical inactivity primarily drives vascular changes in the paralyzed legs. Indeed, we demonstrated a markedly increased femoral artery diameter after FES cycling (~8%) in the present study. This, together with the 7.5-fold higher FES performance after 8 wk, emphasizes the effectiveness of the FES cycle training in our study. Nonetheless, 8 wk of FES cycling did not alter leg CVC responses to local heating. Heat gain by FES cycling is most likely too small to induce significant changes in core temperature and SkBF. Indeed, Holme et al. (22) found a modest increase in heart rate (to 123 beats/min) and oxygen consumption (0.9 l/min) during 30-min FES cycling. Although FES cycling slightly increased core body temperature, no changes in skin temperature were reported (21, 22). The insufficient heat stimulus on core and skin temperature may explain the lack of adaptation found in skin microcirculation after 8-wk FES cycling. This finding, however, does not exclude the possibility that FES cycling has an impact on skeletal muscle microcirculation in SCI individuals. Taken together, this reinforces our finding that physical activity per se may not impact skin microcirculation function, but rather the associated changes in core temperature and skin temperature and blood flow.

These findings also demonstrate that the impact of physical activity depends on the vascular bed examined; while the femoral artery reported a marked outward remodeling, no changes were present in the leg CVC responses. Likely, these adaptations to FES cycling in the distinct vascular beds depend on a different physiological stimulus. While an increase in shear stress in the femoral artery is the key physiological stimulus for diameter enlargement (3, 34), changes in skin microcirculation are likely the result of a heat stimulus. Although FES cycling will increase leg muscle metabolism and redness in the skin under the surface electrodes, only 30% of the stimulated muscle mass is truly activated, while the redness is primarily limited to the skin under the small surface electrodes only. Accordingly, this exercise modus unlikely resulted in a large thermo-physiological stimulus, which could result in changes in leg CVC. In addition, the intensity (2–3 times/wk) and time frame (8 wk) of FES cycle training are lower than usually applied in studies examining effects of exercise training in skin microcirculation in other groups (1, 39). Therefore, our intensity of training might be too low for long-term adaptations in the skin microcirculation associated with ther-

moregulatory responses, while it was sufficient for conduit artery changes.

Clinical Relevance

Pressure sores, skin breakdown lesions, and poor wound healing represent one of the most important health problems in SCI subjects, potentially leading to morbidity and even mortality. As attenuated skin perfusion is correlated with poor wound healing (7, 41), the impaired skin microcirculation reported in our study may also contribute to these health problems in SCI subjects. While we demonstrated no effect of lower limb FES cycling on skin microcirculatory function, anecdotal evidence indicates that the skin under and directly around the surface electrodes is red and much warmer than the surrounding tissue (i.e., where we did not examine skin microcirculation). Local surface stimulation may, therefore, be more efficient to locally improve skin microcirculatory function than FES cycling training. A recent paper reported beneficial effects of local surface electrostimulation to restore interface pressure (40), which was suggested to restore blood flow in this region. Future studies should further examine the impact of such interventions to (partly) reverse the impaired skin microcirculation in SCI.

Limitations

The strengths of this study include the cross-sectional and longitudinal study designs and the comprehensive way to examine skin microcirculation, including skin NO function. However, there are also some limitations. First, we included a group of SCI subjects that demonstrated a large variation in age. However, the SCI subjects were matched with healthy able-bodied subjects to exclude the impact of age in our study, and some of the principal comparisons, for example, between the arm and leg responses, were within subjects. Finally, the use of laser-Doppler for SkBF assessment has some limitations. While peak blood flow normalization is important for interpretation of the data, peak blood flow can differ in response to an intervention (e.g., exercise) without changes in the corrected data. This could mask possible changes in the absolute SkBF responses to a local heating stimulus. Regardless, it seems unlikely that the maximal SkBF response in both the legs and arms of SCI subjects would be greater than the controls. Thus our findings provide evidence for reduced cutaneous vascular responses in SCI subjects, both above and below the lesions. In the longitudinal part of our study, forearm and leg peak SkBF was higher after training, but did not reach a significance level. Nonetheless, the limitations of presenting proportional data, when slight changes may occur in peak values, must be considered when interpreting these findings of our study.

In conclusion, our results suggest that a generalized impairment in skin microcirculatory function to local heating is present in SCI subjects compared with able-bodied controls. Despite the marked difference in physical activity level between the upper and lower limb in SCI subjects, both limbs demonstrated a similarly impaired skin microcirculatory function. These findings suggest that physical activity level per se may not be responsible for the impaired skin microcirculatory function in SCI. This finding contrasts with the common finding of localized adaptation in conduit and resistance vessels

in the paralyzed legs, but not in the active upper limbs. Our hypothesis is reinforced by the longitudinal part of our study, where we found no difference in skin microcirculatory function after 8 wk of FES cycling training, while a significant increase in femoral artery diameter after FES cycling was present. Although a higher intensity physical exercise may have resulted in adaptations of the skin microcirculation as well, our novel and unexpected findings indicate that a low-to-moderate level of physical (in)activity has a different impact on skin microcirculatory function than on conduit arteries. Future studies should further elucidate the exact stimuli for the skin microcirculation to adapt to a change in physical activity level.

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