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Rapid and Extensive Arterial Adaptations After Spinal Cord Injury

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ABSTRACT. de Groot PC, Bleeker MW, van Kuppevelt DH, van der Woude LH, Hopman MT. Rapid and extensive arterial adaptations after spinal cord injury. *Arch Phys Med Rehabil* 2006;87:688-96.

Objective: To assess the time course of adaptations in leg vascular dimension and function within the first 6 weeks after a spinal cord injury (SCI).

Design: Longitudinal study design.

Setting: University medical center and rehabilitation clinic.

Participants: Six men were studied serially at 1, 2, 3, 4, and 6 weeks after SCI.

Interventions: Not applicable.

Main Outcome Measures: Diameter, blood flow, and shear rate levels of the common femoral artery (CFA), superficial femoral artery (SFA), brachial artery, and carotid artery were measured with echo Doppler ultrasound (diameter, blood flow, shear rate). Endothelial function in the SFA was measured with flow-mediated dilation (FMD). In addition, leg volume and blood pressure measurements were performed.

Results: Femoral artery diameter (CFA, 25%; SFA, 16%; $P < .01$) and leg volume (22%, $P < .01$) decreased simultaneously, and these reductions were largely accomplished within 3 weeks postinjury. Significant increases were observed for basal shear rate levels (64% increase at week 3; 117% increase at week 6; $P < .01$), absolute FMD responses (8% increase at week 3, 23% increase at week 6; $P < .05$) and relative FMD responses (26% increase at week 3, 44% increase at week 6; $P < .001$).

Conclusions: Our findings show a rapid onset of adaptations in arterial dimension and function to extreme inactivity in humans. Vascular adaptations include extensive reductions in femoral diameter and leg volume, as well as increased basal shear rate levels and FMD responses, which all appear to be largely accomplished within 3 weeks after an SCI.

Key Words: Arteries; Cardiovascular deconditioning; Doppler ultrasound; Rehabilitation.

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IN HUMANS, VASCULAR ADAPTATIONS in diameter size, blood flow, and shear stress to deconditioning have been reported to be largely completed within 6 weeks.¹ However, the time course of vascular changes to deconditioning within these first 6 weeks is unknown. Shear stress represents the frictional force of the blood cells on the endothelial layer and is supposed to play an important role in endothelial function and vascular adaptation processes. The human arterial system strives to maintain a constant shear stress by adjusting the diameter size to chronic changes in blood flow.²

A spinal cord injury (SCI) may be considered as a human model of extreme exposure to inactivity and offers a unique opportunity to study early vascular adaptations to deconditioning. Animal studies show a rapid onset of vascular adaptations to persistent alterations in blood flow. Adaptations in vascular tone occur within days, whereas chronic and structural changes of the vessel wall are completed within 2 to 3 weeks.³⁻⁵

In humans with longstanding SCI, extensive adaptations occur in the peripheral circulation such as a 30% decrease in diameter, a reduction in blood flow, and an almost doubling of stress levels in the femoral artery.^{1,6-8} Results on vascular changes derived from other models of deconditioning like bedrest studies⁹⁻¹¹ conflict with some studies showing a decrease in leg blood flow and others showing no changes after a period of bedrest varying from 10 to 41 days. However, none of these studies provides information related to changes in diameter size, and the magnitude of physical inactivity during bedrest may vary, because movements of the legs are still possible. Furthermore, vascular changes during bedrest may be seriously confounded by the effects of microgravity and concomitant decrease in plasma volume.¹² Two recent studies assessed vascular changes after a period of lower-limb immobilization and reported a 6% and 12% decrease in femoral artery diameter after 1 week of lower-limb casting¹³ and after 4 weeks of unilateral lower-limb suspension,¹⁴ respectively.

Flow-mediated dilation (FMD) involves direct imaging of artery diameter change using ultrasound, consequent to a brief period of limb ischemia and subsequent hyperemia. The increase in arterial diameter in response to this stimulus provides an index of conduit artery endothelium-dependent nitric oxide (NO) function.¹⁵ Previous studies have shown that this FMD response is enhanced or at least preserved in arteries after a period of deconditioning.^{7,14,16} The finding of an enhanced FMD in deconditioned arteries is surprising, because it has been shown previously that FMD also increases after exercise training.^{17,18} These findings may imply that vascular adaptations to deconditioning are not simply the opposite of exercise and that a different mechanism might be involved.

The following study was conducted to assess the time course of early changes in vascular dimension and endothelial function after extreme inactivity in humans. For this purpose, 6 acutely injured SCI patients were included, and vascular dimension, blood flow, endothelial function, and limb volume were measured 1, 2, 3, 4, and 6 weeks posttrauma. Based on animal research and limited information from human studies,

Table 1: Subjects' Characteristics

Subject		Age (y)	Body Mass (kg)	Height (cm)	Blood Pressure (mmHg)	Lesion Level (ASIA grade)	Time Since Injury (d)
1	■	42	74	183	128/72	T9 (A)	7
2	●	65	71	180	140/70	L1 (A)	9
3	○	37	75	180	120/70	T10 (A)	12
4		28	55	174	115/72	T9 (A)	22
5	□	33	60	165	116/82	T12 (B)	20
6	△	33	65	167	90/65	C4 (A)	27
Mean		39	67	175	118/72		16
SD		13	8	8	17/6		9

NOTE. The symbols of the subjects correspond with the individual symbols in figures 1, 2, 3, and 4. Abbreviation: ASIA, American Spinal Injury Association; SD, standard deviation.

we hypothesized that vascular adaptations in function and dimension occur within 3 to 6 weeks of extreme inactivity.

METHODS

Participants

Six male SCI patients with recent, traumatic, motor-complete spinal cord lesions (American Spinal Injury Association grade A or B)¹⁹ between the C4 and L1 vertebrae participated in this study. Patients were included as soon as their clinical and personal situations allowed conversation and measurements needed for this study (mean time since injury, 16±9d). Patients with a known history of cardiovascular disease, diabetes, hypercholesterolemia, or high blood pressure were excluded from the study. The Ethical Committee of the Radboud University Nijmegen Medical Centre approved the study and all patients provided written informed consent before participating. Individual patient characteristics are presented in table 1.

Protocol

Based on the severity of the trauma-related complications, patients were measured repetitively, from week 1 to week 6 postinjury. All measurements were conducted in the supine position under standardized quiet conditions after an overnight fast or controlled low-fat breakfast at the University Nijmegen Medical Centre or at the rehabilitation clinic. Subjects were asked to empty their bladders before examination and they refrained from alcohol, caffeine, and nicotine for at least 12 hours before the test. The same investigator performed all the measurements and analyses.

Measurements and Data Analyses

Baseline and hyperemic vascular characteristics. Resting red blood cell velocity and diameter of the right common femoral artery (CFA), right superficial femoral artery (SFA), right brachial artery, and left carotid artery were measured using echo Doppler ultrasound^a with a 5- to 7.5-MHz broadband linear array transducer. The sample volume was adjusted to cover the width of the vessel and, thus, the complete blood velocity distribution.²⁰ For the carotid artery, images were made 1.5cm proximal from the bifurcation of the external and internal carotid artery. For the CFA, images were obtained just below the inguinal ligament, about 2cm proximal to the bifurcation into the deep femoral artery and SFA. SFA images were made approximately 3cm distal to the bifurcation of the CFA. Images of the brachial artery were obtained approximately 3cm proximal to the olecranon process. The angle of inclination for the velocity measurements was consistently below 60°, and the vessel area was adjusted parallel to the transducer. From each

artery, 4 images with a total of 10 to 12 velocity profiles were obtained and traced manually afterward by a single investigator.

Offline analyses. For resting diameter measurements, 2 consecutive images in the longitudinal view were frozen at the peak-systolic and end-diastolic phase. Offline, 3 measurements were performed per diameter image, and the mean diameter (D) was calculated by using the following formula: $\frac{1}{3} \times \text{systolic diameter} + \frac{2}{3} \times \text{diastolic diameter}$. The average of 10 to 12 Doppler spectra waveforms was used to calculate mean red blood cell velocity (Vmean).

For hyperemic red blood cell velocity (the flow velocity response during the first 25 seconds after cuff release; see section on endothelial function), we obtained a total of 6 to 8 velocity profiles, and from each velocity profile, the flow velocity integral was manually traced. The average of these 6 to 8 velocity profiles was used to calculate peak and mean hyperemic velocity. For both resting images and hyperemic responses, mean blood flow in millimeters per minute was calculated as $\frac{1}{4} \times \pi \times (D)^2 \times V_{\text{mean}}$ (in cm/s) $\times 60$. Regional mean wall shear rate (MWSR) was calculated as $4 \times V_{\text{mean}}/D$ (in s⁻¹). Delta flow and ΔMWSR were defined as the differences between baseline values and hyperemic responses.

Endothelial function. FMD represents the vasodilation in a conduit artery in response to flow-associated increases in shear stress and provides an index for conduit artery endothelium dependent. For this measurement, a large cuff was placed around the upper thigh, approximately 10cm distally from the greater trochanter. The cuff was inflated to suprasystolic pressure (220mmHg) for 10 minutes. After cuff deflation, hyperemic blood flow velocity in the SFA was recorded on videotape for the first 25 seconds, followed by a continuous registration of the vessel diameter for 5 minutes. A spray of nitroglycerine (NTG) (0.4mg) was administered sublingually after a resting period of 10 minutes to determine the endothelium-independent vasodilatation, which is indicative for sensitivity of smooth muscle to NO.²¹

Vessel diameter of the SFA was recorded continuously between 2 and 6 minutes after the administration of NTG.

Offline, vessel diameters of the SFA were measured from videotape at 45, 60, 90, 120, and 240 seconds after cuff release and at 2, 3, 4, 5, and 6 minutes after NTG administration. All diameters were measured at the end-diastolic phase of the cardiac cycle, corresponding to the R wave of a simultaneous electrocardiogram signal. FMD in the SFA and endothelium-independent vasodilatation in the SFA were expressed as both the maximal absolute and relative diameter change in end-diastolic baseline diameter. Because the FMD response is directly proportional to the magnitude of the stimulus,²² the FMD response was also expressed relative to the ΔMWSR . Ratios were calculated for FMD/ ΔMWSR . Reproducibility of the

vascular measurements was assessed previously and varied from 1% to 3% for vessel diameter, 9% to 18% for resting and hyperemic flow velocity parameters, and 15% for relative FMD responses.^{1,7}

Blood pressure. Blood pressure was measured by auscultation at the brachial artery before and after the echo Doppler measurements, using a sphygmomanometer.

Leg volume. Leg circumferences were measured at 7 pre-defined sites on the leg, and the height between these points was determined. These measures divide the leg into 6 segments, similar to truncated cones. Then limb volume was calculated as described by Jones and Pearson.²³

Statistical Analyses

Data analyses in this study were performed with the repeated-measures procedure PROC MIXED.^b In the model, the dependency of the measurements within the same subject was taken into account, and equal variances at different time points and equal correlations between the time points are assumed. To assess a time trend, time was incorporated into the model as a continuous variable. If there was a significant trend, additional post hoc analyses were performed with time as a nominal factor

to determine specific changes over time. *P* values less than .05 were considered statistically significant.

RESULTS

Baseline and Hyperemic Vascular Characteristics

In the femoral artery, a significant decrease over time was observed for vessel diameter ($P < .01$) (fig 1A, table 2). Basal MWSR levels increased significantly during the 6-week period ($P < .01$) (see fig 1B, table 1). No significant changes over time were observed for resting blood flow in CFA (see fig 1C) and hyperemic flow in the SFA (see fig 1D), although a trend for a decrease in hyperemic flow seems present.

No changes were observed for diameter, shear rate, and blood flow in the brachial artery and the carotid artery (see table 2).

Endothelial Function

In the SFA, a significant increase over time was observed for absolute ($P < .01$) and relative ($P < .05$) FMD responses (figs 2A, B).

Although a trend toward an increase was evident, the ratio of FMD/ Δ MWSR did not change significantly over time (see fig

Fig 1. Changes in (A) vessel diameter, (B) MWSR, (C) basal leg blood flow of the CFA, and (D) reactive hyperemic flow in the SFA at weeks 1, 2, 3, 4, and 6 postinjury. Results of early adaptation are represented as individual data points. Diagonal blocks represent the range of values in able-bodied controls and solid blocks represent values in chronic SCI subjects from previous studies.^{1,7} *Significant differences between weeks ($P < .01$).

Table 2: Time Course Changes 1 Week, 2 Weeks, 3 Weeks, 4 Weeks, and 6 Weeks Postinjury in Vascular Properties of the Brachial Artery, Carotid Artery, SFA, and CFA in Acute SCI Subjects

Artery	1 Week (n=2)	2 Weeks (n=3)	3 Weeks (n=4)	4 Weeks (n=6)	6 Weeks (n=6)
Brachial artery					
Diameter (cm)	.42±.04	.42±.04	.42±.02	.43±.02	.42±.03
MWSR (s ⁻¹)	42±3	69±53	44±10	52±23	60±26
Flow (mL/min)	38±14	56±48	39±16	45±15	55±23
Carotid artery					
Diameter (cm)	.67±.01	.68±.03	.68±.03	.67±.03	.67±.03
MWSR (s ⁻¹)	99±37	96±11	84±15	103±31	104±18
Flow (mL/min)	336±101	355±80	320±87	359±75	362±50
SFA					
Diameter (cm)	.69±.08*†	.66±.07*	.59±.05	.58±.08	.59±.08
MWSR (s ⁻¹)	22±7†	34±4†	38±7†	43±16	61±28
Flow (mL/min)	80±11 [§]	115±30 [‡]	94±45 [‡]	100±45 [‡]	155±84
CFA					
Diameter (cm)	.99±.05*†	.90±.06*	.75±.06	.76±.10	.76±.11
MWSR (s ⁻¹)	31±14 [§]	14±14 [§]	51±13	56±15	71±19
Flow (mL/min)	348±106	301±76	254±76	272±132	323±127

NOTE. Values are mean ± SD.

*Significantly different from weeks 3, 4, and 6 postinjury ($P<.01$).

†Significant differences week 1 versus week 2 ($P<.01$).

‡ $P<.05$ significantly different from 6 weeks postinjury.

§ $P<.01$ significantly different from 6 weeks postinjury.

2C). NTG responses could be assessed in only 3 people. No differences over time were observed for NTG responses (range, 11%–12%).

Blood Pressure

Systolic blood pressure and mean arterial pressure (MAP) decreased significantly ($P<.05$) over time with no changes for diastolic blood pressure (fig 3).

Leg Volume

Leg volume decreased significantly over time ($P<.01$) (fig 4A). If the diameter of the CFA was normalized to leg volume, no significant changes over time were observed (see fig 4B).

DISCUSSION

The present study provides important information on the time course and the magnitude of adaptations of vascular dimension and endothelial function during the first 6 weeks of extreme deconditioning in humans. In accordance with data from animal studies, a rapid onset of arterial adaptations after acute SCI was observed. Changes include an approximately 25% reduction in femoral artery size and leg volume, a doubling in basal shear rate levels, and a significant increase in FMD response. All these adaptations were largely accomplished within 3 weeks postinjury.

Baseline and Hyperemic Vascular Characteristics

The carotid artery (an elastic type of artery) and the brachial artery (a muscular type of artery) are both located above the lesion level. No changes were found for any of the vascular characteristics (vessel diameter, shear rate, blood flow), which is in accordance with previous studies^{1,6} that report no differences in carotid and brachial vascular characteristics between chronic SCI subjects and controls.

Resting blood flow in the femoral artery did not change over time. In previous studies, conflicting results have been reported, with some studies^{24,25} showing a decrease in basal blood flow in SCI and other studies^{7,8} reporting no differences

in leg blood flow between subjects with SCI and controls. Our results support these latter studies and are in line with findings of a recent study that showed no changes in resting blood flow after 4 weeks of leg suspension.¹⁴

Because the skeletal muscle extracts only one third of the delivered oxygen of the blood, an oxygen reserve is present in the resting situation. Hence, resting blood may not be the regulating factor for vascular remodeling of the femoral artery, as will be discussed later.

The diameter of the femoral conduit arteries decreased significantly over time. At 3 weeks postinjury reductions in diameter seem to plateau, and the magnitude of the vessel diameter at that time (CFA, 7.5mm; SFA, 5.6mm) approaches the vessel dimension in chronic SCI subjects (5–7.5mm).^{6,24} Recently, 2 studies assessed vascular changes after lower-limb immobilization and reported a 6% reduction after 1 week of lower-limb casting¹³ and a 12% reduction after 4 weeks of unilateral lower-limb suspension.¹⁴ Hence, the 25% decrease in vessel size of femoral artery within 3 weeks after an SCI represents the largest reduction in diameter in response to the most extreme form of deconditioning. Figure 5 illustrates the wide range of femoral artery size across the total spectrum of physical activity from the patients with SCI to endurance-trained athletes.

Although postocclusion hyperemic blood flow, typically used to evaluate arteriolar structural changes in the circulation, showed no significant decrease over time, a trend toward decrease seems to be visible from figure 1D. It may be possible that mechanisms and time course of vascular adaptations to deconditioning may differ between conduit (diameter) and resistance vessels (hyperemic flow response), as has been indicated previously in exercise-training studies in animals^{26,27} and humans.²⁸ This hypothesis, however, needs further investigation.

Arterial remodeling represents the process of chronic and structural changes in the arterial system. Persistent changes in blood flow cause alterations in blood vessel architecture to normalize wall shear stress.^{3,5} Previous training studies^{29,30} in humans have suggested that conduit arteries adapt their base-

Fig 2. Individual data points of changes in (A) relative FMD response (B) absolute FMD responses, and (C) ratio of FMD/ Δ MWSR at weeks 1, 2, 3, 4, and 6 postinjury. Diagonal blocks represent the range of values in able-bodied controls and solid blocks represent values from chronic SCI subjects from previous studies.^{1,7} *Significant differences between weeks ($P < .05$).

line diameters to peak shear stress and peak oxygen consumption rather than to resting blood flow. Parallel to this reasoning, the decrease in diameter in SCI may represent an inward remodeling as an adaptation to a total lack of periods of high shear stress in the paralyzed legs of people with SCI. Our findings support the assumption that baseline diameter adapts to peak flow (see fig 6A) instead of resting blood flow (see fig 6B). During reactive hyperemia, shear stress levels are kept constant across a wide spectrum of hyperemic flows, from very low in chronic SCI patients to high in able-bodied controls.

Endothelial Function

It has been shown that an intact endothelium is essential for normal arterial remodeling,⁵ and NO has emerged as the major endothelium-derived mediator controlling vascular remodeling.³¹ The present study shows that already within 3 to 6 weeks postinjury, basal shear rate levels are doubled in the conduit arteries of the inactive and denervated legs of patients with SCI (see fig 6B), which is in agreement with findings in chronic SCI.^{6,7,32} FMD is a measure of NO production in response to shear stress stimulus. Absolute and relative FMD responses increased significantly during the first 6 weeks of extreme inactivity, with most changes evident at 3 weeks postinjury. Although not significant, a trend toward an increase was still evident when FMD was corrected for the maximal hyperemic shear rate stimulus (see fig 2C). An increased relative FMD response in deconditioned arteries is also reported in recent studies using different human models for physical inactivity such as chronic SCI,⁷ bedrest,¹⁶ and unilateral lower-limb suspension.¹⁴ Because it is well established that exercise training causes an increase in FMD,^{17,18} these findings may be somewhat surprising, because they imply that endothelial adaptations to deconditioning are not simply the inverse of adaptation to exercise.

Possible explanations for an increased FMD response in deconditioned vessels may be related to the chronically enhanced baseline shear stress levels in leg conduit arteries. Because it is well known that shear stress is a potent physiologic stimulus for NO release, the increased levels of basal shear stress may lead to an upregulation of endothelial nitric oxide synthase (eNOS). A recent training study in patients with coronary artery disease³³ and previous in vivo³⁴ and cell culture

Fig 3. Individual data point of changes in MAP at weeks 1, 2, 3, 4, and 6 postinjury. *Significant differences between weeks ($P < .05$).

Fig 4. Individual data point of time course changes in (A) leg volume and (B) for diameter normalized for leg volume at weeks 1, 2, 3, 4, and 6 postinjury. Diagonal blocks represent the range of values in able-bodied controls and solid blocks represent values from chronic SCI subjects from previous studies.^{1,7} *Significant differences between weeks ($P < .01$).

studies^{2,35} have shown that increases in shear stress levels are associated with an elevation of eNOS messenger ribonucleic acid protein and NOS activity. A second possible explanation may be the lack of periods of high shear stress in the vessels supplying the paralyzed and inactive leg muscles of people with SCI, which may contribute to an upregulation of NO responsiveness.

FMD implies endothelial NO production in response to a stimulus or smooth muscle characteristics such as NO sensitivity or vasodilator capacity. In the present study, no differences in absolute and relative NTG responses were observed over time, indicating that smooth muscle sensitivity to NO or vasodilator capacity was unaltered. However, the results should be interpreted with caution because NTG responses could be assessed in only 3 people. Findings of our study are supported by a previous study in patients with chronic SCI⁷ in which no differences in relative NTG response were observed between subjects with SCI and able-bodied controls, but they contrast with recent observations showing an increased NTG response after 4 weeks of deconditioning induced by limb suspension.¹⁴ Possibly, the vasodilation response to nitroglycerin in SCI may be limited by structural changes in the vessel wall, thereby masking a possible increase in NO sensitivity.

Leg Volume and Blood Pressure

It is well documented that people with SCI suffer from dramatic muscle atrophy in the paralyzed legs, which is indicated by 35% to 50% reduction in lower-limb cross-sectional area.^{8,36} At 6 weeks postinjury, Castro et al³⁶ reported a 40% smaller fiber size in the SCI group compared with controls with a further decline in fiber size (27%–56%) from 6 to 24 weeks after the injury. Although one may speculate that muscle atrophy precedes vascular atrophy (oxygen demand adjusted by oxygen delivery), it has been shown in animals with congestive heart failure that apoptosis of endothelial cells precedes the apoptosis of skeletal muscle fibers.³⁷ However, the mechanism of muscular and vascular adaptations and their mutual dependency in humans is still a largely unexplored area. In a recent cross-sectional study in chronic SCI subjects, Olive et al⁸ reported that significant changes in femoral vessel diameter did not exist when diameter size was expressed per unit muscle mass. The results of our longitudinal study do not only support these findings, but we observed a simultaneous decrease in limb volume and arterial diameter over time, which was evident from 3 weeks postinjury. When we corrected femoral artery diameter for limb volume, no differences over the 6-week time period were observed, and values in SCI subjects are comparable with control values (see fig 4B). These findings may suggest a strong functional link between adaptations in vascular dimension and muscle atrophy during deconditioning.

Changes in blood pressure may elicit changes in vascular structure and tone.³⁸ In the present study, we observed a decrease in systolic and MAP in the 6 weeks after SCI. In a previous deconditioning study in hindlimb unloaded rats, Delp et al⁴ observed that reductions in transmural pressure induced atrophy of smooth muscle cells with no changes in vessel diameter. In addition, vascular adaptations to deconditioning with no changes in blood pressure were reported previously after 4 weeks of lower-limb suspension.¹⁴ We believe, therefore, that pressure changes do not importantly contribute to the vascular remodeling in people with SCI.

Study Limitations

Two subjects were smokers until the time of accident. Most evidence suggests that smoking decreases FMD.³⁹ Although the withdrawal of cigarettes at the time of hospitalization may affect endothelial function, data on the effect of short-term cessation of smoking (ie, 6wk) on vascular function are lack-

Fig 5. Femoral artery diameter size across the whole spectrum of physical activity from extreme deconditioning (SCI) to endurance-trained athletes. Abbreviations: BR, bedrest; ULLS, unilateral limb suspension.

A **B**

Fig 6. Shear rate values (y axis) plotted against the blood flow (x axis). (A) Hyperemic responses and (B) resting values are presented for SCI patients in the present study at weeks 1, 2, 3, 4, and 6 postinjury from a group of controls (lower line; open squares) and from a group of chronic SCI subjects (upper line; open circles).

ing. In addition, an increased FMD response was evident for the 4 nonsmokers in the present study and in a previous study in nonsmoking chronic SCI subjects.⁷

In our study, it was not possible to perform all measurements in the fasting state. To minimize the confounding effects of food intake, subjects received a controlled low-fat meal, which has been shown not to affect resting arterial diameter and FMD responses.^{40,41}

We consider the SCI population as a unique human model of nature for assessing peripheral vascular adaptations to extreme inactivity. As valuable as information is from this patient population, one should be cautious in extrapolating these re-

sults to the general population because of other unique pathologies underlying SCI. Besides the extreme deconditioning, people with SCI have a loss of supraspinal sympathetic vascular tone of the legs, which may affect vascular adaptations and FMD responses. Previously, Hijmering et al⁴² showed that increased sympathetic outflow by lower body negative pressure can acutely blunt FMD responses, mediated by an α -adrenergic mechanism. It has recently been shown, however, that α -adrenergic-mediated tone in the leg vascular bed of people with SCI did not differ from that of able-bodied controls.⁴³ Also, sympathectomized patients with lack of sympathetic vascular innervation but with normal physical activity do not show

vascular adaptations.⁴⁴ In addition, previous studies in SCI have shown that most of the adaptations in the circulatory system in SCI are reversible by functional electrostimulation training,^{45,46} which suggests that the adaptations in the inactive and paralyzed legs in SCI seem to result primarily from deconditioning.

CONCLUSIONS

Our findings show a rapid onset of adaptations in vascular dimension and function to extreme deconditioning in humans. Vascular adaptations include extensive reductions in femoral diameter and leg volume and increased basal shear rate levels and FMD responses, all of which appear to be largely accomplished within 3 weeks after an SCI. The decrease in diameter in SCI most likely represents an inward remodeling as an adaptation to a total lack of peak shear stress and not to basal shear stress levels. When femoral diameter was corrected for limb volume, no differences over the 6-week time period were observed, which suggests a strong functional link between adaptations in vascular dimension and muscular atrophy.

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References

- de Groot PC, Van Kuppevelt DH, Pons C, Snoek G, van der Woude LH, Hopman MT. Time course of arterial vascular adaptations to inactivity and paralyzes in humans. *Med Sci Sports Exerc* 2003;35:1977-85.
- Kamiya A, Ando J, Shibata M, Masuda H. Roles of fluid shear stress in physiological regulation of vascular structure and function. *Biorheology* 1988;25:271-8.
- Brownlee RD, Langille BL. Arterial adaptations to altered blood flow. *Can J Physiol Pharmacol* 1991;69:978-83.
- Delp MD, Collieran PN, Wilkerson MK, McCurdy MR, Muller-Delp J. Structural and functional remodeling of skeletal muscle microvasculature is induced by simulated microgravity. *Am J Physiol Heart Circ Physiol* 2000;278:H1866-73.
- Langille BL, O'Donnell F. Reductions in arterial diameter produced by chronic decreases in blood flow are endothelium-dependent. *Science* 1986;231:405-7.
- Schmidt-Trucksass A, Schmid A, Brunner C, et al. Arterial properties of the carotid and femoral artery in endurance-trained and paraplegic subjects. *J Appl Physiol* 2000;89:1956-63.
- de Groot PC, Poelkens F, Kooijman M, Hopman MT. Preserved flow-mediated dilation in the inactive legs of spinal cord-injured individuals. *Am J Physiol Heart Circ Physiol* 2004;287:H374-80.
- Olive JL, Dudley GA, McCully KK. Vascular remodeling after spinal cord injury. *Med Sci Sports Exerc* 2003;35:901-7.
- Pawelczyk J, Zuckerman JH, Blomqvist GC, Levine BD. Regulation of muscle sympathetic nerve activity after bed rest deconditioning. *Am J Physiol Heart Circ Physiol* 2001;280:H2230-9.
- Louisy F, Schroiff P, Guell A. Changes in leg vein filling and emptying characteristics and leg volumes during long-term head-down bed rest. *J Appl Physiol* 1997;82:1726-33.
- Takenaka K, Suzuki Y, Kawakubo K, et al. Cardiovascular effects of 20 days bed rest in healthy young subjects. *Acta Physiol Scand Suppl* 1994;616:59-63.
- Convertino VA. Clinical aspects of the control of plasma volume at microgravity and during return to one gravity. *Med Sci Sports Exerc* 1996;28:S45-52.
- Sugawara J, Hayashi K, Kaneko F, Yamada H, Kizuka T, Tanaka H. Reductions in basal limb blood flow and lumen diameter after short-term leg casting. *Med Sci Sports Exerc* 2004;36:1689-94.
- Bleeker MW, de Groot PC, Poelkens F, Rongen GA, Smits P, Hopman MT. Vascular adaptation to 4 wk of deconditioning by unilateral lower limb suspension. *Am J Physiol Heart Circ Physiol* 2005;288:H1747-55.
- Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992;340:1111-5.
- Bonnin P, Ben Driss A, Benessiano J, Maillet A, Pavy le Traon A, Levy BI. Enhanced flow-dependent vasodilatation after bed rest, a possible mechanism for orthostatic intolerance in humans. *Eur J Appl Physiol* 2001;85:420-6.
- Clarkson P, Montgomery HE, Mullen MJ, et al. Exercise training enhances endothelial function in young men. *J Am Coll Cardiol* 1999;33:1379-85.
- Fuchsjager-Mayrl G, Pleiner J, Wiesinger GF, et al. Exercise training improves vascular endothelial function in patients with type 1 diabetes. *Diabetes Care* 2002;25:1795-801.
- Maynard FM Jr, Bracken MB, Creasey G, et al. International Standards for Neurological and Functional Classification of Spinal Cord Injury. American Spinal Injury Association. *Spinal Cord* 1997;35:266-74.
- Gill RW. Measurement of blood flow by ultrasound: accuracy and sources of error. *Ultrasound Med Biol* 1985;11:625-41.
- Berkenboom G, Unger P, Fontaine J. Atherosclerosis and responses of human isolated coronary arteries to endothelium-dependent and -independent vasodilators. *J Cardiovasc Pharmacol* 1989;14(Suppl 11):S35-9.
- Levenson J, Pessana F, Garipey J, Armentano R, Simon A. Gender differences in wall shear-mediated brachial artery vasoconstriction and vasodilation. *J Am Coll Cardiol* 2001;38:1668-74.
- Jones PR, Pearson J. Anthropometric determination of leg fat and muscle plus bone volumes in young male and female adults. *J Physiol* 1969;204:63P-66P.
- Hopman MT, van Asten WN, Oeseburg B. Changes in blood flow in the common femoral artery related to inactivity and muscle atrophy in individuals with long-standing paraplegia. *Adv Exp Med Biol* 1996;388:379-83.
- Huonker M, Schmid A, Schmidt-Trucksass A, Grathwohl D, Keul J. Size and blood flow of central and peripheral arteries in highly trained able-bodied and disabled athletes. *J Appl Physiol* 2003;95:685-91.
- Laughlin MH, Rubin LJ, Rush JW, Price EM, Schrage WG, Woodman CR. Short-term training enhances endothelium-dependent dilation of coronary arteries, not arterioles. *J Appl Physiol* 2003;94:234-44.
- Laughlin MH, Pollock JS, Amann JF, Hollis ML, Woodman CR, Price EM. Training induces nonuniform increases in eNOS content along the coronary arterial tree. *J Appl Physiol* 2001;90:501-10.
- Green DJ, Walsh JH, Maiorana A, Burke V, Taylor RR, O'Driscoll JG. Comparison of resistance and conduit vessel nitric oxide-mediated vascular function in vivo: effects of exercise training. *J Appl Physiol* 2004;97:749-55; discussion 748.
- Miyachi M, Tanaka H, Yamamoto K, Yoshioka A, Takahashi K, Onodera S. Effects of one-legged endurance training on femoral arterial and venous size in healthy humans. *J Appl Physiol* 2001;90:2439-44.
- Dinenno FA, Tanaka H, Monahan KD, et al. Regular endurance exercise induces expansive arterial remodelling in the trained limbs of healthy men. *J Physiol* 2001;534:287-95.
- Rudic RD, Shesely EG, Maeda N, Smithies O, Segal SS, Sessa WC. Direct evidence for the importance of endothelium-derived nitric oxide in vascular remodeling. *J Clin Invest* 1998;101:731-6.

32. Boot CR, Groothuis JT, van Langen H, Hopman MT. Shear stress levels in paralyzed legs of spinal cord-injured individuals with and without nerve degeneration. *J Appl Physiol* 2002;92:2335-40.
33. Hambrecht R, Adams V, Erbs S, et al. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. *Circulation* 2003;107:3152-8.
34. Tuttle JL, Nachreiner RD, Bhuller AS, et al. Shear level influences resistance artery remodeling: wall dimensions, cell density, and eNOS expression. *Am J Physiol Heart Circ Physiol* 2001;281:H1380-9.
35. Ziegler T, Silacci P, Harrison VJ, Hayoz D. Nitric oxide synthase expression in endothelial cells exposed to mechanical forces. *Hypertension* 1998;32:351-5.
36. Castro MJ, Apple DF Jr, Hillegass EA, Dudley GA. Influence of complete spinal cord injury on skeletal muscle cross-sectional area within the first 6 months of injury. *Eur J Appl Physiol Occup Physiol* 1999;80:373-8.
37. Vescovo G, Zennaro R, Sandri M, et al. Apoptosis of skeletal muscle myofibers and interstitial cells in experimental heart failure. *J Mol Cell Cardiol* 1998;30:2449-59.
38. Zulliger MA, Montorzi G, Stergiopoulos N. Biomechanical adaptation of porcine carotid vascular smooth muscle to hypo and hypertension in vitro. *J Biomech* 2002;35:757-65.
39. Celermajer DS, Sorensen KE, Georgakopoulos D, et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation* 1993;88:2149-55.
40. Vogel RA, Corretti MC, Plotnick GD. Effect of a single high-fat meal on endothelial function in healthy subjects. *Am J Cardiol* 1997;79:350-4.
41. Gokce N, Duffy SJ, Hunter LM, Keaney JF, Vita JA. Acute hypertriglyceridemia is associated with peripheral vasodilation and increased basal flow in healthy young adults. *Am J Cardiol* 2001;88:153-9.
42. Hijmering ML, Stroes ES, Olijhoek J, Hutten BA, Blankestijn PJ, Rabelink TJ. Sympathetic activation markedly reduces endothelium-dependent, flow-mediated vasodilation. *J Am Coll Cardiol* 2002;39:683-8.
43. Kooijman M, Rongen GA, Smits P, Hopman MT. Preserved alpha-adrenergic tone in the leg vascular bed of spinal cord-injured individuals. *Circulation* 2003;108:2361-7.
44. Eisenach JH, Clark ES, Charkoudian N, et al. Effects of chronic sympathectomy on vascular function in the human forearm. *J Appl Physiol* 2002;92:2019-25.
45. Gerrits HL, de Haan A, Sargeant AJ, van Langen H, Hopman MT. Peripheral vascular changes after electrically stimulated cycle training in people with spinal cord injury. *Arch Phys Med Rehabil* 2001;82:832-9.
46. Hopman MT, Groothuis JT, Flendrie M, Gerrits KH, Houtman S. Increased vascular resistance in paralyzed legs after spinal cord injury is reversible by training. *J Appl Physiol* 2002;93:1966-72.

Suppliers

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- b. Version 8.2; SAS Institute Inc, 100 SAS Campus Dr, Cary, NC 27513.