ARTICLE

Magnitude and Time Course of Arterial Vascular Adaptations to Inactivity in Humans

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DE GROOT, P.C.E., M.W.P. BLEEKER, and M.T.E. HOPMAN. Magnitude and time course of arterial vascular adaptations to inactivity in humans. *Exerc. Sport Sci. Rev.*, Vol. 34, No. 2, pp. 65–71, 2006. *We demonstrate that extensive arterial vascular adaptations occur within 3–8 wk of inactivity in humans. We put forth the hypothesis that the diameter decrease represents an adaptation to a lack of variation in peak shear stress. Furthermore, an enhanced flow-mediated dilation in deconditioned arteries implies that functional vascular adaptations to inactivity are not simply the inverse of adaptations to exercise.* **Key Words:** deconditioning, humans, conduit artery diameter, flow-mediated dilation, ultrasound

INTRODUCTION

Physical inactivity is an important and independent risk factor for atherosclerosis and cardiovascular diseases (1). Endothelial dysfunction plays an important role in the pathogeneses of cardiovascular diseases, and impaired endothelium dependent dilation is directly linked with cardiovascular morbidity and mortality. Although the effects of exercise training on vascular dimension and endothelial function are well described, the knowledge of vascular adaptations that occur as a result of inactivity in humans is less clear. Most evidence on vascular changes, especially on its time course, is derived from animal studies. Animal studies demonstrate a rapid onset of vascular changes to persistent changes in blood flow with functional adaptations occurring within days, whereas structural remodeling of the vessel wall is completed within 2–3 wk (11).

The main aim of this review is to present an overview of the current knowledge on the time course and magnitude of arterial vascular changes to inactivity in humans. We will focus on data from recent studies in this field, that is, the effects on vascular dimension and function after 4 wk of unilateral limb suspension (2), 52 d of strict horizontal bed rest (3), and the vascular changes that occur within the first year after a spinal cord injury (SCI) (6,7). Results will be presented for baseline and hyperemic vascular characteristics (blood flow and shear rate), baseline and maximal vessel dimension of the femoral artery, and conduit artery endothelial function.

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BASELINE AND HYPEREAMIC VASCULAR CHARACTERISTICS

Baseline Blood Flow

Current literature on the effect of inactivity on resting blood flow in humans shows inconsistent results with some studies showing a decrease, whereas others report no change in resting blood flow (Table 1).

The majority of studies that have used venous occlusion plethysmography to measure resting blood flow at the arteriolar level reported a decrease in basal blood flow after periods of head down tilt bed rest, space flight, limb immobilization, and SCI.

In our recent studies, we demonstrated that 52 d of strict horizontal bed rest deconditioning (3), 4 wk of unilateral limb suspension (2), and the first 6 wk after an SCI (7) did not change basal blood flow in common and superficial femoral arteries, as measured by Doppler ultrasound. These results are confirmed by previous studies in SCI individuals (13). In line with this is the observation that cross-sectional and longitudinal exercise studies indicate that, in general, conduit artery resting blood flow is not affected by exercise training (8). These findings suggest that physical (in)activity does not strongly affect conduit artery resting blood flow. It has been suggested that the mechanism and time course of vascular adaptations to exercise or inactivity may differ between conduit arteries and resistance vessels. This hypothesis, however, needs further investigation. In conclusion, there is no definite evidence that deconditioning in humans causes a change in *conduit artery* basal blood flow.

TABLE 1
Time Course and Magnitude of Arterial Vascular Adaptations to Inactivity in Humans[a]

	Limb Immobilization	Microgravity	SCI
Duration	1–12 wk	1–8 wk	3 wk to yr
Baseline blood flow	0–25% ↓	= 0–50% ↓	= 0–70% ↓
Baseline shear stress	= 75% ↑	↑	100% ↑
Structural changes			
Conduit artery: diameter	6–12% ↓	13–17% ↓	25–40% ↓
Arterioles: hyperemic flow	↓	↓ =	40–60% ↓
Functional changes			
Baseline NO production			
Conduit arteries	?	?	?
Arterioles	=	?	=
Stimulated NO production			?
Conduit arteries: flow mediated dilation (FMD)	↑	↑	↑
Arterioles	?	?	?

[a]Human models of deconditioning include limb immobilization (leg casting and limb suspension), microgravity (bed rest and space flight), and SCI. The symbols =, ↓ and ↑ represent no change, decrease, and increase, respectively. The symbol ? represents data not available or direction of change not clear.

Baseline Shear Rate

Wall shear stress represents the frictional force of blood on the endothelium layer and is directly proportional to blood viscosity and red blood cell velocity, and inversely related to vessel diameter. Shear stress is supposed to play an important role in arterial regulation and adaptation processes. Usually, shear stress levels are kept at a constant level by adapting the internal diameter to chronic changes in blood flow. This remodeling process has been shown to depend on an intact endothelium (11). Baseline shear rate levels were found to be almost doubled in the femoral artery of chronic SCI individuals compared with able-bodied subjects (5,6). No changes were observed in shear rate levels after 1 wk of leg casting (14), whereas baseline shear rate levels were significantly enhanced after 4 wks of unilateral limb suspension, returning to baseline again after 4 wk of recovery (2). In addition, evidence from a recent study demonstrates that the twofold increase in femoral shear rate levels in the inactive legs of SCI individuals is already evident within 3–6 wk after the SCI (7). These inconsistent results may be due to the short (only 7 d) and the less-pronounced state of deconditioning in the study of Sugawara *et al.* (14).

In general, several lines of evidence indicate that deconditioned arteries are not able to maintain basal shear rate levels (Table 1).

Hyperemic Blood Flow

Reactive hyperemic blood flow refers to the phenomenon of a substantial increase in blood flow in response to relief of ischemia or an exercise stimulus. Hyperemic blood flow is a marker for the vasodilator capacity of the resistance vascular bed and typically used to evaluate structural changes in the circulation. Reactive hyperemic blood flow in the superficial femoral artery decreased by 28% after 52 d of bed rest (3). In chronic SCI individuals, reactive hyperemia was 40–60% lower in the legs of SCI compared with controls (5). Although not significant, a trend towards a decrease in hyperemic flow was present after 4 wk of limb immobilization (2) and during the first 6 wk after an SCI (7). It is possible that mechanisms and time course of vascular adaptations to deconditioning may differ between conduit arteries and resistance vessels, as has been indicated in

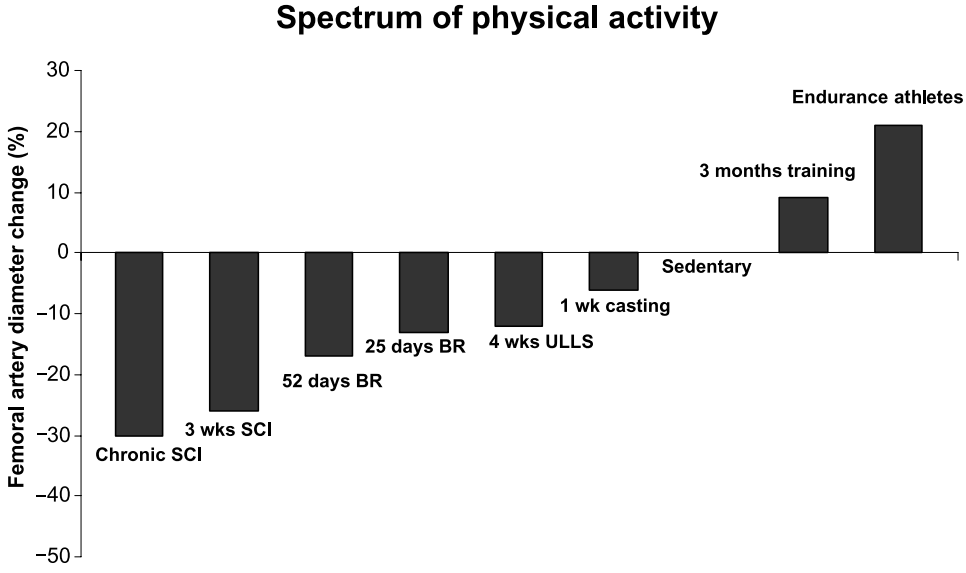

Figure 1. Magnitude of diameter adaptation across the total spectrum of physical activity, that is, chronic endurance trained athletes, different models and duration of deconditioning, that is, leg casting, unilateral limb suspension (ULLS), bed rest (BR) to the most extreme on the spectrum of deconditioning, an SCI.

exercise training studies in animals and humans. In summary, reactive hyperemic blood flow after a period of inactivity is reduced in most deconditioning models of sufficient duration (Table 1).

BASELINE AND MAXIMAL CONDUIT ARTERY DIMENSION

Baseline Diameter

Arterial remodeling represents the process of structural changes in the arterial system. Remodeling occurs in response to changes in hemodynamic stimuli (flow or pressure) and takes places during physiological conditions, but also in clinical conditions such as atherosclerosis, aging, and hypertension. In normal conduit arteries, increases in blood flow are associated with outward remodeling (increase in vessel size and cross-sectional area), whereas decreases in blood flow are associated with inward remodeling, that is, a reduction of the vessel size. The magnitude of the baseline diameter of the common femoral artery varies substantially across the total spectrum of physical activity, as illustrated in Figure 1. The diameter of the common femoral artery is approximately 20% larger in endurance-trained athletes compared with able-bodied controls and has been shown to increase by 9% after 3 months of aerobic exercise training (8). On the other hand, diameter size decreases after deconditioning, which is indicated by a 6% reduction after 1 wk of leg casting (14), a 13% decrease after 4 wk of ULLS (2), 13% and 17% reduction after 25 and 52 d of bed rest (3), respectively, a 25% decrease after 3 wk of SCI (7), and an approximately 30% reduction in vessel size diameter in individuals with chronic SCI (5,7) (Table 1). Hence, the decrease in femoral artery vessel size in the inactive and paralyzed legs of SCI individuals represents the largest reduction in diameter in response to the most extreme form of deconditioning.

In a previous cross-sectional study in chronic SCI individuals, Olive *et al.* (13) reported that the significant reduction in femoral vessel diameter was no longer different when diameter was expressed per unit muscle mass. Decreases in muscle cross-sectional area and muscle mass have also been demonstrated after a short period, that is, weeks, of bed rest deconditioning and limb immobilization. In a recent longitudinal study (7), we specifically assessed the time course of early changes in vascular properties and limb volume during the first 6 wk after an SCI. It was shown that femoral artery size decreases substantially over time already at 3 wk postinjury. The reduction in diameter size at 3 wk approaches the vessel dimension of chronic SCI individuals that have been extremely inactive for years. Furthermore, a simultaneous decrease in limb volume over time was evident. Although one should take into account that the changes in limb volume do not completely reflect changes in muscle mass, limb volume measurements may be considered as an indication for muscle mass. When we corrected femoral artery diameter for limb volume, no differences over the 6-wk time period were observed and values in SCI are comparable with control values (Fig. 2). These findings suggest a strong functional link between adaptations in vascular dimension and muscle atrophy during deconditioning.

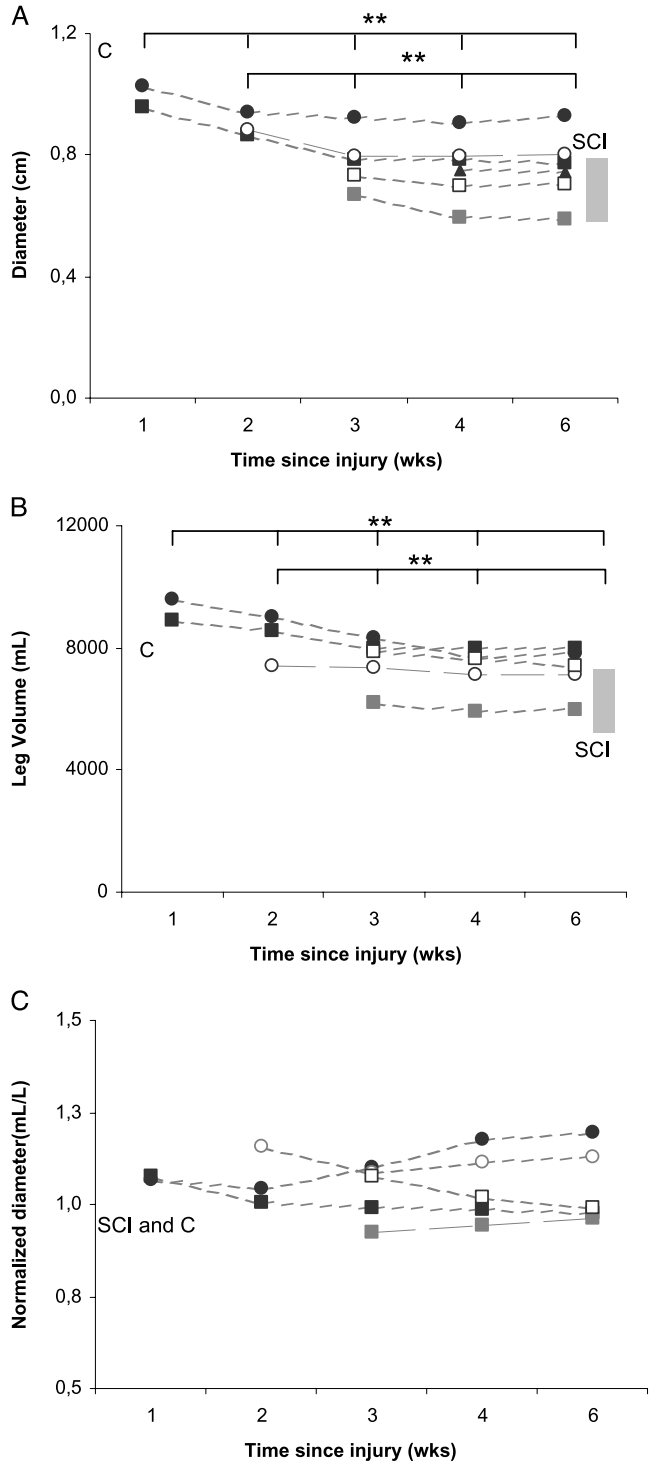

Figure 2. Individual data point of time course of changes in femoral diameter dimension (A), leg volume (B), and for diameter normalized for leg volume (C) at weeks 1, 2, 3, 4, and 6 after an SCI. *Blocks* represent the range of values in able-bodied controls and blocks represent values from chronic SCI individuals. Significant differences between weeks are indicated, $*P < 0.05$; $**P < 0.001$. Results suggest a strong functional link between vascular atrophy and muscle atrophy.

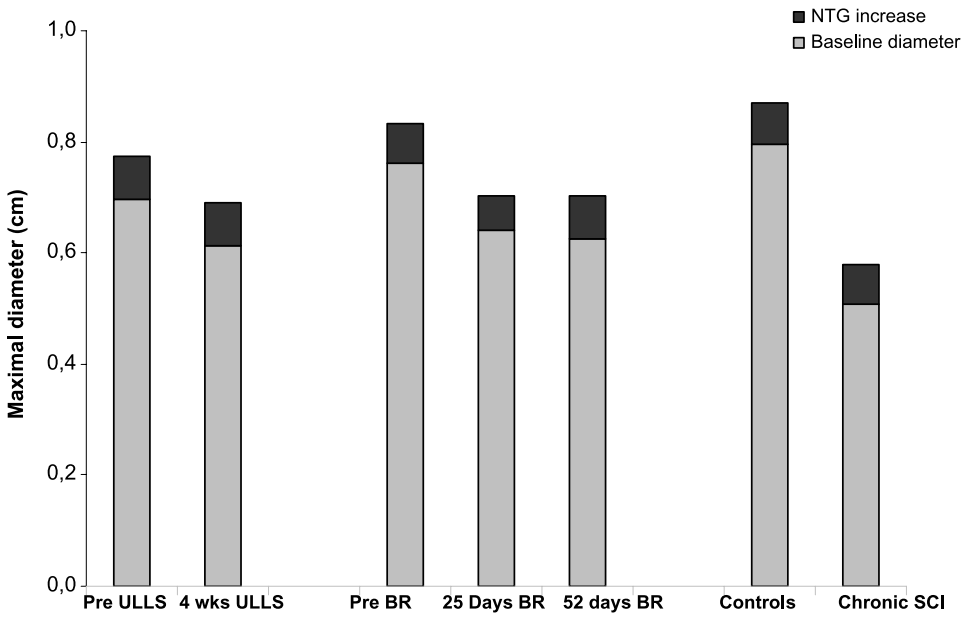

Figure 3. Maximal absolute diameter after NTG administration before and after 4 wk of ULLS, 52 d of bed rest (BR) and in persons with chronic SCI compared with able-bodied controls.

Maximal Diameter

Baseline conduit artery diameter is determined by both vascular structure and vascular tone. Recently, the importance of measuring maximal diameter of conduit arteries to assess structural changes has been recognized (2,12). It has been suggested that the maximal vasodilation response to nitroglycerin (NTG) gives a suitable indication of the near maximal attainable diameter (12). In Figure 3, diameter adaptations to deconditioning are expressed as maximal diameter after NTG administration and the results demonstrate that maximal diameter decreased by 9% after 4 wk of ULLS (2), 16% after 25 and 52 d of bed rest (3), and by 35% in chronic SCI individuals (5). These findings are more or less similar to the observed changes in baseline diameter and indicate that most of the changes in baseline diameter dimension after deconditioning are due to structural changes. The human arterial system strives to maintain a constant shear stress by adapting the diameter to chronic changes in blood flow. Recent training studies in humans have suggested that conduit arteries adapt their baseline diameter to peak shear stress and peak oxygen consumption rather than to resting blood flow (8). Parallel to this reasoning, the decrease in diameter after deconditioning may represent an inward remodeling as an adaptation to a total lack of periods of high shear stress. Our findings in SCI individuals support the assumption that baseline diameter adapts to peak flow (Fig. 4B) instead of resting blood flow (Fig. 4A). During reactive hyperemia, shear stress levels are kept constant across a wide spectrum of hyperemic flows, from very low in chronic SCI to high in able-bodied controls. On the other hand it is shown that deconditioned arteries are not able to maintain basal shear rate levels (Fig. 4A). These chronically enhanced resting shear rate levels may have important implications for conduit artery endothelium-derived nitric oxide (NO) function as will be discussed in the following section.

ENDOTHELIAL FUNCTION CONDUIT ARTERIES

Endothelial function in conduit arteries is commonly assessed with flow mediated dilation (FMD) (Fig. 5). In arm arteries it has been shown that the increase in diameter after a brief period of ischemia and the subsequent reactive hyperemia is almost exclusively mediated by NO (10). Therefore, FMD provides an index of conduit artery endothelium dependent NO function. On the other hand, NTG causes endothelium independent vasodilation and is indicative of smooth muscle function and NO responsiveness.

Endothelial dysfunction plays an important role in the pathogeneses of cardiovascular diseases, and impaired endothelium dependent dilation is directly linked with cardiovascular morbidity and mortality. Localized and systemic exercise training consistently improves endothelial derived NO function in the presence of endothelial dysfunction (9). In general, endothelium independent vasodilation does not change, indicating that specific changes occur at the level of the endothelium. Improved endothelial NO function has been suggested as the key to the beneficial effect of exercise on the risk of cardiovascular disease (9). Abnormal endothelial NO dilator function has been uniformly observed in subjects with cardiovascular risk factors.

Surprisingly, an enhanced relative FMD response was observed after 25 and 52 d of bed rest (3), 4 wk of limb suspension (2), and in acute (7) (within 3–6 wk postinjury) as well as in chronic SCI (5) (Table 1). In previous studies, an inverse relationship between vessel size and FMD has been reported. In accordance with this, relative FMD responses can be expected to be higher in deconditioned arteries, which have smaller femoral baseline diameters. However, absolute FMD responses did not differ between deconditioned arteries and controls and when FMD responses were expressed as diameter change relative to

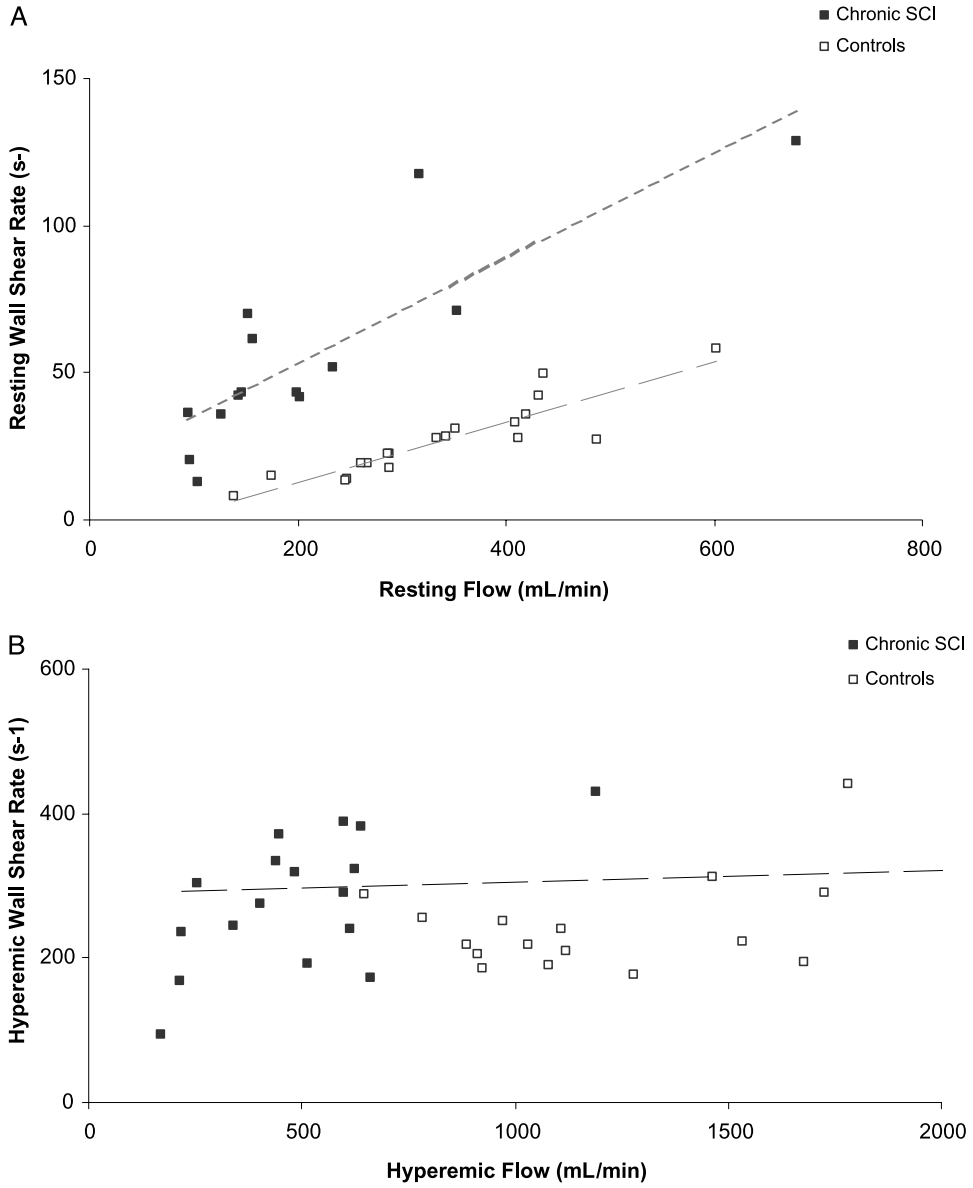

Figure 4. Shear rate values (s_{-1}) (*y axis*) plotted against the blood flow (mL/min_{-1}) (*x axis*). Resting values (A) and hyperemic responses (B) are presented for chronic SCI individuals and able-bodied controls. Shear rate was calculated from echo Doppler measurements according to the formula (4 * mean red blood cell velocity/mean arterial diameter).

the trigger (i.e., the difference between maximal hyperemic shear rate and resting shear rate, in which shear rate is calculated as 4*velocity/diameter), FMD responses were found to be increased (4) or, at least, preserved (2,3,5).

Endothelium independent dilation was increased after 4 wk of limb suspension (2) and after 52 d of bed rest (3), whereas no changes were observed in SCI.

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 (Fig. 4A). Because it is well known that shear stress is a potent physiological stimulus for NO release, the increased levels of basal shear stress may lead to an upregulation of eNOS. Previous studies (15) have demonstrated that increases in shear stress level are associated with an elevation of eNOS mRNA protein and NOS activity.

A second explanation may be the lack of periods of high shear stress in the deconditioned vessels, which may contribute to an upregulation of NO responsiveness.

Vessel dilation after FMD implies endothelial NO production in response to a stimulus, but also smooth muscle characteristics such as NO sensitivity and vasodilator capacity. Data derived from bed rest (3) and limb suspension (2) suggest that mainly NO responsiveness is enhanced after deconditioning.

Data show that in SCI, the maximal diameter after FMD does not differ from the NTG response, whereas in able-bodied controls and other models of deconditioning (i.e., 4 wk of limb immobilization and 52 d of bed rest), the maximal obtainable diameter after NTG is larger than the maximal diameter after FMD. These data suggest that in SCI, the vasodilation response to NTG is limited by structural

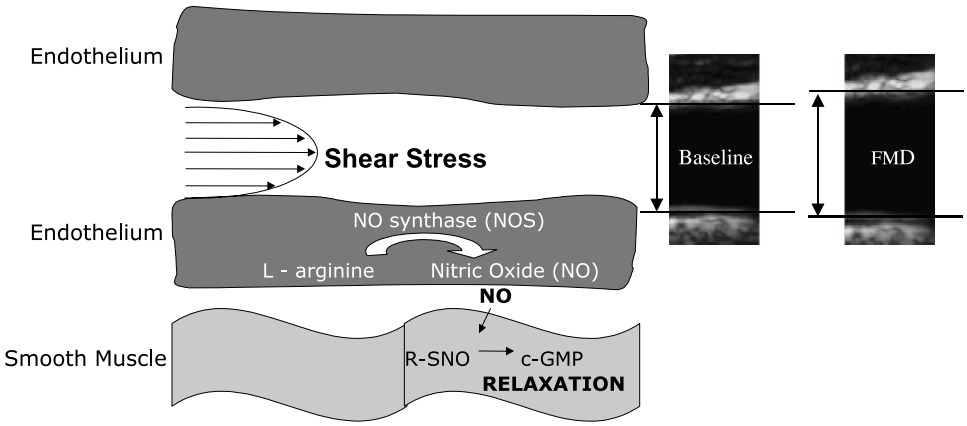

Figure 5. Flow-mediated Dilation (FMD). The physiological stimulus for endothelial NO production is increased shear stress from increased blood flow. NO is synthesized from L-arginine by the action of nitric oxide synthase (NOS). It activates smooth muscle cell guanylate cyclase, which relaxes smooth muscle by increasing the intracellular concentration of guanosine 3,5 cyclic monophosphate. FMD involves direct imaging of conduit artery diameter change using high resolution B-mode ultrasound, and the percentage change from baseline diameter is a marker for conduit artery endothelium dependant NO function.

changes in the vessel wall, thereby masking a possible increase in NO sensitivity (Fig. 6).

Collectively, an increased FMD response in deconditioned arteries is evident within 3–8 wk of inactivity. Data from different human models of deconditioning indicate that adaptations occur also at the level of the smooth muscle cell, and not only in the endothelium.

Model Limitations

The different models of deconditioning may confound the effect of physical inactivity on vascular adaptations in humans. SCI individuals have a loss of supraspinal sympathetic vascular tone of the legs, which may affect vascular adaptations and endothelial function. However, sympathectomized patients with lack of sympathetic vascular innervation but with normal physical activity do not show vascular adaptations. In addition, previous studies in SCI and bed rest have demonstrated that vascular adaptations are partly reversible by electrical stimulation training of the inactive paralyzed legs in SCI (4), which suggests that the vascular adaptations seem to result primarily from inactivity. Furthermore, it has been shown that plasma volume is reduced by 10–20% within 24–48 h of exposure to actual or simulated microgravity by bed rest, which may seriously confound the vascular changes that occur during microgravity. In the studies that casted limbs after fracture or trauma vascular changes to inactivity may be seriously confounded by possible increases in

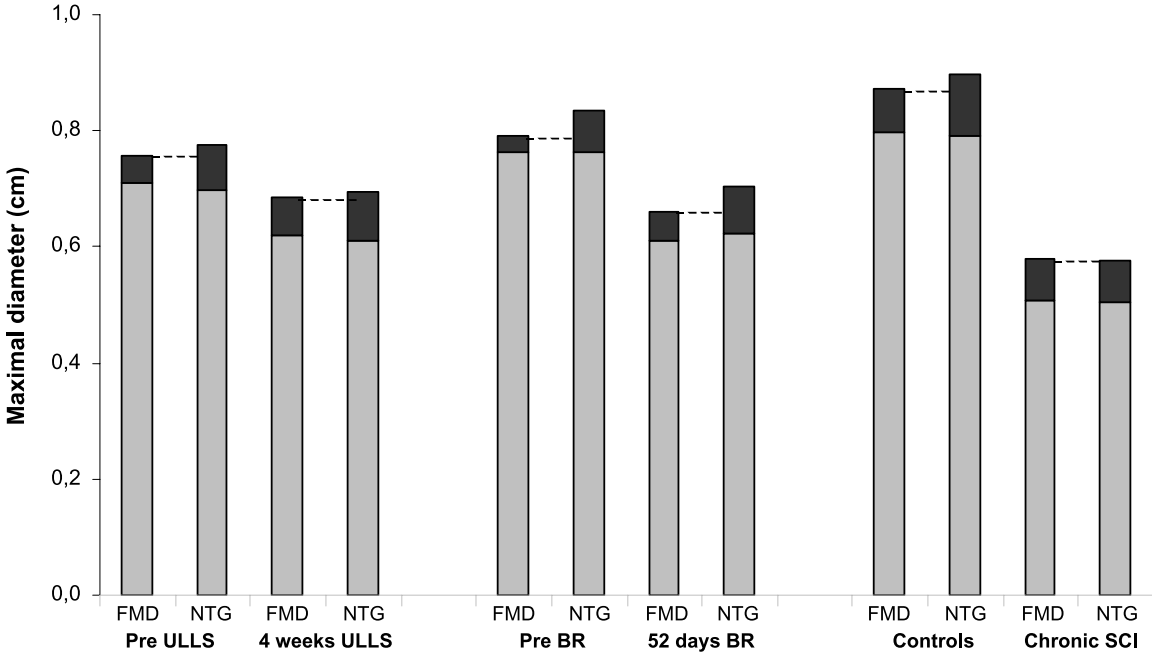

Figure 6. Maximal diameter after reactive hyperemia (FMD, a measure for endothelium dependant NO dilation) and after administration of NTG (a measure for NO responsiveness and smooth muscle function) before and after 4 wk of ULLS, 52 d of bed rest (BR) and in chronic SCI individuals and able-bodied controls.

blood flow due to healing processes of the trauma. In the casting/immobilization studies described in this article, healthy controls were included. Although limb suspension is associated with less pronounced deconditioning than SCI and bed rest, this is a relatively new and promising human model to assess local vascular and muscular adaptations.

CONCLUSIONS

A rapid onset of vascular adaptations after inactivity is evident in humans. A substantial reduction in femoral diameter size was observed varying from 6% after 1 wk of leg casting to 25% decrease after 3 wk of extreme inactivity after an SCI. The decrease in diameter after deconditioning most likely represents an inward remodeling as an adaptation to a total lack of variation in peak shear stress and not to basal shear stress levels. During 6 wk of extreme inactivity, a simultaneous decrease over time was observed for femoral artery size and limb volume, which suggests a strong functional link between adaptations in vascular dimension and muscular atrophy. In addition, decreased hyperemic leg blood flow, an almost doubling of resting shear rate levels in the femoral artery, and increased FMD responses in the superficial femoral artery are all evident within 3–8 wk in different human models of inactivity. Possible explanations for an increased FMD response in deconditioned arteries may be related to increased NO release to a shear stress stimulus or increased NO responsiveness. The enhanced FMD responses in deconditioned arteries imply that the functional vascular adaptations to inactivity are not simply the inverse of adaptations to exercise.

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