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Impact of Bed Rest on Conduit Artery Remodeling Effect of Exercise Countermeasures

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Abstract—Physical inactivity is a potent stimulus for vascular remodeling, leading to a marked decrease in conduit artery diameter. However, little is known about the impact of physical inactivity on artery wall thickness or wall:lumen ratio or the potential of exercise countermeasures to modify artery wall thickness. The purpose of the study was to examine the impact of 60 days of bed rest, with or without exercise countermeasures, on carotid and superficial femoral artery wall thickness. Eighteen men were assigned to bed rest (second Berlin Bed Rest Study) and randomly allocated to control, resistive exercise, or resistive vibration exercise. Both exercise countermeasures were applied 3 times per week while the subjects were in the supine position on the bed. Sonography was used to examine baseline diameter and wall thickness of the carotid and femoral arteries. Bed rest decreased diameter of the superficial femoral artery ($P=0.001$) but not the carotid artery ($P=0.29$). Bed rest induced a significant increase in carotid and superficial femoral artery wall thickness ($P=0.007$ and 0.03) and wall:lumen ratio ($P=0.009$ and 0.001). Exercise prevented the increase in wall thickness of the carotid artery. In addition, exercise partly prevented the increased wall:lumen ratio in the superficial femoral artery. In conclusion, 8 weeks of bed rest resulted in $\approx 20\%$ increase in conduit artery wall thickness. Exercise countermeasures completely (carotid artery) or partly (superficial femoral artery) abolished the increase in wall thickness. These findings suggest that conduit artery wall thickness, a vascular characteristic associated previously with atherosclerosis, can rapidly adapt to physical inactivity and exercise in humans. (*Hypertension*. 2010;56:240-246.)

Key Words: microgravity ■ arterial wall ■ atherosclerosis ■ cardiovascular risk ■ inactivity ■ exercise training

Physical inactivity is a strong and independent risk factor for cardiovascular disease.¹ Several studies have demonstrated detrimental effects of physical inactivity in humans on conduit and resistance artery structures. Using various models of deconditioning, such as spinal cord injury,^{2,3} bed rest,⁴ unilateral lower limb suspension,⁵ and casting, a “dose”-dependent relation has been observed between physical inactivity and change in conduit and resistance artery diameter (ie, arterial remodeling).^{6–8} Changes in vascular function and structure may contribute to the link between cardiovascular risk and physical (in)activity,⁹ which cannot be completely explained by detrimental effects of inactivity on traditional cardiovascular risk factors.^{10,11} Another vascular trait that may have important physiological and pathophysiological implications is the arterial wall thickness.^{12–15}

Conduit arterial wall thickening has been regarded as an integral part of the atherosclerotic process and has been used in intervention trials as a surrogate outcome measure.^{13,15–18} Moreover, changes in the wall thickness of arteries exert an impact on vasomotor responsiveness in conditions such as

primary hypertension,^{12,19} potentially explaining differences in dilator and constrictor behavior in arteries of different sizes and architectures.^{12,20} Physical inactivity, such as that associated with prolonged bed rest, may, therefore, have detrimental impacts on conduit artery wall thickness.

Resistance (vibration) exercise has been examined previously as a countermeasure for the detrimental effects of physical inactivity during bed rest, primarily because of its practical advantages. Indeed, previous studies found that vibration exercise during bed rest amplifies exercise gains in skeletal muscle morphology and function.²¹ Moreover, others found that vibration exercise involving a resistive component at least partly prevents detrimental changes in vascular function^{4,22} and structure.^{4,22,23} However, no previous studies have examined the potential of exercise countermeasures to prevent changes in artery wall characteristics associated with chronic bed rest. To examine this, we assessed the impact of countermeasures involving resistive exercise alone, or in combination with vibration, on carotid and superficial femoral arterial wall thickness and wall:lumen ratio before and after 60 days of bed rest in healthy, young volunteers.

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Table. Subject Characteristics and Common Carotid Artery Diameter, Superficial Artery Diameter, IMT, and IMT:Lumen Ratio Before and After 60 Days of Bed Rest Without (CTR) or With Exercise Countermeasures (RE+RVE)

Parameter	CTR		RE		RVE		ANOVA	
	Before	After	Before	After	Before	After	<i>P</i> _{time}	<i>P</i> _{time*group}
Age, y	32±9		31±6		31±10			
Body mass, kg	81.6±5.7	79.3±5.7†	69.7±4.3*	69.6±3.6	78.9±6.8	77.6±3.6		
BMI, kg/m ²	25.4±2.0	24.6±1.8†	22.3±2.0	22.3±1.8	25.1±1.1	24.7±0.4		
Systolic BP, mm Hg	111±4	114±9	118±6	109±9	113±15	114±8		
Diastolic BP, mm Hg	70±8	68±6	68±8	68±8	68±10	69±6		
Heart rate, bpm	70±8	71±4	68±7	62±4	75±7	65±6		
Carotid artery								
Diameter, mm	7.0±0.4	6.9±0.5	6.9±0.2	6.9±0.4	7.0±0.6	6.9±0.6	0.29	0.78
Shear rate, s	43±17	42±10	46±14	40±17	44±13	49±20	0.93	0.71
IMT, mm	0.59±0.08	0.69±0.12‡	0.58±0.09	0.55±0.08	0.53±0.06	0.52±0.08	0.12	0.004
IMT:lumen	0.085±0.015	0.101±0.023‡	0.083±0.011	0.080±0.009	0.076±0.008	0.076±0.013	0.06	0.004
IMT-CSA, mm ²	14.1±1.8	16.1±2.2†	13.3±2.8	12.9±2.9	12.4±2.3	12.1±2.0	0.31	0.01
Superficial femoral artery								
Diameter, mm	7.1±0.5	5.4±0.5‡	7.1±0.3	5.6±0.3‡	6.8±0.7	5.9±0.5†	<0.001	0.01
Shear rate, s	13±7	17±8	15±1	26±4†	12±8	20±12†	0.004	0.35
IMT, mm	0.48±0.07	0.54±0.05†	0.48±0.04	0.51±0.04	0.49±0.05	0.49±0.06	0.047	0.20
IMT:lumen	0.067±0.007	0.100±0.014‡	0.068±0.004	0.091±0.006‡	0.073±0.012	0.083±0.012†	<0.001	0.01
IMT-CSA, mm ²	11.4±2.3	10.0±1.2†	11.6±1.7	9.7±1.3	11.1±0.9	9.8±1.5	0.002	0.98

Data are presented as mean±SD. BP indicates blood pressure; BMI, body mass index.

**P*<0.05 CTR vs RE.

Post hoc was different from before bed rest at †*P*<0.05 or ‡*P*<0.01.

Methods

Subjects

Eighteen healthy men (31±8 years) participated in this study. All of the subjects were screened using a medical history and physical and psychological examination and did not have any medical problems. None experienced diabetes mellitus or cardiovascular disease or used any medication (Table). All of the subjects gave their written, informed consent before participation of the study. The second Berlin Bed Rest Study was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association and was approved by the ethical committee of the Charité Universitätsmedizin Berlin.

Procedures

After measurement of baseline vascular characteristics, subjects were randomly assigned to 60 days of complete 6° head-down tilt bed rest, bed rest with resistive exercise (RE), or bed rest with resistive vibration exercise (RVE). All personal hygiene activities were performed in the supine position. Subjects were housed in a dedicated clinical ward of the Charité Campus Benjamin Franklin and were continuously monitored with video cameras to guarantee compliance with the bed rest protocol. The diet of the subjects was controlled carefully. The second Berlin Bed Rest Study was conceived to examine the putative impact of resistive exercise countermeasures with and without whole body vibration on the physiological effects of space flight.²⁴

Resistive (Vibration) Exercise Protocol

Before randomization, all of the subjects were familiarized with the exercise on 3 separate, consecutive days to ensure that an optimal training intervention was achieved during bed rest. Familiarization exercise bouts were performed under low load (65% of body weight) and without whole body vibration. After randomization, subjects in the RE and RVE groups were exposed to 3 sessions of exercise per

week, which lasted 5 to 7 minutes per session. Both groups performed exercise on a device that was specifically developed for application under microgravity and bed rest conditions (Galileo Space, Novotec Medical GmbH). Subjects were positioned in head-down tilt on a moveable platform with shoulder pads and hand grips, preventing downward movement and permitting application of force via the platform. Force, generated by a pneumatic system, was applied through the platform, against which the subject needed to resist and move. The feet were positioned on either side of a platform, which was activated in the RVE group only, to add a whole body vibration component. Subjects were given oral and visual feedback of their current and target position during exercise via a monitor to ensure that the subjects exercised in the desired range of motion and at the desired speed. Each training session consisted of 5 different exercise units, which were similar for RE and RVE and were supervised by a well-trained exercise physiologist, and all of the exercise types were performed in the supine position in the bed, as described below.²⁴

Warm Up

Warm up consisted of bilateral squat exercise (from 10° to 90° knee flexion and back) with 50% of maximal force for 64 seconds. Subjects performed the concentric and eccentric phases of the exercise in 4 seconds each. Eight repetitions were performed, followed by a 2-minute break. Vibration frequency was 24 Hz in RVE.

Bilateral Squats

During training sessions 1 and 2, bilateral squat exercise was performed at 75% and 80% of maximum force, respectively, continuing exercise until exhaustion. Subsequently, force level was increased by 5% during each session until the subject could only perform 8 repetitions. When performing ≥10 repetitions in 2 consecutive sessions, force level was increased by 5%, whereas the level was decreased by 5% if ≤6 repetitions were completed in 2 consecutive sessions. In RVE, vibration frequency was progressed

from 20 Hz at session 1 to 24 Hz at session 2, after which this level was maintained. A 5-minute break was given after this exercise.

Single-Leg Heel Raises

With the knee in full extension, the heel was raised from maximal plantar flexion to dorsal flexion against a force equivalent to ≈ 1.3 times body weight. Movements were performed as quickly as possible, typically achieving a frequency of 0.4 to 0.7 Hz and were continued until exhaustion. When exercise was performed for ≥ 50 seconds, load was increased by 5%, whereas this was decreased by 5% when ≤ 30 seconds was performed. Vibration frequency was 26 Hz in RVE. After 90 seconds, the exercise was repeated using the contralateral leg. Subsequently, a 4-minute break was given.

Double-Leg Heel Raises

This exercise is similar to single-leg heel raises until exhaustion but with a resistive force of ≈ 1.8 times body weight. When performing for ≥ 55 seconds, load was increased by 5%, whereas this was decreased by 5% if exercise could not be performed for ≤ 40 seconds. In RVE, vibration frequency was 24 Hz. A 2-minute break was given after completion.

Back and Heel Raises

Positioning the feet on the platform, hips and lumbar spine were extended, ankles were dorsal flexed, and knees were maintained at full extension during 60 seconds, with a force of 1.5 times body weight. Vibration frequency was 16 Hz in RVE.

Measurements

Measurements were performed at the same time of day in each individual subject. Only low-fat meals were supplied before the measurement, and these were identical before each measurement. Subjects refrained from caffeine, chocolate, alcohol, and vitamin C-containing fruits for 12 hours before testing, whereas no exercise was performed 24 hours before testing. Before testing, the bed was positioned at 0° for ≥ 30 minutes before performing the first measurement.

Baseline resting diameter, wall thickness, and blood cell velocity of the left common carotid artery and superficial artery were performed using an echo Doppler device (Megasonics, ESAOTE) with a 5.0- to 7.5-MHz broadband linear transducer. Images of the common carotid artery were performed 3 cm before the bifurcation. Superficial femoral artery diameter images were made 3 cm distal to the bifurcation of the femoral artery. The angle of inclination for the velocity measurements was consistently at 60°, and the vessel area was adjusted parallel to the transducer. The diameter and wall thickness were continuously registered on videotape for ≥ 30 seconds.

Data Analysis

Offline analysis was performed using custom-designed wall-tracking software, which is independent of investigator bias,^{21,22} by an experienced sonographer who was blinded to group allocation. Briefly, the initial video signal was encoded and stored as a digital DICOM file on a personal computer, using an IMAQ-PCI-1407 card. Software analysis was performed at 30 Hz using an icon-based graphical programming language and toolkit (LabView 6.02, National Instruments). By identifying a region of interest on each first frame of every individual study, an automated calibration was made of diameters on the B mode and velocity on the Doppler waveform. Within the identified region of interest in the diameter image, a pixel-density algorithm automatically identified the angle-corrected near and far wall e-lines for every pixel column for diameter assessment. In addition, the same algorithm is used to identify the far wall media-adventitia interface. Detection of the near and far wall lumen edges and the far wall media-adventitia interface is performed on every frame selected. These data were used to calculate the wall thickness, as well as the wall:lumen ratio, which corrects for differences in baseline diameter. We also calculated the cross-sectional area of the wall.^{25,26}

Within the region of interest in the Doppler waveform, the peak of the envelope of this waveform was automatically detected 30 times per second for offline analysis. These data were stored and retrieved for analysis in a custom-designed analysis package. Mean resting velocity was then used to calculate mean resting shear rate.²⁷ The use of this semiautomatic software results in better reproducibility than with manual methods and has minimal interobserver and intraobserver variance.²⁸ Reproducibility of the within-subject measurements of baseline diameter and blood flow in our laboratory is 1.5% and 14.0%, respectively.²⁹ In addition, within- and between-subject reproducibility of the conduit artery wall thickness using our technique is 2.4% and 3.5%.³⁰

Statistical Analysis

Assuming an α of 0.05 and an SD of 0.06 mm,³¹ our study had 80% power to detect a difference of 0.1 mm in wall thickness between interventions with 6 subjects. A 1-way ANOVA was applied to assess baseline differences between groups for subject characteristics. Differences in the response to bed rest between groups were tested with repeated-measures ANOVA with time as a within-subject factor and group as a between-subject factor (Statistical Package for Social Sciences 16.0, SPSS Inc). Statistically significant differences were further analyzed using *t* tests with Bonferroni correction. The level of statistical significance was defined at $\alpha=0.05$. Data are presented as mean \pm SD, unless stated otherwise.

Results

Because of reasons unrelated to this study, 2 subjects did not complete the study (RE+RVE). Except for a lower body mass in the RE group, subject characteristics were not different across groups (Table). Body mass and body mass index were significantly decreased in the bed rest group only (Table).

Carotid artery diameter and shear rate showed no change after bed rest or after bed rest combined with RE or RVE (Table). Significant increases in carotid artery wall thickness, wall:lumen ratio, and cross-sectional area were observed after bed rest (Figure and Table). RE and RVE completely prevented these changes in carotid artery wall thickness, wall:lumen ratio, and cross-sectional area (Figure and Table).

Bed rest induced a significant decrease in the superficial femoral artery diameter of 24% (Table). Combining bed rest with RVE, but not RE, partly prevented the decrease in superficial femoral artery diameter (Figure). Shear rate increased similarly across the 3 groups (Table). Bed rest induced a significant increase in superficial femoral artery wall thickness, which was prevented by performing RE or RVE. In addition, a significant increase in superficial femoral artery wall:lumen ratio was observed after bed rest, with or without performing an exercise countermeasure. However, the increase in wall:lumen ratio of the superficial femoral artery was partly prevented when bed rest was combined with RVE but not RE (Figure). The wall thickness cross-sectional area showed a decrease, which was similar across groups (Table).

Discussion

We found that 60 days of strict bed rest resulted in a 17% increase in carotid artery wall thickness and a 13% increase in the superficial femoral artery wall thickness. The typical annual increase in wall thickness in a young cohort is 0.0087 mm,³² such that a change of 0.0013 mm might have been expected across the 8-week period of this study. The increase observed in carotid wall thickness as a result of bed

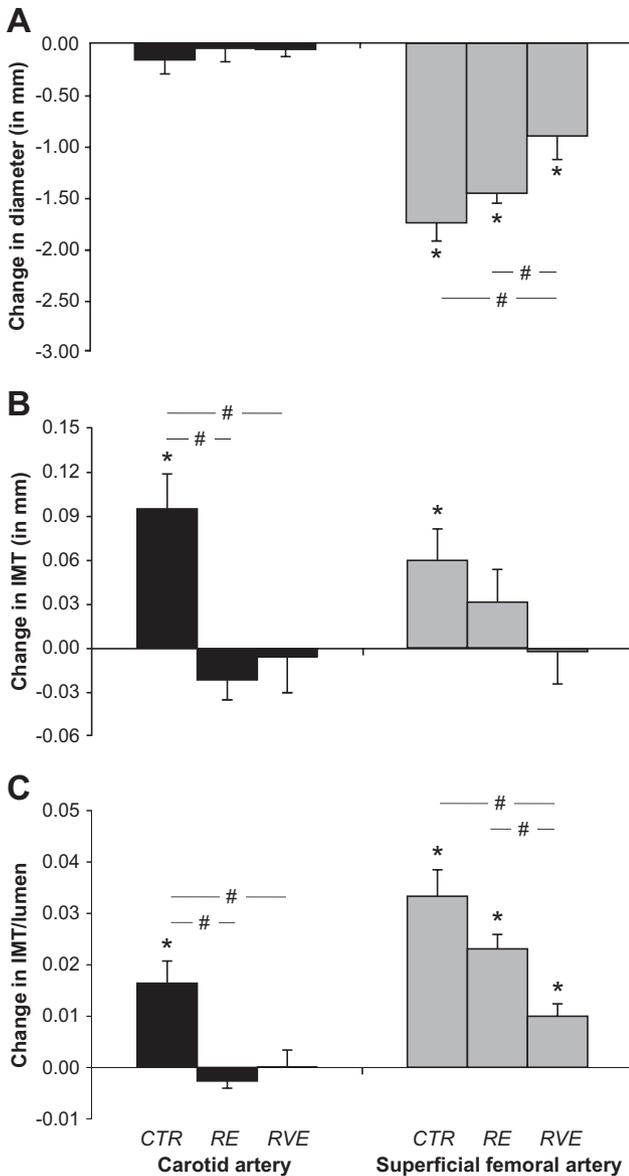


Figure. Change in common carotid artery (black) and superficial artery diameter (gray; A), IMT (B), and IMT:lumen ratio (C) after bed rest in controls (CTR), RE, and RVE. Error bars represent SEM. Post hoc was significant from baseline (* $P < 0.05$) or between groups (# $P < 0.05$).

rest was 0.1 mm, or ≈ 75 times greater than the expected effect of aging, per se. This indicates that marked increases in artery wall thickness can take place in humans after relatively short periods of physical inactivity. This finding has implications for the use of intima-media thickness (IMT) as a surrogate measure of atherosclerosis in studies that take no account of differences in activity or inactivity levels between or within groups.

Physical inactivity represents a strong stimulus to induce inward remodeling of femoral artery diameter: 6% decrease after 7 days of lower limb casting, 12% after 28 days of unilateral lower limb suspension,⁵ 13% after 25 days of bed rest,⁴ and 30% in chronic spinal cord injury.² These data suggest a “dose-dependent” relationship between the “stimulus” of deconditioning and change in diameter, which is

reinforced by the 24% decrease in superficial femoral artery after 60 days of bed rest in the present study. The decrease in physical activity level represents the primary stimulus for the decrease in superficial femoral artery diameter. Previous studies found that exercise training in subjects undergoing bed rest⁴ or in spinal cord-injured subjects³³ reverses the decrease in femoral artery diameter. The present study adds the novel observation that performing RVE during bed rest significantly attenuates the decrease in diameter by 13%, which confirms the idea that the change in physical activity level is primarily responsible for the smaller conduit artery diameter.

An interesting observation in our study is that effects of bed rest and exercise countermeasures on arterial diameter and baseline shear rate differed between the carotid and superficial femoral arteries. The carotid artery IMT-cross-sectional area (CSA) increased after bed rest, whereas no change was found in subjects who performed an exercise countermeasure during bed rest. These results are in accordance with findings obtained with wall thickness alone. However, carotid diameter and wall shear rate may not be involved in these carotid wall thickness responses, because they did not change after bed rest, irrespective of exercise. In contrast, superficial femoral artery diameter decreased, whereas wall thickness increased. Because IMT-CSA did not increase after bed rest, femoral diameter reduction associated with bed rest may confound the wall thickness response. The addition of exercise to bed resting did not change superficial femoral artery IMT-CSA. However, the main effect of bed rest in the superficial femoral artery, irrespective of exercise, was the reduction in diameter and a consequent increase in shear rate.

The findings above raise questions about the mechanisms of diameter change observed in the superficial femoral and carotid arteries. Classic studies have established that repetitive increases in shear induce endothelium-mediated changes in artery size and, presumably, wall architecture.^{34–36} The relationship between shear and diameter in the femoral artery is complicated. Possibly, decreases in (peak) shear initially lead to inward arterial remodeling, which, in turn, results in higher basal shear levels. Only a time course study of the relationships between bed rest-induced initial changes in shear and consequent changes in arterial diameter will resolve this question.

Another potential explanation for differences that we observed in carotid and femoral artery diameters relates to differences in wall architecture in the elastic (carotid) and the muscular (superficial femoral) arteries. Indeed, we recently found different wall thickness and wall:lumen ratios between atherosclerosis-prone (popliteal artery) and -resistant arteries (brachial artery).³⁷ These vessels may, therefore, respond differently to a similar bed rest stimulus. Finally, differences in transmural pressure may contribute to the diameter changes.³⁸ In daily living, transmural pressure is substantially higher in the lower limbs than in the carotid artery. Bed rest will significantly attenuate transmural pressure for the superficial femoral artery but not across the carotid artery. This may contribute to the distinct findings between both conduit arteries after bed rest. Other effects of prolonged bed rest in

humans include an increase in sympathetic nerve activity.^{24,25} Because sustained elevations in sympathetic-adrenergic tone stimulate smooth muscle hypertrophy,^{39,40} bed rest may induce an increase in wall thickness through an increased smooth muscle cell tone. Finally, endothelial release of vasoconstrictors (eg, endothelin 1 and angiotensin II) and production of oxidative stress can influence vessel wall structural adaptation. Future studies will be required to more thoroughly investigate the impacts of changes in shear on wall thickness changes in different arterial territories.

This is the first study, to our knowledge, to assess changes in wall thickness in response to inactivity using a within-subjects longitudinal approach in humans. We demonstrated that a short period of physical inactivity results in marked conduit artery wall thickening. This finding is in agreement with a recent cross-sectional study that found an increased carotid artery wall thickness in chronic wheelchair-bound subjects, who are typically subject to prolonged physical inactivity but also to various cardiovascular risk factors.⁴¹ The increase in arterial wall thickness in our study was observed in the absence of clinical observation of atherosclerosis and/or hypertension. This raises an important question related to the mechanisms contributing to the rapid and large increase in wall thickness. Although previous studies have used conduit artery wall thickness as a surrogate measure for atherosclerosis,^{11,16,17} it is unlikely that the increased wall thickening in our study reflects pathological thickening of the subintima layer, which typically occurs after many years of exposure to cardiovascular risk factors. We think it more likely that we observed a form of “physiological” remodeling, perhaps involving smooth muscle cell hypertrophy, which consequently leads to an increase in wall thickness.⁴²

A few previous studies have examined the impact of exercise on artery wall thickness,^{43,44} but none have assessed the impact of exercise as a countermeasure for inactivity. We found that both exercise countermeasures prevented the increase in carotid artery wall thickness. In the superficial femoral artery, RVE was more effective than RE in preventing the decrease in diameter and increase in wall thickness. This suggests a superior effect of RVE in the prevention of adaptations in wall characteristics to bed rest. Previous studies have demonstrated a benefit of the addition of vibration to the traditional form of exercise (see Review).⁴⁵ For example, skeletal muscle function improved more as a result of RVE than RE alone.⁴⁶ The precise physiological mechanisms responsible for the putative benefits of vibration exercise are currently not well understood but may relate to an increase in muscle metabolism, muscle/tendon stress, and/or shear rate.⁴⁵ In addition, various other modalities of exercise have generated beneficial effects on the vasculature, such as the commonly applied aerobic endurance exercise. Although this endurance exercise has a number of practical limitations as a countermeasure during bed rest, this type of exercise may potentially have larger effects on the vasculature. In any event, the clinical relevance of our findings is that vibration exercise may be an effective strategy for preventing the detrimental effects of prolonged inactivity in various nonambulatory patient groups.

Strengths of this study include a within-subject approach, long duration of bed rest, countermeasures, and the use of novel operator-independent techniques to measure wall thickness. A potential limitation relates to the relatively small sample size of 18 subjects. However, previous studies have recruited similar or smaller groups and have typically examined the effects of 5 to 7 days of bed rest only.^{47,48} Because the magnitude of physical inactivity is time dependent,⁴⁹ 60 days clearly resulted in a large impact on the vasculature. The profound stimulus of complete bed rest,⁴⁹ combined with the excellent reproducibility of our technique,²² allowed us to detect these important findings in a relatively small group of participants. It should also be emphasized that bed rest such as that used in the present experiment does not represent a sedentary lifestyle, and our findings cannot necessarily be extrapolated to those of sedentary, yet ambulatory, individuals.

Clinical Relevance

Conduit arterial wall thickening has been regarded as an integral part of the atherosclerotic process and has been used in intervention trials as a surrogate outcome measure.^{13,15–18} This study provides evidence that physical (in)activity is a potent stimulus for marked and rapid changes in artery wall thickness. Remarkably, the magnitude of change in wall thickness after 60 days of bed rest ($\approx 15\%$) is similar or even larger to that found in clinical trials that examined the impact of pharmacological interventions (eg, rosuvastatin and vitamin C) across a 1- to 3-year period.^{50–52} Although the underlying mechanisms for the increase in wall thickness after bed rest are unclear and may not relate to the pathological atherosclerotic process, our observations have important clinical implications for future studies. Given the rapid changes in artery wall thickness in response to physical (in)activity, other studies using conduit artery wall thickness need to consider the impact of between-subject differences or within-subject changes in physical activity levels.

Perspectives

Bed rest induces a rapid increase in wall thickness of the carotid and femoral arteries in healthy subjects, which can be counteracted completely (carotid artery) or largely (superficial femoral artery) by exercise countermeasures. The latter finding reinforces the importance of exercise to prevent changes in vascular remodeling induced by deconditioning. Our findings have clinical relevance for studies using the IMT as a surrogate marker for atherosclerosis. Because a change in physical activity level may induce changes in wall thickness, which are unrelated to atherosclerosis, our findings emphasize the importance of controlling for between- or within-group differences in physical activity levels when IMT is used as an outcome measure.

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Disclosures

None.

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