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Resistive exercise versus resistive vibration exercise to counteract vascular adaptations to bed rest

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van Duijnhoven NT, Thijssen DH, Green DJ, Felsenberg D, Belavý DL, Hopman MT. Resistive exercise versus resistive vibration exercise to counteract vascular adaptations to bed rest. *J Appl Physiol* 108: 28–33, 2010; doi:10.1152/japplphysiol.00760.2009.—Bed rest results in marked vascular adaptations, and resistive vibration exercise (RVE) has been shown to be an effective countermeasure. As vibration exercise has practical and logistical limitations, the use of resistive exercise (RES) alone has the preference under specific circumstances. However, it is unknown if RES is sufficient to prevent vascular adaptations to bed rest. Therefore, the purpose of the present study was to examine the impact of RES and RVE on the vascular function and structure of the superficial femoral artery in young men exposed to 60 days of bed rest. Eighteen healthy men (age: 31 ± 8 yr) were assigned to bed rest and randomly allocated to control, RES, or RVE groups. Exercise was applied 3 times/wk for 5–7 min/session. Resting diameter, blood flow, flow-mediated dilation (FMD), and dilator capacity of the superficial femoral artery were measured using echo-Doppler ultrasound. Bed rest decreased superficial femoral artery diameter and dilator capacity ($P < 0.001$), which were significantly attenuated in the RVE group ($P < 0.01$ and $P < 0.05$, respectively) but not in the RES group ($P = 0.202$ and $P = 0.696$, respectively). Bed rest significantly increased FMD ($P < 0.001$), an effect that was abolished by RVE ($P < 0.005$) but not RES ($P = 0.078$). Resting and hyperemic blood flow did not change in any of the groups. Thus, RVE abolished the marked increase in FMD and decrease in baseline diameter and dilator capacity normally associated with prolonged bed rest. However, the stimulus provided by RES alone was insufficient to counteract the vascular adaptations to bed rest.

physical deconditioning; endothelial function; exercise countermeasure; vascular remodeling

PHYSICAL INACTIVITY is a strong and independent risk factor for cardiovascular disease (9). Human models of prolonged physical inactivity, for example, bed rest, induce rapid and marked vascular adaptations (6), such as inward remodeling of conduit arteries (6). In addition, an increase in flow-mediated vasodilation (FMD) in conduit arteries is typically observed after deconditioning (2, 3, 7). The elevated FMD may be explained by the large decrease in diameter (26) and/or an increase in the shear-stress stimulus experienced by smaller arteries.

Exercise training is a well-established and potent physiological stimulus that reduces primary (18, 22, 24) and secondary cardiovascular events (12, 20), possibly through changes in vascular function and structure (10). Also, vascular adaptations to physical deconditioning can, at least in part, be counteracted by regular exercise (2, 3, 27). For example, resistance exercise (RES) combined with whole body vibration partly prevents vascular adaptations to bed rest (3).

In healthy subjects, RES alone (23) as well as whole body vibration exercise alone (13, 17, 21) can induce vascular adaptations. However, it is unknown whether RES alone is able to prevent the vascular changes to bed rest inactivity. Therefore, the purpose of this study was to examine if RES has a similar counteractive effect as resistive vibration exercise (RVE) on the vascular adaptations to 60 days of strict bed rest in healthy young men. We hypothesized that both exercise types would attenuate the vascular changes to bed rest, with RVE having superior effects to counteract these vascular adaptations compared with RES alone.

METHODS

Subjects

Eighteen healthy men (age: 31 ± 8 yr) participated in this study. All subjects were screened using a medical history, physical and psychological examination, and did not have any medical problems. None of them suffered from diabetes or cardiovascular disease or used any medication. Subjects who participated in strength and/or endurance training 6 mo before the start of the study were excluded. Subject characteristics are shown in Table 1. All subjects gave their written informed consent before participation in the study. The 2nd 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 bed rest (CTR group), bed rest with RES (RES group), or bed rest with RVE (RVE group).

Bed rest protocol. After the initial series of experiments, subjects were placed at complete 6° head-down tilt bed rest. 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 carefully controlled.

RVE protocol. The protocol for the countermeasures is based on a previous RVE protocol during bed rest (3) with a small adaptation to be more time efficient. Before randomization, all subjects were familiarised with the exercises types on 3 separate, consecutive days to ensure optimal training possibilities during bed rest. Familiarization exercise bouts were performed under low load (65% of body weight)

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Table 1. *Subject characteristics*

	Control Group		Resistive Exercise Group		Resistive Vibration Exercise Group	
	Before bed rest	After bed rest	Before bed rest	After bed rest	Before bed rest	After bed rest
Age, yr	34 ± 8		31 ± 6		28 ± 9	
Height, cm	179 ± 6		177 ± 3		177 ± 5	
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
Body mass index, 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 blood pressure, mmHg	111 ± 4	114 ± 9	118 ± 6	109 ± 9	113 ± 15	114 ± 8
Diastolic blood pressure, mmHg	70 ± 8	68 ± 6	68 ± 8	68 ± 8	68 ± 10	69 ± 6
Heart rate, beats/min	70 ± 8	71 ± 4	68 ± 7	62 ± 4	75 ± 7	65 ± 6

Values are means ± SD; $n = 6$ subjects/group. *$P < 0.05$, after vs. before bed rest; †$P < 0.05$, resistive exercise group vs. control and resistive vibration exercise groups.

and without whole body vibration. After randomization, subjects in the RES and RVE groups were exposed to three sessions of exercise per week (Monday, Wednesday, and Friday), which lasted 5–7 min 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, Pforzheim, Germany). 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 either side of a platform, which activated in the RVE group only to add the whole body vibration component. Subjects were given oral and visual feedback of their current and target positions 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 the following five different exercise units, which were similar for RES and RVE groups.

1. WARM-UP. The warm-up consisted of ilateral squat exercise (from 10° to 90° knee flexion and back) with 50% of maximal force for 64 s. Subjects performed the concentric and eccentric phases of the exercise in 4 s each. Eight repetitions were performed, without an intermediate pause, after which a 2-min break was given. During RVE, the vibration frequency was 24 Hz.

2. BILATERAL SQUATS (AS DESCRIBED IN THE WARM-UP). During *training sessions 1* and *2*, bilateral squat exercise was performed at 75% and 80% of maximum force, respectively, with subjects continuing exercise until exhaustion. Subsequently, the force level was increased by 5% during each session until the subject could only perform eight repetitions. When performing ≥10 repetitions in 2 consecutive sessions, the force level was increased by 5%, whereas the level was decreased by 5% if ≤6 repetitions were completed in 2 consecutive sessions. In RVE, the vibration frequency was progressed from 20 Hz at *session 1* to 24 Hz at *session 2*, after which this level was maintained. A 5-min break was given after this exercise.

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

4. DOUBLE-LEG HEEL RAISES. The double-leg heel raises were performed similarly to the single-leg heel raises, until exhaustion, but with a resistive force of ~1.8 times body weight. When subjects performed in ≥55 s, the load was increased by 5%, whereas this was decreased by 5% if exercise could not be performed for ≤40 s. In RVE, the vibration frequency was 24 Hz. A 2-min break was given after completion.

5. BACK AND HEEL RAISES. With the subject's feet positioned on the platform, their hips and lumbar spine were extended, ankles were dorsal flexed, and knees were maintained at full extension for 60 s, with a force of 1.5 times body weight. The vibration frequency was 16 Hz in RVE.

A well-trained exercise physiologist supervised all training sessions.

Experimental protocol. 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 h before being tested, while no exercise was performed 24 h before subjects were tested. Before subjects were tested, the bed was positioned at 0° for at least 30 min before the first measurement was performed.

Ultrasound measurements. Baseline resting diameter and blood cell velocity of the left carotid artery (CA) and superficial femoral artery (SFA) were performed using an echo Doppler device (Megas, ESAOTE, Firenze, Italy) with a 5- to 7.5-MHz broadband linear transducer. SFA 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. Both diameter images and velocity spectra were continuously registered on videotape for at least 30 s. FMD of the SFA was examined proximal from a 12-cm-wide cuff placed around the proximal part of the left upper leg, which was inflated to a suprasystolic pressure of 220 mmHg for 5 min. After cuff deflation, hyperemic velocity in the SFA was recorded for the first 35 s, followed by a continuous registration of the vessel diameter for 5 min to determine FMD (14, 26). FMD, representing largely nitric oxide (NO)-mediated endothelium-dependent vasodilation (14), was expressed as the relative change from baseline diameter.

To determine SFA dilator capacity, the cuff was inflated a second time for 5 min while subjects received a single spray of sublingual nitroglycerin (NO donor, 400 μg) after 3.5 min of cuff inflation (19). Hyperemic flow velocity in the SFA was obtained during the first 35 s after cuff release, followed by an assessment of diameter up to 6 min. All measurements were performed by a single investigator.

Data analysis. Offline analysis was performed using custom-designed edge detection and wall-tracking software, which is independent of investigator bias (32). Briefly, the initial video signal was encoded and stored as a digital DICOM file on a PC 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, Austin, TX). By identifying a region of interest (ROI) 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 ROI in the diameter image, a pixel-density algorithm automatically identified the angle-corrected near and far wall e-lines for every pixel column. The point where pixel intensity changes most rapidly was determined as the position of the edge. Typical B-mode ROIs (during resting diameter) contained ~200–300 diameter measures/frame, occurring for 30 frames/s, the average of which was

calculated and stored (D_{mean}). During FMD and dilator capacity procedures, a median diameter was detected from 100 consecutive frames (~3 s) according to an algorithm that identified the maximum bracket of data subsequent to the performance of a moving ROI (1). Peak diameter was presented by the maximum value of all calculated mean values. FMD was calculated as the percent rise of this peak diameter from the preceding resting diameter. Within the ROI in the Doppler waveform (during resting velocity and FMD), the peak of the envelope of this waveform was automatically detected 30 times/s for offline analysis. These data were stored and retrieved for analysis in a custom-designed analysis package. Mean resting velocity (V_{mean}) was then used to calculate mean resting blood flow (BF_{mean}) as follows: $[\pi(D_{mean}/2)^2][(V_{mean}/2)60]$, where BF_{mean} was measured in milliliters per minute, D_{mean} was measured in centimeters, and V_{mean} was measured in centimeters per second. Hyperemic blood flow during FMD was determined as the mean of the highest flow profiles after cuff deflation during 10 s (19).

The use of this semiautomatic software results in better reproducibility than with manual methods and has minimal inter- and intraobserver variance (32).

Statistical Analysis

Given a sample size of six subjects in the CTR, RES, and RVE groups, a power of 80%, an α-level of 0.05, and an assumed SD of 2.7% for change in FMD after bed rest (3), an effect size of 3.9% difference between interventions could be detected.

One-way ANOVA was applied to assess baseline differences between the CTR, RES, and RVE groups for subject characteristics. Differences in the response to bed rest between the CTR, RES, and RVE groups were tested with repeated-measures ANOVA with time as the within-subject factor and group as the between-subject factor (Statistical Package for Social Sciences 16.0, SPSS, Chicago, IL). Statistical significant differences were further analyzed using *t*-tests with the Bonferroni correction. To examine the contribution of resting diameter (dependent variable) to the magnitude of the FMD response (independent variable), a linear regression model was used. The level of statistical significance was defined at $\alpha = 0.05$. Data are presented as means ± SE unless stated otherwise.

RESULTS

Due to medical reasons unrelated to the current investigation, one subject in the RES group ended his participation in the study after 4 wk of bed rest. One subject was physically unable to continue RVE training and was therefore switched to the CTR group after three unsuccessful training sessions. Another subject in the RVE group ended the study after 1 day due to personal reasons.

Subject characteristics were not different across groups except for body mass and body mass index, which were lower in the RES group compared with the CTR and RVE groups (Table 1). After 60 days of bed rest, no differences were found in subject characteristics except for body mass and body mass index, which were decreased in the CTR group (Table 1). All subjects randomized to the RES and RVE groups completed the 25 exercise sessions.

Resting Diameter and Dilator Capacity

CA resting diameter did not change after 60 days of bed rest in the CTR, RES, and RVE groups (Table 2). Bed rest significantly decreased SFA diameter in the CTR, RES, and RVE groups ($P < 0.001$; Fig. 1). A significant interaction was present between the RVE and CTR groups ($P < 0.01$) but not between the RES and CTR groups ($P = 0.202$). SFA dilator capacity was significantly reduced after bed rest ($P < 0.001$; Fig. 1) in the CTR and RES groups but not in the RVE group. A significant interaction effect was observed between the RVE and CTR groups ($P < 0.05$) but not between the RES and CTR groups ($P = 0.696$).

Resting CA and SFA blood flow showed no change after bed rest in all groups (Table 2).

FMD

Bed rest significantly increased the FMD of the SFA ($P < 0.001$; Fig. 2) in the CTR and RES group but not in the RVE group. A significant interaction was observed between the RVE and CTR groups ($P = 0.002$) but not between the RES and CTR groups ($P = 0.078$).

Hyperemic SFA blood flow showed no change after bed rest in all groups (Table 2).

Including the before and after bed rest values of all subjects, a significant inverse correlation was found between resting diameter and FMD of the SFA ($r = -0.621$, $P < 0.001$; Fig. 3).

DISCUSSION

The purpose of the present study was to examine the effect of RES to counteract vascular adaptations to bed rest deconditioning, particularly compared with the efficacy of RVE. We confirmed the previous observation that bed rest induces a decrease in conduit artery diameter and an increase in FMD of the SFA. More importantly, RVE significantly attenuated or even prevented the changes in SFA diameter and FMD to bed rest. However, when excluding vibration exercise, RES alone was insufficient to counteract the vascular adaptations to bed rest. These results suggest that vibration exercise is of importance to counteract the detrimental structural and functional vascular adaptations to bed rest in healthy men.

Table 2. *Diameter and blood flow before and after bed rest*

	Control Group		Resistive Exercise Group		Resistive Vibration Exercise Group		ANOVA	
	Before bed rest	After bed rest	Before bed rest	After bed rest	Before bed rest	After bed rest	*P* value (time)	*P* value (time × group)
Carotid artery								
Diameter, cm	0.70 ± 0.04	0.69 ± 0.05	0.69 ± 0.02	0.69 ± 0.04	0.70 ± 0.06	0.69 ± 0.05	0.29	0.78
BF_{rest}, ml/min	284 ± 75	251 ± 68	288 ± 95	303 ± 85	298 ± 89	252 ± 85	0.47	0.68
Superficial femoral artery								
BF_{rest}, ml/min	92 ± 38	52 ± 28	80 ± 46	70 ± 37	93 ± 28	109 ± 40	0.32	0.14
BF_{peak}, ml/min	470 ± 228	343 ± 172	536 ± 93	401 ± 173	594 ± 218	441 ± 277	0.07	0.88

Values are means ± SD. BF_{rest}, resting blood flow; BF_{peak}, hyperemic blood flow.

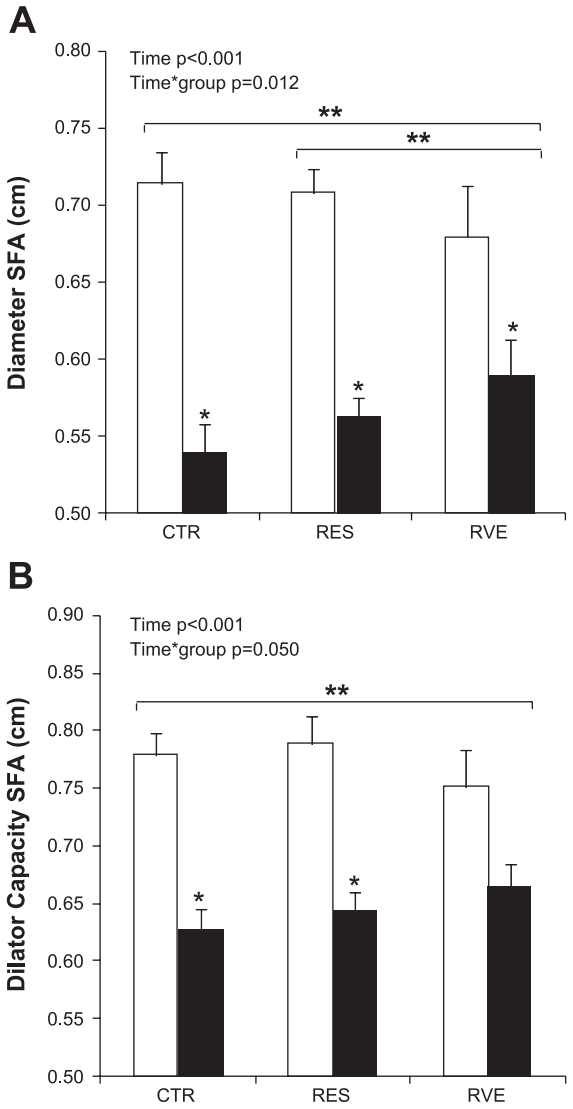

Fig. 1. *A* and *B*: resting diameter (*A*) and dilator capacity (*B*) of the superficial femoral artery (SFA) before (open bars) and after (solid bars) bed rest in the control (CTR), resistive exercise (RES), and resistive vibration exercise (RVE) groups. Data are presented as means ± SE. *$P < 0.05$, after vs. before bed rest; **$P < 0.05$, RVE group vs. CTR/RES groups.

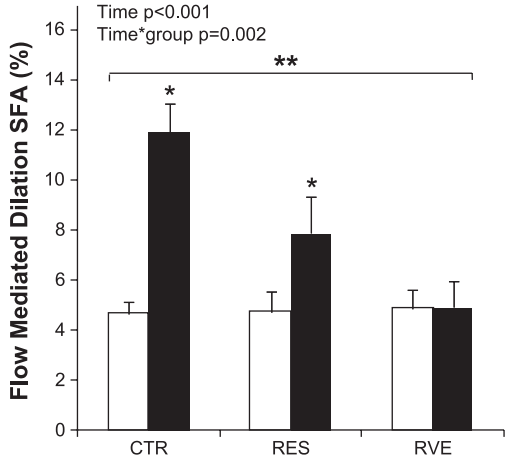

Fig. 2. Flow-mediated dilation of the SFA before (open bars) and after (solid bars) bed rest in the CTR, RES, and RVE groups. Data are presented as means ± SE. *$P < 0.05$, after vs. before bed rest; **$P < 0.05$, RVE group vs. CTR group.

FMD, which represents conduit artery endothelial function, was markedly increased after bed rest, which essentially reinforces previous studies on deconditioning (2, 3, 7, 8). Nonetheless, this finding remains somewhat counterintuitive as cardiovascular risk factors (5) and/or diseases (31) are typically associated with a lower FMD. Recently, we (28) demonstrated that increased NO sensitivity of the smooth muscle cell cannot explain the elevated FMD in the extremely inactive legs of spinal cord-injured subjects. Alternatively, the large FMD value during deconditioning may reflect a counterregulatory response to the marked inward remodeling. Thijssen et al. (26, 29) recently described, within and between arteries, that smaller arteries are typically associated with a larger dilation when examining the FMD. Such an inverse correlation between baseline diameter and FMD is also present in our data (Fig. 3). Moreover, we found a stronger and steeper relation between baseline diameter and FMD in the smaller-sized vessels, which is in agreement with previous findings (26). Bed rest deconditioning results in a marked inward remodeling. Therefore, the elevation in FMD after deconditioning may not represent an improvement in endothelial function, and therefore a cardioprotective effect, but rather relate to the smaller artery size, which is the primary reason for the larger dilation.

Vascular Adaptations to Bed rest Deconditioning

The evident decrease in resting diameter (−24%) of the SFA is in line with previous findings of structural inward remodeling of the conduit arteries after various models of physical deconditioning (2, 3, 7, 8, 25, 28). As baseline resting diameter is regulated by several factors (e.g., sympathetic activity and vasoactive substances), using the baseline diameter to assess structural remodeling has important limitations (11). Therefore, we examined the vasodilator capacity as a novel and valid measure for remodeling of a conduit artery (19). The vasodilator capacity confirms that RVE partly prevents the inward remodeling to bed rest, as the maximal diameter during the vasodilator capacity test was significantly higher after bed rest than in the CTR group. The difference in the magnitude of change of the resting diameter and dilator capacity to bed rest indicates that both values do not present the same information and are therefore both of additional value.

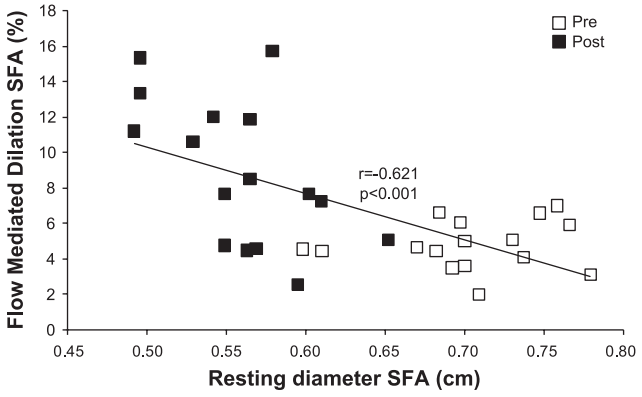

Fig. 3. Relation between resting diameter and flow-mediated dilation of the SFA before (open bars) and after (solid bars) bed rest. Individual data of all subjects are presented.

Indeed, the CTR and RES groups showed a marked decrease in resting and maximal SFA diameter, which was associated with an elevation in FMD. However, the RVE group demonstrated no significant change in diameter, whereas RVE also abolished the change in FMD to bed rest. The findings from the vasodilator capacity reinforce these findings, reporting structural adaptations in the CTR and RES groups but not in the RVE group. Based on the relation between relative FMD and baseline diameter, we recommend to interpret FMD outcomes with caution when comparing groups that differ in baseline diameter or when interventions are evaluated that cause significant changes in baseline diameter.

Exercise Countermeasure

RES has been shown to induce several vascular changes in healthy subjects and patients with cardiovascular disease (4). These findings, combined with the practical issues associated with the provision of vibration exercise, encouraged us to examine the efficacy of RES without vibration. While our data reinforce previous observations that RVE can attenuate the vascular adaptations to bed rest (3), our data also suggest that a difference exists in the magnitude of the counteractive effects of the two types of exercise. RVE demonstrated a significant attenuation of the effect of bed rest on SFA vascular function and structure, which was not found for RES.

Whole body vibration exercise in healthy subjects has been reported to immediately increase femoral (17) and popliteal (13) artery blood flow and shear rate, i.e., the most important stimulus for vascular adaptation (15, 16, 30). Indeed, brachial ankle pulse wave velocity decreased immediately after a session of vibration exercise in healthy sedentary subjects, suggesting an acute impact on the artery wall (21). Although the mechanisms responsible for the acute changes in blood flow during whole body vibration exercise are not clear at present, an increase in shear will provide an important stimulus for arteries to adapt functionally as well as structurally. Indeed, the stimulus provided by only three short-lasting (~6 min) sessions of RVE per week prevented the diameter decrease after 60 days of bed rest deconditioning. However, the stimulus provided by RES was insufficient to induce significant changes.

Conclusions

In conclusion, 60 days of 6° head-down tilt bed rest deconditioning results in large arterial adaptations in a group of young men. These vascular adaptations to bed rest cannot be counteracted by three sessions of RES per week during the entire bed rest period. RVE, however, effectively attenuates the reduction in conduit artery diameter and even preserves endothelial function to bed rest.

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DISCLOSURES

This study was investigator initiated, and all data were collected, stored, and interpreted by the investigators without external interference.

No conflicts of interest are declared by the author(s).

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