WISE 2005: chronic bed rest impairs microcirculatory endothelium in women

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Sedentary behavior has deleterious effects on the cardiovascular system, including reduced endothelial functions. A 2-mo bed rest study in healthy women [women international space simulation for exploration (WISE) 2005 program] presented a unique opportunity to analyze the specific effects of prolonged inactivity without other vascular risk factors on the endothelium. We investigated endothelial properties before and after 56 days of bed rest in 8 subjects who performed no exercise (control group: No-EX) and in 8 subjects who regularly performed treadmill exercise in a lower body negative pressure chamber as well as resistance exercise (countermeasure group, EX). A functional evaluation of the microcirculation in the skin was assessed with laser Doppler. We studied endothelium-dependent and -independent vasodilation using iontophoresis of acetylcholine and sodium nitroprusside, respectively. We also measured circulating endothelial cells (CECs), an index of endothelial damage. In the No-EX group, endothelium-dependent vasodilation was significantly reduced (35.4 ± 4.8% vs. 24.1 ± 3.8%, P < 0.05) by bed rest with a significant increase in the number of CECs (3.6 ± 1.4 vs. 10.6 ± 2.7 ml⁻¹, P < 0.05). In the EX group, endothelium-dependent vasodilation and number of CECs were preserved. Our study shows that in humans prolonged bed rest causes impairment of endothelium-dependent function at the microcirculatory level, along with an increase in circulating endothelial cells. Microcirculatory endothelial dysfunction might participate in cardiovascular deconditioning, as well as in several bed rest-induced pathologies. We therefore conclude that the endothelium should be a target for countermeasures during periods of prolonged deconditioning.

bed rest studies; cardiovascular deconditioning; iontophoresis; circulating endothelial cells

Physical inactivity is usually associated with other strong cardiovascular risk factors such as obesity (31) or diabetes (7). The metabolic syndrome includes several risk factors and is very often associated with physical inactivity. In this context, bed rest studies in healthy volunteers present a unique opportunity to analyze specifically the effects of enforced physical inactivity on vascular function (28). Moreover, during hospitalization bedridden patients have increased morbidity with pressure ulcers at the skin level. Muscle atrophy, bone osteoporosis, metabolic changes, and cardiovascular deconditioning occur after bed rest. Finally, microgravity exposure (space travel) induces similar problems to those seen during bed rest, because the human body does not need to continuously fight gravity.

The endothelium plays a crucial role in the regulation of vascular homeostasis and local blood flow. Thus endothelial impairment might be associated with bed rest-induced pathologies. Under normal conditions, the endothelium induces vasodilation, limits vascular inflammation, and maintains blood fluidity. Endothelial dysfunction appears as an early event in the pathogenesis of atherosclerosis. During the development of atherosclerosis, the endothelium adopts a phenotype that facilitates vasoconstriction, thrombosis, and inflammation.

Circulating blood exerts tangential forces (shear forces) at the surface of endothelial cells, the first layer to be in contact with blood. This shear stress has been shown to exhibit higher shearing in small arteries and in the arterial side of the microcirculation (vascular peripheral resistance) than in large arteries (4). A chronic decrease in shear stress in vascular lumen impairs endothelial functions with increased apoptosis, as shown in cell culture studies (14). Endothelial dysfunction may be a key factor in the deleterious effect of physical inactivity induced by bed rest at the level of the microcirculation, where the shear stress is important in normal function. These hypothetical changes may also be expected in patients with illness acutely requiring bed rest.

We hypothesized that prolonged physical inactivity induced by 2 mo of bed rest in healthy women would cause endothelial dysfunction at the microcirculatory level accompanied by an increase of circulating endothelial cells (CECs), a biological marker of endothelial damage. Our secondary hypothesis was that regular physical activity in bedridden subjects would prevent this endothelial impairment.
METHODS

Subjects. Sixteen healthy, young female volunteers participating in the 2-mo bed rest in a head-down position (−6°) at the French Institute for Space Medicine and Physiology (MEDES) Medical Facility (Toulouse, France) were included in this study. These subjects were divided into two groups: a control group and a countermeasure group with exercise. The mean age (±SE) was 33.5 ± 0.9 (range: 28–40) yr, their height 164 ± 2 cm, and their weight 58 ± 1 kg. All subjects passed the orthostatic tolerance test (10 min + 80° head-up tilt test) performed during the selection process.

They received a complete description of the experimental procedure before giving their written informed consent to follow the protocol approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Midi-Pyrénées (France, 2005). The entire protocol was in accordance with the declaration of Helsinki, Finland.

None of the subjects was taking cardiovascular medication at the time of the study. Before the bed rest, all subjects did not present cardiovascular risks with normal biological parameters (standard biochemistry including normal levels of cholesterol and triglycerides, and standard hematological analysis including phlebitis markers) or with normal arterial pressure, and all subjects were nonsmokers.

The subjects were randomly divided into two groups. Eight subjects were included in a control no-exercise group (No-EX) and 8 subjects in a countermeasure exercise group (EX), which included treadmill exercise in a lower body negative pressure (LBNP) chamber as well as resistance exercise training (see Physical exercise programs).

WISE program. The study design consisted of a 20-day ambulatory control period followed by 60 days of antithorostatic bed rest [6° head-down tilt (HDT)] and then by 20 days of post-bed rest recovery. During the bed rest, the subjects remained in antithorostatic bed rest (6° HDT) continuously for all activities. The subjects were given a diet of 2,000 ± 300 kcal day⁻¹ with a sodium input of 3 g day⁻¹. Water intake was limited to 3 l/day⁻¹. Energy (~600 kcal) and water (~1 l) supplements were delivered to the exercise group on days when exercise was performed. The subjects were supervised and monitored 24 h/day⁻¹. Room lighting was on between 7 and 23 h daily. All studies were conducted in a quiet room at ~24°C. All volunteers had normal menstrual cycles without hormonal contraception during the previous 2 mo.

Physical exercise programs. This program combined two sessions of countermeasures that were carried out while lying down; one exercise session involved resistance training using a flywheel apparatus, and one session included aerobic training involving treadmill exercise against the force generated by LBNP.

The flywheel was used to carry out a resistance exercise while in a lying position that mainly involved the muscles of the calves and thighs in a fairly intensive manner over short repeated periods. Each session lasted for ~30 min, including an initial warm-up and stretching period that lasted 10–15 min. The protocol was published previously (36). Flywheel was performed every third day during bed rest.

The aerobic exercise consisted of running 35 min on a vertical treadmill [at 40–80% oxygen consumption (V̇O₂peak) in an interval fashion], while lying down, with the lower part of the body in a chamber within which a negative pressure of ~50 to ~60 mmHg was applied (LBNP) (6). This exercise was followed by a period of 10 min in the chamber without running. The negative pressure applied to the lower part of the body simulates the upright position because it leads to a redistribution of the volume of blood and fluids from the upper part of the body to the lower part of the body. LBNP + treadmill was performed between 3 and 4 times/wk.

The two types of exercise (flywheel and aerobic) never took place on the same day.

Iontophoresis of pharmacological agents coupled with laser Doppler. This measurement was performed in the supine position 7 days before the beginning of bed rest [basal data collection (BDC)-7] and on day 56 of the bed rest (HDT + 56). Iontophoresis allows for local delivery of small amounts of pharmacological agents, thus avoiding potential systemic effects while delivering drugs in the area of blood flow measurement. A few centimeters distant from the iontophoretic site, blood flow measured by a control laser-Doppler (LD) probe remained stable (16). Iontophoresis involves the use of a low electrical current to deliver pharmacological agents to the skin; in this study, we used acetylcholine (ACh) and sodium nitroprusside (SNP). The effect of these drugs on the microcirculation is measured with skin LD to estimate changes in blood flow induced by these substances. Our iontophoretic protocol was in accordance with other publications (24, 25) that studied endothelial and nonendothelial vasodilatation. We elected to use the iontophoresis method because it is a less invasive way for administration of drugs compared with microdialysis and intra-arterial administrations, which are also applicable for human studies and allow for specific measurement of the skin microvascular response.

Endothelium-dependent and -independent vasodilation. The cutaneous blood flow response to iontophoresis was assessed at the calf level using three LD probes positioned 5 cm apart. We used two specially designed iontophoretic probes (PF 481-1; Perimed) to allow for current application, local heating, and simultaneous cutaneous blood flow recording.

The iontophoretic probes used had a chamber where we positioned a 0.6-cm² sponge. At the center of the sponge, cutaneous LD flowmetry (LDF) was measured through a multifiber laser probe (780 nm). The two iontophoretic probes were also connected to temperature-regulated heating systems (Peritemp PF4005; Perimed) and to regulated current suppliers (Periont PF 382; Perimed), allowing for the delivery of regulated-intensity currents for programmable durations. A third probe (PF408; Perimed) was used as a reference to confirm the absence of response to current application at an adjacent control site.

Local cutaneous temperature was measured by a surface thermocouple probe positioned 5 cm from each LD probes. The thermocouple was connected to an electronic thermometer (BAT-12, Physitemp Instruments). Systemic blood pressure was monitored noninvasively using Cardiopres (BMEye) positioned on the third finger of the hand.

We measured the blood flow changes in response to iontophoresis of 2% ACh chloride solution (to study endothelium-dependent vasodilation) and 1% SNP (to study endothelium-independent vasodilation). These measurements were performed simultaneously with a current application of a 10-s, 100-µA anodal current for the experiment with ACh and a 20-s, 100-µA cathodal current for the experiment with SNP (25). Measurement of the vasodilation level was performed at the peak as the maximum value within 5 min following current application and at the plateau of the response reached 20 min after the stimulation. We have chosen a low, single dose for iontophoresis instead of multiple electrical stimulations to avoid the nonspecific current-induced vasodilation. It has been clearly demonstrated that prolonged or repeated electrical stimulations, as required for dose-response curves, increase nonspecific vasodilation (15, 35).

A stable baseline blood flow was measured for 2 min before current application was performed. Twenty minutes after the end of the current application, the site was locally warmed to 44°C to cause maximal cutaneous vasodilation during 20 min (34).

Endothelium biological parameter: CECs. Blood samples were collected from an antecubital vein in EDTA tubes for determination of CECs before bed rest (BDC)-7 and at the end of bed rest (HDT + 56). To avoid contamination by endothelial cells from the punctured vessel wall, the first 2 ml of blood drawn were discarded. Five milliliters of total blood were used for this analysis. Immunocapture of CECs from whole blood was performed at 4°C (18) with magnetic beads (Dynabeads M-450, Dynal) coated with S-Endo 1 (BioCytex), a monoclonal antibody raised against the endothelial CD146 antigen.
To avoid nonspecific binding of leukocytes to CD146-coated beads, the cell suspensions were flushed vigorously through the pipette tip during the washing steps and then suspended in acridine orange (10 µg/ml in PBS; Sigma) for counting under an optical fluorescence microscope (λexc = 490 nm).

Data analysis. Data were analyzed in a standardized way and blinded for the status of the participants. The results are presented as means ± SE. Skin blood flow responses to ACh and SNP are presented as percentage of maximal vasodilation (10). Blood flow measured by the control probe and maximal vasodilation to heating are expressed as nonnormalized values. Variation in skin blood flow responses and CECs were analyzed using a two-way factorial ANOVA. For each parameter, we studied the bed rest and the group effects. A protected least significance difference Fisher test was used for the post hoc analysis to locate the significant effect when applicable. Statistical significance was set at *P < 0.05.

RESULTS

General data. Mean arterial pressure, LDF on the reference probe (control LDF), and skin temperature did not significantly differ before and after bed rest in either the EX group or the No-EX group (Table 1).

Two volunteers had amenorrhea (1 in No-EX group and 1 in EX group) during the 2-mo bed rest. At BDC-7, two women in the No-EX group and two women in the EX group were menstruating. At HDT + 56, two women in the No-EX group and two women in the EX group were menstruating. Before bed rest, the 4 subjects who were menstruating had similar CEC numbers compared with the 12 other subjects (3.0 ml⁻¹ vs. 3.2 ml⁻¹).

Endothelium-dependent and -independent vasodilation. Mean arterial pressure, control LDF, and skin temperature were stable in all iontophoresis experiments (Table 1). Significant vasodilation occurred during both ACh and SNP delivery by iontophoresis. Skin maximal vasodilation to heating, expressed as nonnormalized values, was similar before and after bed rest in the No-EX group [66.3 ± 4.4 vs. 66.7 ± 6.0 arbitrary units (au)] and in the EX group (58.9 ± 8.1 vs. 68.3 ± 8.2 au).

In the No-EX group, the early vasodilation response to ACh was not impaired by bed rest [38.3% ± 6.3 vs. 38.2% ± 7.9, not significant (NS)], whereas the late vasodilation was significantly reduced (35.4% ± 4.8 vs. 24.1% ± 3.8, *P = 0.019) (Fig. 1). In the EX group, exercise during bed rest preserved both the early vasodilation response to ACh (37.3% ± 5.0 vs. 45.9% ± 9.6, NS) and the late vasodilation response to ACh (35.9 ± 6.7% vs. 41.9 ± 7.3%, NS) (Fig. 1). The maximal endothelium-independent vasodilation response to SNP was not significantly reduced by bed rest in the No-EX group (49.6 ± 7.9% vs. 41.0 ± 10.7%) and in the EX group (41.1 ± 9.9% vs. 42.9 ± 8.1%; Fig. 2).

Endothelial biological parameters: CECs. Bed rest induced a significant increase of CEC number in the No-EX group (3.6 ± 1.4 vs. 10.6 ± 2.7 ml⁻¹, *P < 0.05) (Fig. 3). Exercise appeared to prevent the increase of CECs in the EX group (2.6 ± 0.6 vs. 3.0 ± 0.7 ml⁻¹) (Fig. 3).

Table 1. General parameters

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<th>No-EX Group</th>
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<td>Before</td>
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<td>Mean arterial pressure, mmHg</td>
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<td>Iontophoresis</td>
<td>75.2</td>
<td>73.2</td>
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<td>Control Doppler, au</td>
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Values are means ± SE. Mean arterial pressure, laser-Doppler flow on the reference probe (control Doppler), and skin temperature in 8 subjects who performed no exercise (No-EX group, n = 8) and in 8 subjects who performed treadmill exercise regularly in lower body negative pressure chamber and resistive exercise (EX group, n = 8) during iontophoresis tests before and at the end of bed rest. au, Arbitrary units.
DISCUSSION

The present study shows both mechanistic and functional impairment of endothelial function after prolonged physical inactivity induced by long-term bed rest in humans without other cardiovascular risk factors. We observed an alteration of endothelium-dependent vasodilation of the microcirculation after 2 mo of bed rest. Moreover, this study showed that this endothelium dysfunction is associated with an increase of CECs, which reflects endothelial injury. Importantly, we also demonstrated that regular physical exercise appeared to prevent both indexes of endothelial dysfunction.

Bed rest and microcirculatory endothelial dysfunction. Most of the studies about vascular impairment induced by bed rest have focused on large vessels only. Bonnin et al. (5) showed an enhancement of flow-mediated dilation (FMD) of the brachial artery after 1 wk bed rest in men without changes in endothelium-independent maximal dilation. Bed rest induces a general physical inactivity, but the arms are probably the least affected by this physical inactivity. Unilateral lower-limb unloading in humans reduces blood flow at the segmental level. With this model, after 4 wk, femoral basal diameter and blood flow were reduced, but there was no indication of a decrease in FMD response of the superficial femoral artery (2). Moreover, after 52 days of bed rest, FMD of the superficial femoral artery was increased (3).

Surprisingly, the enhancement of FMD response in deconditioned large arteries is evident within 3 wk to 2 mo of inactivity in bed rest studies in humans. This increased FMD response does not support the existence of endothelial dysfunction at the macrocirculation level. With the combination of the decrease in basal diameter and the decrease in basal blood flow, basal shear rate appears enhanced in large arteries by acute physical inactivity (13). The enhanced levels of resting shear rate might have important implications for the preservation of endothelial function. Shear stress levels are very different in large and resistive arteries (4). It therefore appears likely that the mechanisms and time course of vascular impairment to deconditioning might differ between large arteries and microcirculation.

Longer follow-up of humans regarding the microcirculation suggested an impairment of the endothelium with physical inactivity. For example, a correlation between intima media thickness at the carotid level and physical activity during leisure time has been demonstrated (33).

Although the microcirculation is the key area for regulation of flow to a given area, only a few studies have focused on bed rest and microcirculatory function. In the present study, we observed an impairment of endothelium-dependent vasodilation in the microcirculation induced by bed rest. Vascular smooth muscle vasodilator function was not impaired by bed rest, as shown by the preserved response to SNP (Fig. 2). Thus, in the cutaneous microcirculation, the endothelium appears specifically impaired after a 2-mo bed rest. The potential mechanisms of ACh-induced vasodilation after iontophoresis have been investigated in several studies. ACh-induced vasodilation appears as a bimodal response with an early and a late vasodilation. Durand et al. (16) showed that after a local cutaneous inhibition of the muscarinic receptors, no significant vasodilation was observed following ACh iontophoresis, suggesting that the bimodal vasodilatory response was specifically related to ACh. ACh-mediated dilation of human skin is only partially attenuated following nitric oxide (NO) synthase inhibition (10). In contrast to the limited contribution of NO, a large part of the response seems to be mediated by prostaglandins. More precisely, it has been shown that the late phase of the ACh response is a prolonged vasodilation under contribution of prostaglandins (16), contrary to the early phase that appears independent of prostaglandins and might thus be related to NO. In our study, it is only the late phase of the vascular response to ACh that is altered by bed rest in the No-EX group. The early response to ACh was preserved in both groups. This supports the hypothesis that the impairment of endothelial functions after chronic bed rest implies mainly the prostaglandin pathway. Moreover, we did not observe a significant decrease in the vasodilation response to local prolonged heating (the secondary plateau), which is related to NO (23, 30). This supports the hypothesis that the NO pathway is preserved after bed rest at the skin level. We used the iontophoresis method to be strictly noninvasive; however, this method has some limitations. When compared with other methods, such as microdialysis, it is preferable not to perform dose-response curves to ACh with iontophoresis to reduce nonspecific current effect. Thus we cannot presume the results that would be obtained after a higher dose of ACh delivery. Also, an axon reflex might contribute to the increase of cutaneous blood flow induced by iontophoresis, but this is limited by using low anodal current (10).

We specifically tested skin microcirculatory functions; however, functions of other microvascular beds are more difficult to study. Consistent with our work, but also studying global vascular functions at the arm level, another study suggested microcirculatory endothelial dysfunction induced by bed rest (19). After intra-arterial injection of ACh in the forearm vascular bed, an impairment of vasodilation after 13 days of immobilization was observed. Also, the maximal cutaneous vasodilator capacity in humans (cutaneous vasodilator response to local heating) is reduced at the level of the forearm after 14 days of head-down bed rest, together with a decrease in basal skin blood flow, indicating an impairment of the microcirculation (11). In our study, although it was not statistically significant, basal cutaneous blood flow tended to be lower after bed rest in the No-EX group. The reduction of endothelial vasodilator capacity could participate in the basal decrease in blood flow. In contrast to the study of Crandall et al. (11), we did not observe any change in maximal cutaneo...
ous vasodilation to heating in the present study. Methodological considerations have to be taken into account. We used a very local-heating probe at 44°C, restrained to the blood flow measurement area (4.15 cm²), whereas Crandall et al. (11) performed a regional heating of the entire forearm at 42°C, which could have more general effects on blood flow.

Taken together, data from the present study and from previous work are strongly supportive of the idea that bed rest from 13 days to 2 mo is sufficient to impair endothelial function at the microcirculatory level.

In our study, we observed an increase of CECs showing the disruption of endothelial integrity. Present in very low levels in “healthy” blood, increased numbers of CECs have been demonstrated in acute myocardial infarction, acute coronary syndromes, and critical limb ischemia (27, 32) and are probably the most direct evidence of severe endothelial damage. CECs might be desquamated, damaged, or dysfunctional endothelial cells (27). One study found a correlation between CECs and endothelium-dependent vasodilation levels measured by flow-mediated dilation in congestive heart failure (8), supporting the hypothesis that the increase of CECs is associated with endothelial dysfunction. These results are in accordance with our findings from the microcirculation where we observed an increase of CECs together with endothelial dysfunction. A chronic decrease in shear stress induces endothelial dysfunction and apoptosis. Cell culture studies demonstrated that an increase in shear stress inhibits apoptosis of endothelial cells in response to exogenous endothelium impairment (14). Bed rest may reduce shear stress via two factors: physical inactivity and hypovolemia (29). The chronic decrease in blood flow induced by bed rest might contribute to the increase in CECs by apoptosis. The higher level of shear stress occurs at the arteriolar level in normal conditions (4). It is very likely that physical inactivity reduced shear stress to a larger extent in microcirculation compared with the macrocirculation. Because dysfunction is mainly observed at the microcirculatory level, we could hypothesize that CECs mainly came from the microcirculatory area after acute physical inactivity.

Female sex hormones could have beneficial effects on the endothelium (37). However, at the microcirculatory level, it has been recently shown that the menstrual cycle had no effect on skin endothelial vasodilation tested with ACh iontophoresis (9). In our study, there is no statistical difference in the phase of the cycle between BDC-7 and HDT + 56. The effect of the menstrual cycle was very limited in our results compared with the bed rest effects.

**Countermeasures and microcirculatory endothelial dysfunction.** We performed a combination of countermeasures: resistive exercise and treadmill exercise within LBNP. The resistive exercise with flywheel has been extensively studied and has shown no effect on the cardiovascular system (1, 12). It seems that this type of exercise has very few effects on endothelial function. LBNP could act on the lower-limb skin. LBNP induces blood pooling at the lower part of the body, particularly in the skin. However, during LBNP, skin blood flow decreases at the skin level (39); thus this countermeasure is not likely to increase endothelial functions by itself. It was the aerobic exercise in this work that appeared to have the most beneficial influence on endothelial function. Aerobic exercise training has been shown to enhance endothelial-dependent vasodilation (20, 26). Cutaneous microcirculatory dilation to ACh iontophoresis increases after 8 wk of aerobic training at the forearm skin (38). Aerobic exercise training during a 14-day period of bed rest preserved cutaneous microcirculatory vasodilator function (11). Our data are also consistent with the idea that regular aerobic physical exercise can protect endothelial function.

**Microcirculatory endothelial dysfunction and bed rest-induced pathologies.** Reducing the influence of gravitational forces rapidly leads to a loss of adaptation or deconditioning of the human body to gravity. Both bed rest and weightlessness induce cardiovascular deconditioning with decrease in exercise capacity, increase in heart rate, and impairment of orthostatic tolerance. Many mechanisms are involved, such as vascular impairment, hypovolemia, decrease in left ventricular mass, changes in hormones or impairment of the autonomic nervous system (1).

Endothelial dysfunction of the microcirculation might participate in several bed rest-induced pathologies, such as muscle atrophy, changes in energy metabolism, and skin ulcers formation. A decrease in maximal VO₂max is a symptom of cardiovascular deconditioning (17). Decreased maximal cardiac output and decreased absolute oxidative capacity of muscle cells both appear to contribute to this impairment of VO₂max. However, endothelial dysfunction with a decrease in microvascular vasodilation may also participate to this decrease of VO₂max.

In conclusion, in our present study, we showed in healthy humans that prolonged bed rest induces endothelial impairment in the microcirculation. Endothelial dysfunction at the microcirculatory site might contribute to cardiovascular deconditioning and to several bed rest-induced pathologies, such as muscle atrophy, changes in energy metabolism, and skin ulcer formation. The endothelial dysfunction at the microcirculation level could be an early influence of inactivity on vascular dysfunc-

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