Effects of 18 days of bed rest on leg and arm venous properties

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Abstract

Venous function may be altered by bed rest deconditioning. Yet the contribution of altered venous compliance to the orthostatic intolerance observed after bed rest is uncertain. The purpose of this study was to assess the effect of 18 days of bed rest on leg and arm (respectively large and small change in gravitational gradients and use patterns) venous properties. We hypothesized that the magnitude of these venous changes would be related to orthostatic intolerance. Eleven healthy subjects (10 men, 1 woman) participated in the study. Before and after 18 days of 6º head-down tilt bed rest, strain gauge venous occlusion plethysmography was used to assess limb venous vascular characteristics. Leg venous compliance was significantly decreased after bed rest (pre: 0.048 ± 0.007 ml/100ml/mmHg, post: 0.033 ± 0.007 ml/100ml/mmHg, $p<0.01$), while arm compliance did not change. Leg venous flow resistance increased significantly after bed rest (pre: 1.73 ± 1.08 mmHg/ml/100ml/min, post: 3.10 ± 1.00 mmHg/ml/100ml/min, $p<0.05$). Maximal LBNP tolerance, which was expressed as cumulative stress index (pressure · time), decreased in all subjects after bed rest (pre: 932 mmHg·min, post: 747 mmHg·min). The decrease in orthostatic tolerance was not related to changes in leg venous compliance. In conclusion, this study demonstrates that after bed rest, leg venous compliance is reduced and leg venous outflow resistance is enhanced. However these changes are not related to measures of orthostatic tolerance; therefore alterations in venous compliance do not to play a major role in orthostatic intolerance after 18 days of head-down tilt bed rest.

Keywords

Venous compliance, venous flow resistance, lower body negative pressure tolerance,
Strain gauge plethysmography

Introduction

Humans exposed to microgravity by bed rest or space flight show signs of “cardiovascular deconditioning”, including resting and orthostatic tachycardia (1), reduced exercise capacity (1, 8, 9, 13, 21), and orthostatic intolerance (1). Several potential causes for orthostatic intolerance have been described, such as hypovolemia (1, 17), cardiac changes resulting in lower stroke volume (29), diminished vasoconstrictor capacity (4), and diminished autonomic reflex function (24, 34). While venous hemodynamics play an essential role in cardiovascular homeostasis and are critical in determining venous return and thus cardiac filling and stroke volume (42), their role in orthostatic intolerance after bed rest and space flight in humans remains unclear.

Recent studies in hindlimb-unloaded rats have shown an increase in systemic and mesenteric venous compliance and attenuation of the effect of norepinephrine on the reservoir function in these capacitance beds (14, 15). These studies suggest that altered venous hemodynamics may contribute to the excessive reduction in stroke volume in the upright posture, observed universally after microgravity exposure. In humans, previous studies of venous vascular properties in the leg after bed rest or spaceflight show conflicting results, with some studies reporting an increase in leg compliance (5, 12, 33), others reporting no changes (2, 16, 35, 49), and one study reporting a decrease (7). In only three of these studies orthostatic tolerance or lower body negative pressure (LBNP) tolerance was examined (2, 16, 35), and none of the studies addressed the relationship between changes in venous compliance and changes in orthostatic tolerance. If such a relationship is present it is possible to assess whether changes in venous compliance play a detrimental or beneficial role in the pathogenesis of post bed rest orthostatic intolerance. In contrast to subjects after bed rest or spaceflight, patients with a spinal cord injury, and thus severe prolonged deconditioning, clearly have decreased venous compliance (25). This adaptation has been hypothesized as being an important adaptive mechanism, which may protect these patients, with lack of supraspinal sympathetic control, from orthostatic hypotension.

It is unclear whether the adaptations in the venous system of the leg in humans reflect a generalized systemic adaptation of the venous vasculature, similar to that observed in animals, or rather a regionally specific phenomenon related to altered hydrostatic gradients or to disuse atrophy. We reasoned that for upright humans, since hydrostatic forces and use patterns differ between the legs and the arms, the adaptation of these vascular beds to microgravity may differ and thus may be used to distinguish between local versus generalized “deconditioning effects”. If a systemic effect is present then generalized venous changes, for instance in the mesenteric region may importantly alter orthostatic tolerance. In a recent study a limited, but significant effect of pelvic venous pooling on LBNP tolerance was shown (22). The aim of this study therefore was to assess changes in venous properties (capacitance, compliance, and venous flow resistance) of the leg and arm before and after 18 days of strict head-down tilt bed rest in healthy subjects. In addition, we hypothesized that there would be a direct, linear relationship between changes in venous vascular properties and changes in LBNP tolerance.

Methods

Subjects.

Eleven healthy subjects (10 men, 1 woman) participated in the study after providing written informed consent. These subjects represent a subset of subjects whose information regarding cardiac compliance (29) and regulation of muscle sympathetic nerve activity (39) has been reported previously. Their mean age was 24 ± 6 years (range 18 to 33), height averaged 178 ± 4 cm, and weight 79.1 ± 9.7 kg. Subjects did not smoke, did not use recreational drugs, and had no significant medical problems as determined by medical history and a comprehensive physical examination. Body composition was obtained by use of standard underwater weighting techniques (46). None of the subjects was endurance-trained and subjects were excluded if they exercised more than three times a week for more than 30 minutes with either dynamic or static exercise. The study was approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas.

Procedures

Bed rest protocol. After the initial series of experiments, subjects were placed at complete bed rest, with 6° head-down tilt. The subjects were allowed to elevate on one elbow for meals, but otherwise were restricted to the head-down position at all times. They were housed in the General Clinical Research Center at the University of Texas Southwestern Medical Center and they were given a standard diet, consisting of 2857 ± 629 cal/day including 5.3 ± 1.2 g/day of sodium. Fluids were allowed ad libitum, but all fluid intake and urine output was carefully recorded. The same series of experiments were repeated after 18 days of bed rest.

Lower body negative pressure. LBNP was achieved by placing the subject in a Plexiglas box, sealed at the level of the iliac crest. Suction was provided by vacuum pump controlled with a variable autotransformer.

Experimental conditions and protocol. Mercury strain gauge venous occlusion plethysmography (3, 51) was used to assess leg and arm venous vascular characteristics. For pre and post bed rest measurements, subjects were placed in the supine position with the leg and arm slightly elevated 15-20º above heart level. Subjects were supine for 20-30 minutes before the start of the measurements. They were not allowed to sleep before or during data collection. After instrumentation of the subject, test procedures were started with a venous occlusion of 20 mmHg, followed by subsequent cuff-pressures of 40 mmHg, 60 mmHg, and 80 mmHg. The effective pressure on the venous system was estimated as 0.8 times the cuff pressure (3). The occlusions at 20, 40, 60, and 80 mmHg were sustained for 1, 2, 3, and 4 minutes, respectively. One-minute breaks between occlusions allowed for new baseline formation and prevented excessive edema formation. This protocol was designed with relatively short venous occlusions to emphasize assessment of the venous contribution to calf and arm compliance rather than capillary filtration, as has been reported previously (49). Based on pilot data the protocol allowed us to achieve a plateau in virtually all cases. In six subjects, studied 3-4 times over a period of one year, the typical error of this measurement (calculated as coefficient of variation) was 9.6%.

Maximal orthostatic tolerance was measured using a ramped LBNP test, as described earlier (29). In short LBNP started at –15 mmHg and then increased to –30 and –40 mmHg for 5 minutes each, followed by an increase in LBNP by –10 mmHg every 3 minutes until signs or symptoms of presyncope were achieved. Presyncope was defined as a decrease in systolic blood pressure below 80 mmHg; or a decrease below 90 mmHg with symptoms of lightheadedness, nausea, or diaphoresis; or progressive symptoms of presyncope causing the subject to request a discontinuation of the test. True hemodynamic end points were reached in 95% of the tests. The cumulative stress index (CSI, mmHg·min) was calculated as the sum of the product of negative pressure and duration at each level of LBNP and was used as a continuous measure of orthostatic tolerance.

Measurements

Venous occlusion plethysmography. Mercury-in-silastic strain gauges were stretched around the largest girth of the right calf and forearm. Thigh and upper arm pressure cuffs were connected to a rapid cuff inflator (Model EC-4, Hokanson, Bellevue, Washington, USA) to ensure rapid and accurate filling and deflating of the cuff. Data signals were amplified and printed on a strip chart recorder (Astromed) after which they were analyzed manually. A typical individual venous occlusion curve and pressure-volume curve are illustrated in figure 1. From the plethysmographic recordings the following parameters were calculated, the method of analysis of recordings was described in detail elsewhere (25). Briefly, venous volume variation (VVV in ml/100ml) was defined as the maximal relative volume increase in the limb at a certain cuff pressure; VVV at different occlusion pressures represents the pressure-volume curve. Compliance (ml/100ml/mmHg) was derived from the slope of the pressure-volume curve. Venous emptying rate (VER in ml/100ml/min) was calculated as the slope of the tangent at the curve 0.5 seconds after cuff release (3). The time 0.5 s after cuff deflation was chosen to avoid any cuff artifact. The effective pressure of the cuff on the venous system at 0.5 s was calculated by using the pressure-volume curve (3). A pressure-emptying (PE) curve was then drawn, indicating the relationship between effective cuff pressure and the venous emptying rate. Venous flow resistance (VFR mmHg/ml/100ml/min) was calculated, by analogy with Ohm's Law, as 1 divided by the slope of the pressure-emptying curve (3).

Limb volume. Leg and arm circumferences were measured at fixed positions before and after the bed rest period. Total limb volume was then calculated using a Simpson's rule type of summation of multiple disks, as described by Thornton (47, 48).

Statistics.

For each individual subject compliance and venous flow resistance were determined from the individual pressure-volume and pressure-emptying curve. Variables were compared before and after bed rest with a paired student t-test using SPSS 10.0 computer software (SPSS Inc., Chicago, Illinois, USA). Data are presented as means ± SD. The pressure-volume and pressure-emptying curves present means ± SEM. To test for a linear relationship between changes in leg compliance and changes in LBNP tolerance a linear regression analysis was performed. The statistical significance level was set at 5%.

Results

Body mass and limb volume (n=10)

Body mass and limb volume before and after bed rest are presented in table 1. Data are from 10 subjects, because of missing data post bed rest of one subject. After 18 days of head-down tilt bed rest total body mass was unaltered, but average lean body mass decreased significantly by 1.9 kg. Arm and leg volume did not change during the bed rest period.

Insert Table 1

Venous volume variation and compliance

Venous volume variations of the arm and leg are presented in table 2. Figure 2 depicts the pressure-volume curves and their slopes, which define compliance. Venous volume variation of the leg was significantly lower at any given occlusion pressure after bed rest compared with pre bed rest, whereas no differences in venous volume variation could be observed in the arm. Compliance of the venous system of the leg was significantly decreased after 18 days of bed rest (pre: 0.048 ± 0.007, post: 0.033 ± 0.007 ml/100ml/mmHg, $p<0.01$) and did not change in the arm (pre: 0.065 ± 0.014, post: 0.064 ± 0.016 ml/100ml/mmHg).

Insert Table 2 and Figure 2

Venous flow resistance

Venous flow resistance (the inverse of the slope of the pressure-emptying curve; fig. 3) increased significantly in the leg after the bed rest period (pre: 1.73 ± 1.08

mmHg/ml/100ml/min, post: 3.10 ± 1.00 mmHg/ml/100ml/min, $p<0.05$) and did not change in the arm (pre: 1.22 ± 0.32 mmHg/ml/100ml/min, post: 1.26 ± 0.64 mmHg/ml/100ml/min). Venous flow resistance data are from 10 subjects due to insufficient data from one subject.

Insert Figure 3

LBNP tolerance and its relation with leg venous compliance

LBNP tolerance, expressed as cumulative stress index, was reduced post bed rest compared to pre bed rest in all subjects (pre: 931.6 ± 381.7 mmHg·min, post: 746.9 ± 238.7 mmHg·min, $p<0.01$).

The relation between changes induced by bed rest in leg venous compliance and changes in LBNP tolerance are depicted in figure 4. Simple linear regression resulted in a correlation coefficient of 0.43, the R square was 0.19, the F-test had a significance of 0.183. Therefore, the correlation coefficient is not significantly different from 0 and in this dataset there is no proof that a correlation is present.

Insert Figure 4

Discussion

The primary new findings from the present study are: 1) 18 days of strict head-down tilt bed rest caused a significant reduction in venous volume variations, a decreased venous compliance, and an increased venous outflow resistance in the leg, while no changes occurred in the venous vascular properties of the arm; 2) In this data-set no clear relationship could be detected between changes in leg venous compliance after head-down tilt bed rest and the induced reduction in orthostatic tolerance.

The results of our study indicated a significant reduction of about 30% in leg venous compliance after bed rest exposure and a significant reduction in venous volume variation, ranging from -34 to -54% depending on the cuff pressure applied. Bed rest can influence venous characteristics by several mechanisms. We will first focus on several mechanisms that can explain a decrease in venous compliance. Later on in the discussion we will examine potential explanations for different outcomes between this and other studies.

Possible mechanisms for a reduction in leg compliance with bed rest

First, bed rest is an extreme form of physical inactivity. Several studies have shown that calf venous compliance is decreased in sedentary subjects compared to endurance-trained athletes (32, 36). Some investigators have argued that physical activity affects venous compliance mainly through changes in the venous vessel wall, and less by changes in calf muscle mass (36). This interpretation is in accordance with the observation in the present study of significant changes in venous compliance in the absence of changes in leg volume and probably only minor changes in leg muscle mass. In other bed rest studies, muscle atrophy was more prominent and this may in part explain differences between studies as is discussed further below. Other investigators have also shown that calf compliance is decreased in sedentary compared to active subjects, and is even more decreased in spinal cord injured individuals (50). A spinal cord injury leads to muscle paralysis below the level of injury and may be considered as ‘a model of nature’ for extreme inactivity. One study investigating venous vascular function in chronic spinal cord injured patients observed a 50% reduction in lower limb venous compliance compared with able-bodied individuals (25). Even when such patients have been studied in a relatively early phase, i.e., 8 weeks, after the injury, a 30% reduction in leg venous compliance in spinal cord injured patients compared with healthy controls has been observed (19). Together these data provide convincing evidence that inactivity causes decreased venous compliance.

Second, head-down tilt bed rest not only reduces physical activity, but also alters gravitational gradients within the circulation which may have effects on venous vascular function both directly via hydrostatic forces, and indirectly via cardiovascular reflex responses. For example, in the upright posture in humans, hydrostatic forces exerted on leg veins are considerably higher than the hydrostatic forces affecting arm veins. The specific venous vascular effect of microgravity is therefore likely to be more pronounced in leg veins. In this study 18 days of strict bed rest deconditioning induced no significant differences in arm venous vascular properties, arguing against a systemic effect of bed rest deconditioning on the venous system. These findings are in agreement with the results of an earlier study (2), which showed no significant changes in arm venous compliance during a less strict 20-day bed rest regime. Similarly, a recent study reported diminished venoarteriolar responses in the skin of the legs after 14 days of head-down bed rest, while venoarteriolar responses in the arm were unchanged (52). This differential response provides further evidence that vascular function may be affected differently by head-down bed rest in the leg and in the arm due to either marked differences in the change in hydrostatic gradients, or possibly to differences in the changes in activity patterns in the upper versus lower limbs.

Another adaptation to the upright posture may be greater alpha-adrenergic receptor sensitivity in arteries of the leg than in the arteries of the arm (38). Moreover, as a result of sympathoexcitation via the muscle pressor reflex, pressure-volume curves in the arm and the leg are shifted downward, with no effect on compliance; thus the unstressed volume is decreased by sympathetic activation, while the distensibility is unchanged (23). Finally epinephrine and norepinephrine cause venoconstriction in the human forearm and alpha-adrenoreceptor antagonists have been shown to increase forearm venous compliance (37). Furthermore, spaceflight and hindlimb unloading have been shown to decrease sensitivity to norepinephrine in alpha-1 adrenoreceptors in the rat vena cava (43). In a study by Wecht et al. a relationship between sympathetic vasomotor tone and venous compliance was shown for spinal cord-injured individuals and sedentary and active controls, with the most active subjects having the highest compliance (50).. In addition, Fu has reported a negative correlation between baseline muscle sympathetic nerve activity and leg venous compliance and a negative relationship between changes in muscle sympathetic nerve activity and changes in leg venous compliance (20). Thus when sympathetic activity increases leg compliance decreases. Together these findings suggest, but do not prove, that the sympathetic nervous system can affect venous vascular function, and may provide a unifying mechanism for the wide variation in observations after bed rest and spaceflight. For example, data from the first and second Space Lab Life Sciences Program (SLS-1 and SLS-2) have demonstrated that during quiet standing after spaceflight, there was less, rather than more pooling of blood in the lower extremities (4).

Subsequently, the Neurolab investigators (28) showed that sympathetic nerve activity directed to the skeletal muscle of the lower limb is increased in both the supine and upright positions after spaceflight, which could cause venoconstriction and therefore limit venous pooling. Although the resting sympathetic nerve activity was changed only minimally in the subjects reported in the present study (39), a wide range of alteration in resting sympathetic nerve activity by microgravity has been reported in the literature including a decrease (44), increase (26, 34, 45), and no change (39). We speculate that alterations in sympathetic nerve activity may be different among these studies, and that these alterations explain at least part of the differences in leg venous vascular properties. Assessment of venous characteristics during sympathetic activation before and after bed rest may provide additional insight, but was not possible using our study design.

Whether venous characteristics play an important role in the complex pathogenesis of orthostatic intolerance is still unclear. Some investigators have observed a decreased compliance in patients with idiopathic orthostatic intolerance. However, it is not clear whether these changes are beneficial or not (18). Similarly the role of a decrease in compliance in the pathogenesis of post bed rest orthostatic intolerance is unclear. The venous system serves as a reservoir for adjustment to cardiovascular change. While a decrease in compliance may protect from venous pooling during standing, it also limits the reservoir function and thus the volume that can be mobilized by sympathetic stimulation or the muscle pump. Thus in our opinion the changes in compliance and venous volume variation reflect adaptations to microgravity and deconditioning, but these changes may be more or less beneficial, depending on the specific circumstances. However, the absence of a relationship between changes in compliance and changes in orthostatic tolerance in this study suggests neither a beneficial nor a detrimental role for venous characteristics of the leg in orthostatic intolerance following simulated microgravity. This absence of a relationship between changes in compliance and changes in orthostatic tolerance is in accordance with a study by Engelke, who demonstrated a decrease in orthostatic tolerance after bed rest in the absence of changes in leg venous compliance (16).

The fact that we only used simple linear regression for the assessment of the role of changes in leg venous compliance in the development of post bed rest orthostatic intolerance leaves the possibility that there may be a role for venous changes, but that this role is overridden and masked by changes in other factors such as cardiac function and blood volume. However, if changes in venous compliance would play a dominant role in the pathogenesis of post bed rest orthostatic intolerance, then linear regression should have provided a significant result. Although we did not assess the role of abdominal or pelvic venous function, the absence of changes in venous compliance in the arms argues against systemic effects of bed rest on the venous system. Therefore, it is unlikely that systemic venous alterations contribute to orthostatic intolerance after bed rest.

Venous flow resistance, which indicates venous elasticity and resistance to venous flow, increased by almost 80% in this study. Data on effects of bed rest on venous emptying parameters are scarce. Louisy et al. reported an increase of approximately 30-50% in half emptying time after bed rest, which suggests increased venous flow resistance despite an increase in venous compliance (30, 33). In one of these studies venous emptying rate at 6 seconds after cuff release was reported to be increased (30); however this can not be compared to our data which reflect early (0.5 s) and not late venous emptying (6 s). Early venous emptying may be a passive effect based on elastic recoil of the venous wall, while late venous emptying may be an actively regulated process (40). In accordance with our results, venous emptying rate at 0.5 s has been reported to be significantly lower in the spinal cord injured population (25, 50), with an almost doubled venous flow resistance (25). It has been postulated that this is due to decrease in venous cross sectional area as a result of venous atrophy (25).

Comparison with previous bed rest and space flight studies

Differences in outcome among bed rest and space flight studies may be explained by several factors, in addition to the already discussed variation in sympathetic nerve activity changes. One additional explanation for the reported differences may be related to subject selection. Our subjects were essentially completely sedentary prior to the study. None of the other studies reported on the fitness status of their subjects, except for one study by Louisy et al. (31). In that study the subjects were very well trained divers and a great increase in compliance of 108% after bed rest was reported. In prior studies, increased compliance has been shown to be correlated to reduction in calf muscle volume (10, 12), and muscle atrophy has been postulated as an explanation for increased compliance, resulting in orthostatic intolerance in some (5, 6, 10-12, 33), but not all (27) studies. However, in the present study no leg or arm volume changes were observed during the bed rest period, indicating only minor muscle atrophy. Muscle atrophy after bed rest will likely be more pronounced in trained athletes. If other studies included subjects that were well trained and had more calf muscle volume, muscle atrophy may have had a disproportionately great influence on compliance and may have obscured other changes in calf venous properties favoring a decrease in compliance. In two separate studies

Louisy and colleagues have shown that after an initial rise, compliance began to decrease after 20 or 26 days of bed rest (30, 33). While changes in compliance were related to changes in leg volume during the first 28 days, this relation was absent when compliance began to decline. We speculate that the initial rise may have been related primarily to prominent muscle atrophy in relatively trained subjects. After this atrophy had plateaued, the subsequent decrease in compliance reflected the primary effect of reduced hydrostatic gradients and vascular "deconditioning". Additional support for this speculation can be found in a bed rest study of 118 days in subjects who were specifically selected by an extended physical examination of the Russian Space Agency and showed a decrease in venous compliance (7). This study provides further evidence that even in well-trained subjects during induced deconditioning, after an initial increase, venous compliance will decrease due to factors other than muscle atrophy.

Another explanation for differences among studies may be related to methodological differences in determining venous vascular properties. We chose this specific method because it makes our data directly comparable to the data from the SLS spacelab missions. Since our plethysmography method represents a more classical approach, it was modified to minimize the shortcomings that were recently addressed in a paper introducing a new method to measure venous compliance (23). Our method has been shown to be reproducible over prolonged periods of time with a typical error of measurement of <10%. The present study was designed to measure venous volume variation at multiple occlusion pressures, so we were able to construct pressure-volume curves and report true compliance, without the assumption of a venous pressure of zero at cuff pressure zero. Several studies (2, 11, 12, 30) measured venous volume variation at only one occlusion pressure. When a pressure-volume curve is constructed from measurements at multiple occlusion pressures the line of best fit often does not intersect the y-axis at zero, and the slope of this line represents compliance. Simply dividing the volume variation at one cuff pressure by that cuff pressure may easily over- or underestimate compliance. In a recent paper Risk argues for a biphasic or exponential approach to compliance analysis(41). However in this paper the linear model is described as a reasonable model, and as a good model for pressures between 25 and 45 mmHg. Based on the overall data presented in figure 2 A we are confident that a biphasic or exponential analysis of data would not have altered our conclusions.

In several studies (5, 30, 31, 33) the end of venous occlusion was defined as the volume change reaching a plateau. If prolonged occlusion periods are used to reach a plateau, and the slow volume increase at the end of the filling curve is only due to interstitial fluid accumulation, then compliance may be overestimated. Furthermore, if capillary filtration is increased after bed rest as was shown in a previous study (7) compliance is even further overestimated. In the present study breaks between occlusions allowed for new baseline formation to prevent unwanted effects of long maintained high venous pressures, such as edema formation and vascular wall “creep”. The protocol was designed with relatively short venous occlusions to emphasize venous contribution to volume variation rather than capillary filtration (49). With this protocol we managed to achieve a plateau in most of the cases. This plateau in limb volume represents a steady state between arterial inflow and venous outflow, therefore a decreased leg blood flow, as has been reported previously post bed rest (33) can not have caused an underestimation of venous compliance in the present study.

In conclusion we have demonstrated that 18 days of strict head-down tilt bed rest reduces venous volume variation and venous compliance in the legs, and increases venous outflow resistance. The fact that no such changes were observed in the arms suggests that this change is a direct effect of altered hydrostatic gradients and/or changes in physical activity rather than a systemic effect of bed rest deconditioning on the venous vascular system. We were unable to relate any changes in leg venous vascular properties to measures of orthostatic tolerance and thus conclude that, similar to findings after spaceflight, alterations in venous compliance do not play a major role in orthostatic intolerance after head-down tilt bed rest.

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Figure legends

Fig. 1. A: venous occlusion curve, B: individual pressure-volume (P-V) curve of the leg, C: individual pressure-emptying (P-E) curve of the leg.

Venous volume variation (VVV in ml/100 ml) is the volume increase at a certain occlusion pressure. Multiple VVV form a pressure-volume curve. Compliance is then derived from the slope of this curve. Venous emptying rate (VER ml/100ml/min) is derived from the tangent 0.5 s after cuff release. One divided by the slope of the pressure-emptying curve represents venous flow resistance (VFR mmHg/ml/100ml/min). Pv is the effective pressure on the venous system, Pv 0.5 is the effective pressure 0.5 seconds after cuff deflation.

Fig. 2. Pressure-volume curves for the leg and the arm pre and post bed rest. Venous volume variations (VVV) are depicted with SEM. (Pv) is venous occlusion pressure. Venous compliance (Vc ml/100ml/mmHg) decreased in the leg, but not in the arm (** $p< 0.01$).

Fig. 3. Pressure-emptying curves for the leg and the arm pre and post bed rest. Venous emptying rates (VER) are depicted with SEM. Pv 0.5 seconds is venous pressure 0.5 s after cuff release. Venous flow resistance (VFR mmHg/ml/100ml/min) was calculated as one divided by the slope of these curves, and increased in the leg, but not in the arm. Data are of ten subjects. * $p < 0.05$

Fig. 4. Relationship between changes induced by bed rest in leg venous compliance and changes in lower body negative pressure (LBNP) tolerance. There is no significant relationship between these changes.

Table 1. *Body mass an limb volume before and after bed rest*

Variable	Before bed rest	After bed rest
Body mass, kg	78.7 ± 10.1	78.6 ± 10.8
Lean body mass, kg	63.5 ± 6.3	61.6 ± 6.6 *
Limb volume arm, ml	906 ± 116	909 ± 119
Limb volume leg, ml	9610 ± 1059	9738 ± 1160

Values are means ± SD. Data are from 10 subjects. * $p < 0.05$

Table 2. *Venous Volume Variations of the arm and the leg before and after bed rest*

Pc (Pv), mmHg	VVV leg, ml/100ml/min		VVV arm, ml/100ml/min	
	Before bed rest	After bed rest	Before bed rest	After bed rest
20 (16)	1.14 ± 0.39	0.75 ± 0.25**	1.74 ± 0.43	1.63 ± 0.31
40 (32)	2.14 ± 0.76	1.28 ± 0.37**	3.09 ± 0.64	3.02 ± 0.83
60 (48)	2.80 ± 0.67	1.80 ± 0.45**	4.11 ± 0.78	4.01 ± 0.83
80 (64)	3.50 ± 0.69	2.31 ± 0.48**	4.87 ± 0.86	4.69 ± 0.94

VVV is venous volume variation, Pc is cuff pressure, (Pv) is venous pressure. Values are means ± SD. ** $p < 0.01$

Figure 1.

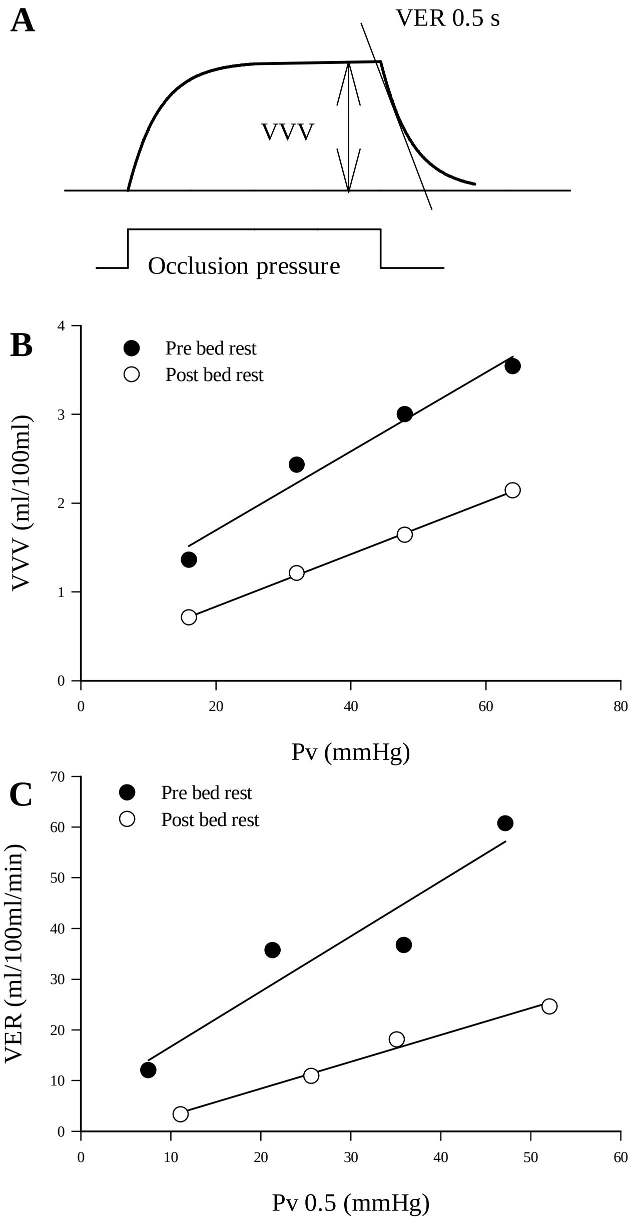

A
VER 0.5 s
VVV
Occlusion pressure
B
Pre bed rest
Post bed rest
VVV (ml/100ml)
0
1
2
3
4
0
20
40
60
80
Pv (mmHg)
C
Pre bed rest
Post bed rest
VER (ml/100ml/min)
0
10
20
30
40
50
60
70
0
10
20
30
40
50
60
Pv 0.5 (mmHg)

Figure 2.

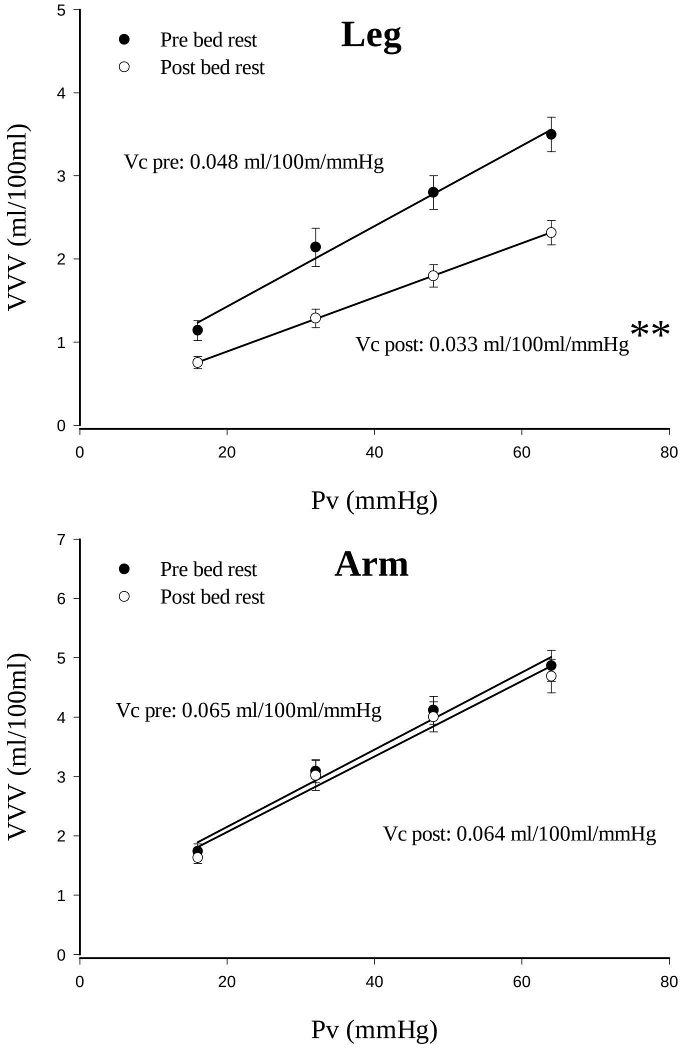

Leg
● Pre bed rest
○ Post bed rest
Vc pre: 0.048 ml/100m/mmHg
Vc post: 0.033 ml/100ml/mmHg**
VVV (ml/100ml)
0
1
2
3
4
5
0
20
40
60
80
Pv (mmHg)
Arm
● Pre bed rest
○ Post bed rest
Vc pre: 0.065 ml/100ml/mmHg
Vc post: 0.064 ml/100ml/mmHg
VVV (ml/100ml)
0
1
2
3
4
5
6
7
0
20
40
60
80
Pv (mmHg)

Figure 3.

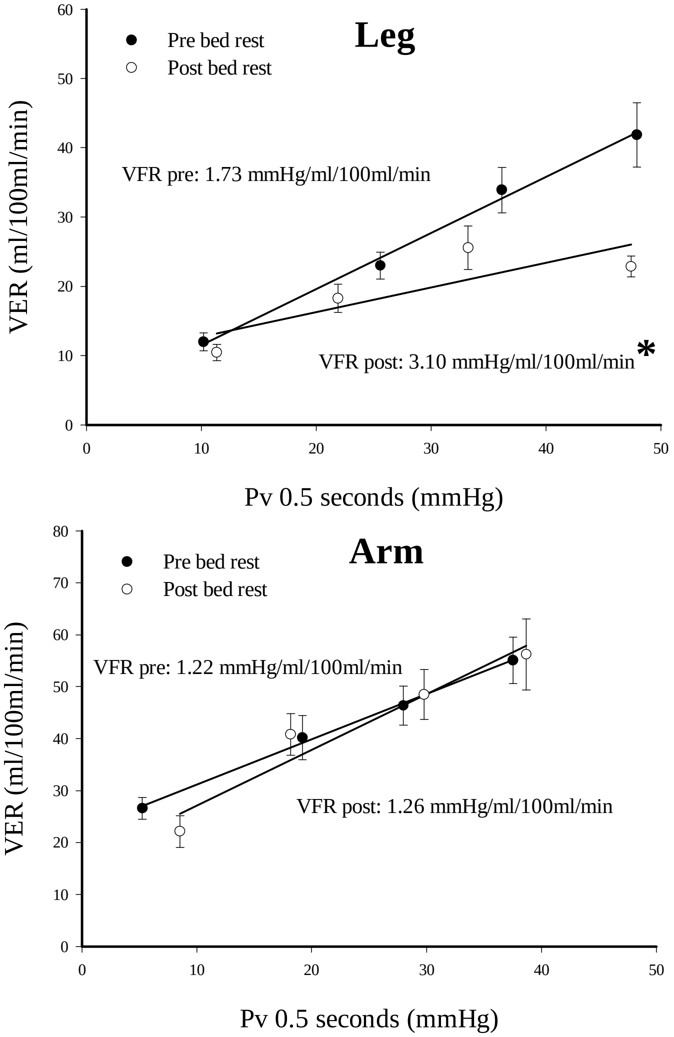
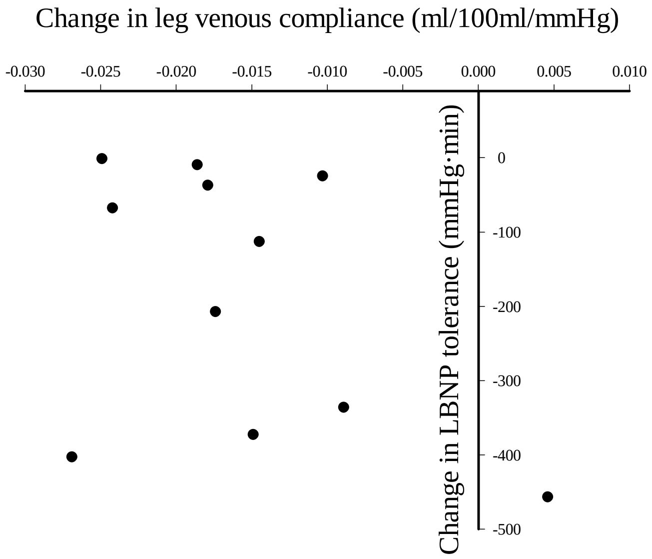

Leg
Pre bed rest
Post bed rest
VFR pre: 1.73 mmHg/ml/100ml/min
VFR post: 3.10 mmHg/ml/100ml/min *
VER (ml/100ml/min)
0
10
20
30
40
50
60
0
10
20
30
40
50
Pv 0.5 seconds (mmHg)
Arm
Pre bed rest
Post bed rest
VFR pre: 1.22 mmHg/ml/100ml/min
VFR post: 1.26 mmHg/ml/100ml/min
VER (ml/100ml/min)
0
10
20
30
40
50
60
70
80
0
10
20
30
40
50
Pv 0.5 seconds (mmHg)

Figure 4.


Change in leg venous compliance (ml/100ml/mmHg)
-0.030
-0.025
-0.020
-0.015
-0.010
-0.005
0.000
0.005
0.010
Change in LBNP tolerance (mmHg·min)
0
-100
-200
-300
-400
-500