Long-term bed rest-induced reductions in stroke volume during rest and exercise: cardiac dysfunction vs. volume depletion

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Spaak, Jonas, Stéphanie Montmerle, Patrik Sundblad, and Dag Linnarsson. Long-term bed rest-induced reductions in stroke volume during rest and exercise: cardiac dysfunction vs. volume depletion. J Appl Physiol 98: 648–654, 2005. First published October 22, 2004; doi:10.1152/japplphysiol.01332.2003.—Long-term head-down-tilt bed rest (HDT) causes cardiovascular deconditioning, attributed to reflex dysfunctions, plasma volume reduction, or cardiac impairments. Our objective with the present study was to evaluate the functional importance and relative contribution of these during rest and exercise in supine and upright postures. We studied six subjects before (baseline, during 6° HDT), during rest (HDT) causes cardiovascular deconditioning, attributed to reflex dysfunctions, plasma volume reduction, or cardiac impairments. Our objective with the present study was to evaluate the functional importance and relative contribution of these during rest and exercise in supine and upright postures. We studied six subjects before (baseline), during days 60 (D60) and 113 (D113), and after [recovery days 0 (R0), 3 (R3), and 15 (R15)] 120 days of −6° HDT. We determined cardiac output, stroke volume (SV), mean arterial pressure, and heart rate during rest and exercise in supine and upright postures. Cardiac output and SV decreased significantly in all four conditions, but the time courses differed for rest and exercise. Upright resting SV was decreased by 24 ± 9% at D60 compared with baseline but had recovered already at R3. Supine exercise SV decreased more slowly (by 5 ± 8% at D60 and by 18 ± 4% at D113) and recovered more slowly after HDT termination. Steady-state mean arterial pressure showed no changes. Heart rate had increased by 18 ± 4% at D60 and had recovered partially at R3. Our data indicate that long-term HDT causes both a rapid, preload-dependent reduction in SV, most evident during rest in the upright position, and a more slowly developing cardiac dysfunction, most evident during supine exercise. However, the ability to maintain blood pressure and to perform sustained low levels of dynamic exercise is not influenced by HDT.

ON EARTH, DAILY ACTIVITIES involve standing, frequent changes of posture, and various types of muscle action, all of which challenge the cardiovascular system. When the orthostatic stress is removed, as during spaceflight or head-down-tilt bed rest (HDT), these challenges are greatly reduced, and a number of adaptations to the new environment take place. These adaptations are generally termed deconditioning. As little as 4 h (2) of strict HDT may provoke orthostatic hypotension when the subject resumes an upright posture. Longer bed rest, lasting from a few days to weeks, consistently causes decreases in exercise capacity and cardiac performance, and most individuals show signs of orthostatic intolerance once HDT is terminated (11).

During the first days of HDT, urinary excretion of electrolytes increases and thirst decreases, causing a marked reduction in the circulating blood volume (11), most likely in parallel with a resetting of the cardiopulmonary baroreflex to a lower range of central venous pressures (6). Reductions in cardiac output and stroke volume develop and are particularly evident in the upright posture (22, 23) or during lower body negative pressure (17, 20). These reductions are to a certain extent due to the reduced blood volume (20, 22). However, during the past years, it has become increasingly evident that other mechanisms are also involved. Thus HDT has been shown to cause both myocardial impairments (18, 19, 22) and altered reflex control, for example, attenuated arterial baroreflex responses (5), which all may further worsen the cardiovascular function.

The physiological implications and relative contributions of these cardiovascular impairments have not yet been consistently defined after long-term HDT. Our objective with the present study was to determine, for the first time in the same group of subjects, and for the first time both during and after a HDT of a very long duration, whether the HDT-induced deconditioning affects subjects differently during exercise compared with rest, and in supine compared with upright postures.

We formulated a series of hypotheses. First, if cardiac performance becomes impaired by structural changes, stroke volume limitations would be most prominent during exercise in a supine position, which normally requires a larger stroke volume than either exercise in an upright position or rest. Second, if structural changes contribute to decreased cardiac performance, these changes would develop gradually over time. Third, if also a reduced cardiac preload impairs stroke volume and cardiac output, stroke volume reductions would be apparent at rest and in an upright position, when venous return is impeded by gravity and unaided by the peripheral muscle pump. Last, because reductions in plasma volume have been shown to develop within a matter of days during HDT (11), we hypothesized that stroke volume decrements caused by reduced preload would develop and recover relatively fast.

MATERIALS AND METHODS

The present 120-day HDT was conducted at the Institute of Biomedical Problems in Moscow, an organization with unique experience of long-term HDT, as a joint project of Institute of Biomedical Problems and the European Space Agency. HDT was conducted in a strict −6° HDT position to accelerate the initial adaptations and to mimic conditions during spaceflight.

HDT and experimental protocols were approved by the Russian National Committee of Bioethics at the Russian Academy of Sciences, and informed consent was obtained by all subjects before the study.

Subjects. Six subjects were studied and had the following characteristics: a mean age of 31 yr (range 23–42 yr), a mean height of 181 cm (range 175–190 cm), a mean weight before HDT of 80 kg (range 63–114 kg), and a mean weight after HDT of 83 kg (range 66–112

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kg). None had any history of cardiac or pulmonary disease, and all underwent an extensive medical examination before being included in the study. The studied group served as control in an experiment evaluating countermeasures to prevent muscle atrophy (26) and bone demineralization during HDT.

The study was performed in a quiet environment controlled at 24.5–25.5°C. Lights were turned on at 0700 and off at 2300. Sleep in the daytime from 0700 to 2300 was discouraged. The subjects were fed three meals daily at 0830, 1200, and 1800. Dietary intake was 2,300 to 2,500 kcal/day, and water intake was 1.0–1.5 l/day. Smoking and caffeinated beverages were prohibited.

During HDT, the subjects performed no exercise except for two 30-min periods of 50-W pedaling at days 60 and 113 (D60 and D113). Subjects received daily physiotherapy to prevent venous thrombosis in the legs and were free to assume prone, supine, or lateral postures. The total time in postures deviating from −6° HDT was 940 min/subject (0.5% of the total duration), of which 440 min (~4 min/day) was in +6° and the remaining time (~4 min/day) in positions between +30° and +90°.

The control [baseline data collection (BDC)] rest protocol was performed 1–2 wk before HDT, and the BDC exercise protocol was performed 1 wk before HDT. During HDT, experiments were performed on D60 and D113. On the day the HDT ended [i.e., recovery day 0 (R0)], experiments were performed <6 h after the subjects had risen from their beds. Thereafter, experiments were performed on days 3 (R3) and 14–17 (R15) of recovery.

Subjects were generally tested consecutively over 3 days, with one subject studied in the morning and one in the afternoon. Care was taken to preserve the same order and timing of the experiments between study days.

Experimental procedures. Experiments were performed with the subjects positioned on a tilt board, on which a cycle ergometer was mounted with the crank axis at the level of the heart in the supine position. The tilt board could be tilted rapidly between 0° (supine) and 90°. Half of the protocol was performed during rest with the subjects having their feet in a resting position below the pedals. The remaining half was performed during 50-W steady-state pedaling. While in the upright posture, subjects were supported by a bicycle saddle mounted on the tilt table. This support prevented unintentional leg muscle load during upright rest.

Before and after HDT, the subjects walked to the laboratory. During HDT, they were brought in lying on a gurney, and at R0 they came in a wheelchair. Immediately on arrival, they were transferred to the tilt table and equipped, in the supine position, with ECG electrodes, impedance-tape electrodes, and a Finapres finger cuff. During supine rest, data were collected after a minimum of 6 min of quiet and undisturbed supine rest. During upright rest, data were collected from the 20 s immediately before the cardiac output determinations (see Fig. 1), which took place after 1 min of rest in the upright position. The measurements were repeated twice in each posture. The time in the upright position for each measurement during rest never exceeded 2 min. The upright period was kept short to avoid confounding orthostatic hypotensive reactions and was well tolerated by all subjects.

After the rest protocol, a similar protocol was performed for steady-state 50-W dynamic leg exercise. During exercise, data were averaged between 1.75 and 2 min in the upright position (see Fig. 1). Measurements were repeated twice in each posture. The time in the upright position for each measurement during exercise was 2 min. The longer upright time was allowed because orthostatic reactions were considered less likely during dynamic leg exercise than at rest (23).

Cardiovascular measurements. Beat-by-beat heart rate (HR) was acquired from ECG chest electrodes with a combined amplifier and beat-by-beat tachometer (Biotach ECG, model 20-4615-65, Gould, Valley View, OH).

Arterial blood pressure was recorded continuously in the right middle finger with a photoplethysmographic device (Finapres type 2300, Ohmeda, Englewood, CO). The Finapres device has previously been shown to provide recordings of mean arterial blood pressure (MAP) in close agreement with concomitant invasive recordings (15). A fluid-filled tube coupled to a pressure transducer (Sensortechnics, Puchheim, Germany) provided continuous information on the difference in hydrostatic pressure between the finger cuff and a reference point at the intersection of a transverse line from the fourth intercostal space at the sternum to the midaxillary line (heart level). In the offline analysis, the beat-by-beat computation of MAP included a correction for the difference in hydrostatic pressure between the finger and the heart.

Transthoracic impedance was recorded from tape electrodes around the lower part of the thorax at the xiphoid level and at the base of the
neck. Transthoracic conductance (TTI⁻¹) was used as an index proportional to intrathoracic fluid volume (8).

Cardiac output and O₂ uptake were measured by a multiple-gas rebreathing technique, as described by Triebwasser et al. (25). The system used for rebreathing measurements consisted of a gas analyzer, a gas supply system, a valve fitted to a rebreathing bag, a flow meter, and a mouthpiece. The gas analyzer was a quadrupole mass spectrometer (QMG 420, Balzers, Liechtenstein), modified for respiratory measurements (Innovation A/S, Odense, Denmark). The gas mixture contained 0.63% C₂H₂, 0.3% C₁₈O, 5% Ar, 45% O₂, balance N₂. Washout periods between repeated rebreathings were at least 10 min during rest and 8 min during exercise. The rebreathing procedure was rehearsed several times during the pre-HDT (baseline) sessions using a slightly hyperoxic N₂-O₂ mixture and at least once before each test session, during which the amount of rebreathing gas was adjusted to the subject’s preferences (from 1.5 to 2.0 liters). O₂ uptake was computed from the linear fall of O₂ concentration in the lung-bag system during rebreathing, and the lung-bag system volume was determined by insoluble inert-gas dilution. The accuracy of this method is, by definition, not as high as that of methods that measure O₂ uptake over a longer period of time.

**Data acquisition and analysis.** HR, MAP, hydrostatic pressure difference, transthoracic impedance, and rebreathing gas concentrations were recorded and stored at a frequency of 100 Hz with a portable, personal computer-based data-collection system (Biopac MP100, with software AcqKnowledge 3.1, Biopac Systems, Goleta, CA). Beat-by-beat recordings were averaged offline (LABView 5.0, National Instruments, Austin, TX) for each subject and for the group of subjects, using the tilt time for time alignment, to create the group-averaged responses shown in Fig. 1. Pulse pressure was determined beat by beat from the difference between systolic and diastolic arterial pressure.

Analysis of the rebreathing procedures was performed offline with a program written in Pascal to calculate O₂ uptake and cardiac output. Stroke volume was then calculated as cardiac output/HR, and total peripheral conductance as cardiac output/MAP.

**Statistics.** Statistical analysis was performed with one-way repeated-measures ANOVA. In case of significance, Duncan’s post hoc test was applied (Statistica version 5.1, StatSoft, Tulsa, OK). Significance was accepted at P values of <0.05. Results are expressed as means ± SE.

**RESULTS**

All six subjects completed the HDT study. Continuously recorded hemodynamic variables reached steady state within the first 30–60 s after both up and down tilts, as illustrated by the group-averaged beat-by-beat recordings in Fig. 1. Values in this section are changes compared with BDC unless otherwise stated.

Steady-state MAP during both rest and exercise showed no consistent change during and after HDT (Fig. 2).

HR tended to increase during HDT in all conditions (Fig. 3A), with a marked increase for steady-state exercise in the upright posture, with +17.6 ± 3.8% at D60 and +20.4 ± 4.2% at D113. At R3, there was already a recovery halfway toward baseline values (+12.1 ± 4.2%), but no full recovery to BDC values occurred, not even at R15 (+9.1 ± 4.2%).

Stroke volume showed a marked decrease during HDT (Fig. 3B). At rest, the decrease was significant at D60 in both postures (supine −19.3 ± 6.5%; upright −24.1 ± 9.0%). During upright exercise, stroke volume decreased at D60 (−17.2 ± 5.5%) and showed a slight tendency to decrease further at D113 and R0. During supine exercise, stroke volume was unchanged between BDC and D60 (−4.7 ± 7.6%) but was lower than BDC at D113 (−18.2 ± 3.5%). There was a tendency to further decrease at R0 (−20.9 ± 4.3%). Stroke volume values at R0 were significantly lower than at D60, and at D113 they tended to be lower than at D60 (P = 0.05). After HDT, stroke volume showed a tendency toward recovery at R3, but this was less pronounced at R15, when stroke volume values during both supine (−15.4 ± 4.9%) and upright (−10.6 ± 6.5%) exercise remained significantly reduced compared with BDC.

The time courses of changes in cardiac output during HDT are presented in Fig. 3C. Cardiac output at rest was decreased at D60 compared with BDC (supine −14.5 ± 6.4%; upright −15.9 ± 11.2%) and tended to be decreased at D113 (supine −7.0 ± 6.1%; upright −8.4 ± 7.1%) and R0 (supine −7.2 ± 5.2%; upright −13.3 ± 7.0%). During exercise, both in supine and upright postures, there was a tendency for cardiac output to decrease at D60 (supine −2.6 ± 8.6%; upright −2.8 ± 5.8%). Cardiac output was decreased at D113 (supine −15.4 ± 4.1%; upright −11.3 ± 2.7%) and tended to be lower at R0 (supine −17.6 ± 4.6%; upright −13.3 ± 5.1%) than at BDC. During supine exercise, cardiac output at R0 was lower than at D60, and values at D113 tended to be lower than at D60 (P = 0.06). The pattern during recovery was similar to that of stroke volume.

The difference in cardiac output at rest between supine and upright postures remained fairly constant throughout the study; upright cardiac output averaged 67–74% of corresponding supine values. Upright cardiac output during exercise averaged 83–89% of supine cardiac output, and the difference between cardiac output in the two postures showed a gradual and significant decrease with time (P = 0.03) from 2.05 ± 0.44 l/min at BDC to 1.04 ± 0.18 l/min at R15.

Total peripheral conductance (Fig. 3D) showed decreases parallel to those of cardiac output and stroke volume during and after HDT.
During rest at BDC, TTI averaged 40.8 ± 1.8 mΩ⁻¹ in supine and 42.6 ± 1.6 mΩ⁻¹ in upright posture. TTI during rest was significantly decreased at R0 (supine -5.9 ± 2.0%; upright -5.6 ± 1.8%) but had recovered at R3. The time course of TTI during exercise showed a similar pattern, although there were no significant changes.

O₂ uptake before HDT averaged 833 ± 54 ml/min during supine exercise and 803 ± 44 ml/min during upright exercise. There were no changes during or after HDT.

Hemoglobin levels did not show any significant changes during HDT and averaged 151 ± 7.2 g/l at BDC, 147 ± 4.7 g/l at D60, 144 ± 4.5 g/l at R0, and 146 ± 5.5 g/l at R30.

DISCUSSION

With the present study, we extend the understanding of cardiovascular deconditioning after very long-term bed rest. For instance, the present HDT study lasted three times longer than the one previously reported by Sundblad et al. (23) and 4 wk longer than for the three subjects studied by Perhonen et al. (19).

Our principal findings were that stroke volume decreased both at rest and during exercise, in both upright and supine postures, and that resting upright stroke volume declined faster and recovered faster than stroke volume during supine exercise. Despite this, MAP and the ability to perform sustained dynamic exercise were preserved. A number of mechanisms may be responsible for bed rest-induced cardiovascular deconditioning. In the following, we will discuss these and their potential contributions to our findings.

Blood pressure control. Arterial blood pressure is the product of cardiac output and systemic vascular resistance. The levels of adrenergic hormones, endothelin, renin, angiotensin, vasoactive prostaglandins, nitric oxide, and several others all affect vascular resistance and may be altered after bed rest. Several of these systems are directly or indirectly controlled by the kidney, and 2 wk of HDT have been shown to, for instance, increase plasma renin activity and increase potassium excretion (13).

Baroreflex-mediated increases in peripheral vasoconstriction and HR are the principal mechanisms that defend arterial blood pressure during shorter orthostatic challenges (21). It is not clear whether long-term HDT impairs baroreflex control of blood pressure. Convertino et al. have demonstrated that vagally mediated carotid baroreflex responsiveness is reduced during rest in the supine position after 30 days of HDT (5), whereas Sundblad et al. have found maintained baroreflex responsiveness to rapid posture changes (tilting) during continuous, steady-state mild exercise (24). In the present study, the potential baroreflex alterations were not sufficient to change steady-state MAP, which was maintained at similar levels in all conditions throughout the study.

After HDT, the balance between cardiac and vascular responses to sympathetic stimuli may be shifted toward an increased β₁- and β₂-adrenoreceptor sensitivity without altered vascular α₁-responses. This pattern would lead to tachycardia and insufficient vasoconstriction in response to orthostatic stimuli (7). These cardiovascular responses would be even more compromising after spaceflight and HDT, which both cause a reduction in plasma volume (1, 10). Such a decrease in plasma volume can lead to impaired cardiac filling and decreased cardiac output and will, in turn, further compromise arterial blood pressure when upright posture is resumed on termination of HDT.

As already mentioned, in the present study, there were no reductions of steady-state MAP in the upright posture at any time during or after HDT, either during rest or during exercise. However, we did find a marked increase in HR during upright exercise consistent with an increased β-adrenoreceptor sensitivity. Exercise is a state with high sympathetic outflow, and marked peripheral vasoconstriction, locally antagonized by factors from the working muscles (21). Our findings indicate that, during brief periods of upright posture, peripheral vaso-
constriction maintains arterial pressure efficiently in the resting subject. In contrast, during the corresponding challenge in exercise, vasoconstriction alone is not sufficient, and an increase in HR is necessary. Moreover, during exercise, the working muscles will demand greater blood flow, which requires an increase in cardiac output, which will, in turn, necessitate an increase in HR, especially if stroke volume is reduced.

**Plasma volume loss and recovery.** During the first days of spaceflight or HDT, increased renal excretion of electrolytes and decreased thirst cause marked reductions in plasma volume; most of this reduction takes place during the first 1–3 days of HDT (10, 13, 16). After a few days to weeks of HDT, plasma volume stabilizes at a reduction of ~15% (11). Hypovolemia results in reduced cardiac preload and is thought to be the major explanation of the reduced orthostatic tolerance found after as little as 4 h (2) of HDT.

It is probable that the reduced plasma volume contributes to the cardiovascular deconditioning also after longer HDT, as in the present study. Unfortunately, due to unforeseen logistic problems, plasma volumes could not be measured during the present study. However, hypovolemia alone is not sufficient to explain cardiovascular deconditioning after longer HDT, as demonstrated by Perhonen et al. (20). They constructed Starling curves from pulmonary capillary wedge pressure and stroke volumes during lower body negative pressure and saline loading in seven men before and after 2 wk of ~6° HDT and after the acute administration of intravenous furosemide. They concluded that HDT causes left ventricular remodeling, leading to a greater decrease in stroke volume during orthostatic stress after bed rest than hypovolemia alone, potentially contributing to orthostatic intolerance.

Interestingly, two previous bed rest studies of durations of 28 and 42 days have shown not only a very fast recovery of plasma volume after HDT but also an overshoot exceeding baseline levels after 7 (10) to 13 days (16) of recovery. This overshoot, which will increase preload, might be a means of compensating for cardiac limitations (18, 19) and impaired vascular function (6) and might explain the rapid, but only partial, recovery that we found in HR, cardiac output, stroke volume, and total peripheral conductance already at R3 (Fig. 3). The rapid plasma volume recovery and possibly overshoot are supported in the present study by the decrease in TTI\(^{-1}\), an index of central blood volume, immediately after HDT at rest and its recovery at R3.

**Exercise.** Long-term HDT has consistently been shown to reduce supine and upright exercise capacity (4). Furthermore, skeletal muscle atrophy (particularly in postural musculature) is common after HDT. The subjects in the present study showed signs of atrophy in soleus muscle biopsies at days 58 and 117 of HDT (26).

In the present study, we used a fairly low level of dynamic exercise (50-W pedaling). At this exercise level, the potential muscular changes did not significantly alter \(O_2\) consumption, indicating a maintained efficacy of the exercising muscles. Also, the subjects’ ability to perform this sustained low-level dynamic exercise remained intact. However, it is also possible that the 50-W pedaling we utilized was causing a relatively larger effort during and after HDT. This would tend to increase cardiac output, and it is possible that the cardiac output would have been further decreased if we had been able to use a workload proportional to the presumably declining peak exercise capacity during HDT.

During exercise in upright posture, blood flow through working muscles, venous return, and cardiac preload are facilitated by the leg muscle pump (9), which has a capacity rivaling that of the left ventricle (21). In the supine posture, the muscle pump is much less critical for maintaining preload. It is quite plausible that the muscle atrophy documented in the present subjects (26) decreased the efficacy of the muscle pump, which would lower venous return, impair cardiac filling, and reduce both stroke volume and cardiac output, particularly during upright exercise.

**Cardiac performance.** As described above, after both spaceflight and HDT, plasma volume is reduced and vascular regulation is impaired, leading to easily provokable tachycardia. These factors may all contribute to a reduced ventricular filling, decreased stroke volume, and reduced cardiac output as shown by several studies (3, 18, 20, 22, 23). Some of these studies have also suggested that longer spaceflight or HDT affects the heart directly by causing cardiac atrophy (18–20, 22, 23). Atrophy has been directly demonstrated in animal experiments; for example, both 14 days of spaceflight and 14 days of hindlimb suspension cause myocardial degeneration in rats (12).

Direct assessment of cardiac atrophy is for several reasons not feasible in human volunteers. However, in a recent study, Perhonen et al. (19) used gated magnetic resonance imaging to assess cardiac volume and mass reductions after spaceflight and after bed rest. They studied four astronauts after 10 days of spaceflight, without inflight exercise as countermeasure, and found a tendency to reduce cardiac left ventricular mass by 12 ± 6.9% (\(P = 0.07\)). These authors also studied five subjects during bed rest and found a 14 ± 1.7% reduction in left ventricular end-diastolic volume after 2 wk of HDT. After 6 wk, left ventricular mass had decreased by 8.0 ± 2.2% with an additional atrophy of 7.6 ± 2.3% in the three subjects who remained in bed for 12 wk.

In our subjects, the reductions in stroke volume during supine exercise averaged 4.7 ± 8% at D60, 18.2 ± 4% at D113, and 20.9 ± 4% at R0. In a previous study by our group (23), our laboratory found larger decreases in supine stroke volume in six men under similar exercise conditions (50-W supine exercise) after 42 days of HDT. In those subjects, the decreases in stroke volume averaged 25%, and there was no recovery even 32 days after HDT. Other groups have found faster reductions in stroke volume during supine exercise than we found in the present study: Saltin et al. found a 24% reduction in five young subjects (aged 19–21 yr) exposed to 20 days of bed rest (22). Several factors might explain the smaller reduction in the present study. In the 42-day study, the subjects were even more restricted than in the present HDT (23). No deviations were allowed from the ~6° HDT position, and no exercise was allowed. In contrast, in the present study, subjects spent on average 4 min/day in postures deviating >30° from the HDT position. However, we believe that these deviations have only minor influence, because it has been shown that quite extensive periods (1.5–2 h) of orthostatic stress (lower-body negative pressure) are required to prevent cardiovascular deconditioning (14). In view of the small number of subjects, it is more likely that individual differences have affected the
results. Our subjects differed from those of the 42-day study and from most previous studies by spanning a greater range in age (23–42 yr), weight (63–114 kg), and height (175–190 cm). Furthermore, they exhibited a higher HR during upright exercise at baseline (114 ± 3.7 beats/min) than in the 42-day study [106 ± 3.8 beats/min (23)], probably reflecting lower fitness. In fact, the present subjects might be more representative of the general population.

In the present subjects after HDT during rest, the stroke volume was virtually equal to BDC values already after R3. During exercise, however, a rapid but only partial recovery compared with R0 occurred in all subjects during the first 3 days of recovery, after which no further recovery was noticed even at R15 (Fig. 3). This initial, rapid recovery can be attributed to a rapid recovery of plasma volume, as previously discussed. However, the absence of full recovery after HDT during exercise, where stroke volume is largest, strongly indicates alterations in cardiac structure. Considered together with previous studies (12, 18–20, 23), our data strongly suggest that the reductions in stroke volume observed in the present study are caused, in part, by ventricular remodeling. Furthermore, the time course of the absolute values of the stroke volume decrease during supine exercise between D60 and D113 in the present study suggests that cardiac remodeling may still be in progress even after 60 days of HDT.

In summary, we have demonstrated that 120 days of HDT cause a progressive decrease and a delayed, partial recovery in stroke volume during exercise. The largest stroke volume reductions were demonstrated during supine exercise, which normally is associated with a larger stroke volume than either rest or upright exercise, indicating that structural changes impose an upper limit on the stroke volume. These two findings strongly indicate that cardiac remodeling is the main contributing factor behind cardiovascular deconditioning during exercise and that it is in progress even after extended periods of HDT.

Furthermore, we have demonstrated that stroke volume during rest declined and recovered more quickly compared with exercise. The stroke volume reductions tended to be larger at upright rest, where venous return and cardiac preload are impeded by gravity and unaided by the peripheral muscle pump. The temporal pattern of stroke volume changes followed that commonly demonstrated for plasma volume loss and recovery. These findings strongly indicate that a reduced cardiac preload, presumably caused by reductions in circulating blood volume, is the main contributing factor behind cardiovascular deconditioning during rest.

Notwithstanding these findings, steady-state MAP did not show any changes during or after HDT in either posture, and the subjects’ ability to perform sustained low-level dynamic exercise remained intact, despite the limitations imposed by reductions in cardiac output and stroke volume.

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