Lung function during and after prolonged head-down bed rest

STÉPHANIE MONTMERLE, JONAS SPAAK, AND DAG LINNARSSON
Section of Environmental Physiology, Department of Physiology and Pharmacology, Karolinska Institutet, SE-171 77 Stockholm, Sweden

Received 19 October 2000; accepted in final form 14 August 2001

Montmerle, Stéphanie, Jonas Spaak, and Dag Linnarsson. Lung function during and after prolonged head-down bed rest. J Appl Physiol 92: 75–83, 2002.—We determined the effects of prolonged head-down tilt bed rest (HDT) on lung mechanics and gas exchange. Six subjects were studied in supine and upright postures before (control), during (day 113 [D113]), and after (R + number of days of recovery) 120 days of HDT. Peak expiratory flow (PF) never differed between positions at any time and never differed from controls. Maximal midexpiratory flow (FEF25–75%) was lower in the supine than in the upright posture before HDT and was reduced in the supine posture by about 20% between baseline and D113, R + 0, and R + 3. The diffusing capacity for carbon monoxide corrected to a standardized alveolar volume (volume-corrected DLCO) was lower in the upright than in the supine posture and decreased in both postures by 20% between baseline and R + 0 and by 15% between baseline and R + 15. Pulmonary blood flow (Q˙C) increased from R + 0 to R + 3 by 20 (supine) and 35% (upright). As PF is mostly effort dependent, our data speak against major respiratory muscle deconditioning after 120 days of HDT. The decrease in FEF25–75% suggests a reduction in elastic recoil. Time courses of volume-corrected DLCO and Q˙C could be explained by a decrease in central blood volume during and immediately after HDT.

head-down tilt; hypokinesia; dynamic spirometry; lung diffusing capacity; lung perfusion

Compared with other organs in the human body, the lungs are exceptionally susceptible to influences from the magnitude and direction of gravity. Lung tissue is a three-dimensional elastic network whose density is 1,000 $\times$ greater than that of the air spaces it contains, yet these spaces constitute most of the lung volume.

So far, most of the experiments to study the effects of gravity on the lungs have been performed at normal gravity or during short-term exposures to increased gravity. More recently, studies in reduced or zero gravity (microgravity) have been used as an additional tool to determine the relative importance of gravitational vs. nongravitational influences on pulmonary function.

Pulmonary function during short-term weightlessness has been described by Paiva et al. (20), Prisk et al. (24), Elliott et al. (7, 8), and Verbanck et al. (34). In those studies, ventilation distribution in the lungs has been found to be slightly more homogeneous; some interregional perfusion differences were abolished, but intraregional perfusion differences were preserved. Diffusing capacity was improved, probably because of a more homogeneous distribution of alveolar gas volume in relation to pulmonary capillary blood volume (23, 33). Functional residual capacity (FRC) was slightly reduced (8, 19). Maximum flow-volume curves remained essentially unchanged compared with those seen under normal gravity (7).

Corresponding results from more prolonged periods of weightlessness during spaceflight have been obtained only to a limited extent. Baranov et al. (4) reported that peak expiratory and inspiratory flows were reduced after prolonged spaceflight. They ascribed this to deconditioning of respiratory muscles or possibly to hyperhydration of the lungs. However, their data on peak flow (PF) were not accompanied by data on dynamic spirometric or gas-exchange parameters that would have enabled a distinction between muscular and lung tissue factors on their results.

The present research was undertaken in an attempt to study the consequences of the absence of the normal gravity vector in the head-to-foot direction, in combination with long-term physical inactivity, on mechanics and gas exchange in the human lung. The 6° head-down tilt bed rest (HDT), which reduces gravity in the head-to-foot direction from 1.0 G in standing posture to $-0.1$ G, was used as an analog of the spaceflight environment with respect to postural muscle unloading and systemic blood volume distribution. We found little evidence of respiratory muscle deconditioning, but our findings show that lung tissue properties and alveolocapillary gas exchange are altered after 120 days of HDT.

MATERIALS AND METHODS

This study was conducted at the Institute of Biomedical Problems, Moscow, in cooperation with the European Space Agency.

Address for reprint requests and other correspondence: S. Montmerle, Section of Environmental Physiology, Dept. of Physiology and Pharmacology, Karolinska Institutet, SE-171 77 Stockholm, Sweden (E-mail: stephanie.montmerle@fyfa.ki.se).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

http://www.jap.org 8750-7587/02 $5.00 Copyright © 2002 the American Physiological Society
Subjects. Six healthy male subjects were studied. For their anthropometric data, see Table 1. They did not have any past medical history of lung or heart disease and underwent an extensive medical examination before the study. They served as the control group in an experiment that focused on countermeasures for muscle atrophy and bone demineralization during prolonged HDT. Informed consent was obtained from each subject, and the protocols were approved by the Russian National Committee of Bioethics of the Russian Academy of Sciences.

Equipment. We used a dedicated respiratory monitoring system (Innovation, Odense, Denmark) (34). This system consisted of a quadruple mass spectrometer for gas analysis and a respiratory valve unit from which the subject could either breathe through non-rebreathing valves or rebreathe from a four-liter bag. A unidirectional impeller-turbine flowmeter (KL Engineering, Northridge, CA) was attached directly to a wide-bore mouthpiece for measurement of expiratory flow. Its range was 0–12 l/s, and its volume was 8 ml. Calibration of the flowmeter was made with a 4-liter syringe (E. Jaeger, Höchberg, Germany) as described by Yeh et al. (35). The gas analyzer was calibrated by using two mixtures of known composition, one of which contained pure neon (BOC, Guildford, UK).

Data were recorded with a Biopac data handling system (Biopac, Goleta, CA) at a sampling frequency of 100 Hz and stored digitally.

Experimental procedures. Subjects rested in bed for 120 days with a 6° head-down tilt. HDT was followed by a 15-day recovery period. Subjects did not exercise, except for 25 min of light leg motion on day 60 (D60) of HDT and on D113. Subjects were not allowed to assume any posture other than HDT except during certain tests and during transportation between labs, which was made with subjects supine and level. The total logged time at postures deviating from HDT was 925 min per subject (0.005 of total time), of which 440 min was at +6°. While in HDT, subjects were free to assume prone, supine, and lateral postures.

Pulmonary function tests of the present study were part of a relatively complex protocol, which also included cardiovascular measurements during rest and exercise. Measurements were performed before the HDT period (baseline), on D113, and after HDT on days R + 0 (first day of recovery), R + 3, and R + 15. Actually, the last measurements were completed between R + 14 and R + 17, but the term R + 15 will be used for convenience. On D113, subjects came to the laboratory supine on a gurney and on R + 0 sitting in a wheelchair; otherwise, they were ambulatory. Before, during, and after HDT, spirometric and rebreathing tests were made with subjects placed on a tilt board, first in the supine (horizontal, 0°) position and then in upright (80°) posture. In the 80° posture, the subject sat on a saddle with his feet on a footplate and with more than half of the body weight supported by the saddle. He rested on his back against the board, and his arms were laid on an armrest in front of the board.

Measurements were made in both supine and upright postures for two reasons. First, we expected some degree of orthostatic intolerance after prolonged HDT and were not sure whether, at the time of testing, we would be able to complete the upright tests. Second, upright tests, when tolerated, would give the opportunity to measure the effects of central blood shifts on the parameters under study.

All measurements were supervised by a Russian-speaking physiologist and/or physician. During the performance of the spirometric maneuvers, subjects were shown a diagrammatic representation of the requested time course of lung volumes with Russian text. Subjects were guided through the maneuvers with oral encouragement according to a predetermined protocol and always by the same person.

Spirometric tests. Supine tests were performed after about 10 min of supine rest. Subjects first performed three slow vital capacity (VC) maneuvers that needed 1–1.5 min to be completed, and then three maximum expiratory flow volume (MEFV) maneuvers, starting from a maximal inspiration.

Upright tests were performed after 2 min of rest in the 80° posture. This duration of rest was longer because of the possible correlation between conflicting considerations. We wanted to avoid subjects being in an upright posture for so long that vasovagal reactions could occur; however, time was needed to achieve a downward blood redistribution and to stabilize heart rate and blood pressure. Subjects rested supine between upright tests. Three slow VC maneuvers were followed by three MEFV maneuvers. MEFV tests were thus performed after about 4 min in the upright posture. The total time in upright posture was 4.5–4.8 min each time.

The above sequence with three repetitions for each combination of maneuver and posture was performed four times during baseline measurements about 2 wk before the onset of HDT and once on the other occasions. Forced expiratory flow curves were then analyzed offline with AcqKnowledge Software package 3.2 (Biopac).

Rebreathing tests. Two rebreathing gas mixtures were used and contained an inert blood- and tissue-soluble component (acetylene), an inert insoluble component (argon), and a hemoglobin-specific component (carbon monoxide). Isotopic 18CO (molecular weight 30) was chosen to enable analysis in the presence of N2 (molecular weight 28) by the mass spectrometer. Both mixtures contained 0.63% C2H2, 0.3% C18O, and 5% Ar. This amount was completed by 45% O2 and a balance of N2 in the first mixture, and by 3% SF6, 5% He, and a balance of O2 (~84%), in the second mixture.

Procedures included first a rehearsal of the rebreathing procedure with a slightly hyperoxic O2–N2 mixture. Rebreathing measurements were then performed at rest during a 53-min protocol of which a total of 18 min were intermittently in the 80° posture at each occasion. Subjects rested supine between upright tests. Upright rebreathings were preceded by 1 min in upright posture, and supine rebreathings were preceded by at least 8 min in supine posture. Two rebreathing maneuvers were performed in each posture: the first with gas mixture 1 and the second with mixture 2.

Maneuvers with inhalation of blood-soluble gases were always separated by at least 10 min in which maneuvers that did not include soluble gases were performed. The rebreathing bag was filled with 1.5–2.5 liters of rebreathing gas according to the subject’s total lung capacity (TLC) and preference. The subject donned a nose clip and took a few normal breaths with the valve in the non-rebreathing mode. The subject then switched the valves to rebreathe the full bag volume eight times, starting from FRC, within ~25 s.

Data analysis. Postexperimental analysis of the spirometric data included integration of flows to obtain volumes and
subsequent correction to BTPS units. The following spirometric parameters were extracted from the recorded data according to the principles suggested by Quanjer et al. (25) and the American Thoracic Society (1): 1) VC from slow VC maneuvers; 2) forced VC (FVC) by integrating expiratory flow during MEFV maneuvers; 3) forced expiratory volume during 1 s (FEV1.0) by integrating expiratory flow from the onset of expiration until the end of the first second; 4) maximal midexpiratory flow rate between 25 and 75% of FVC (FEF25–75%) by integrating the area under the flow curve between 25 and 75% of the FVC and dividing by the time between these volumes; and 5) PF during MEFV maneuvers.

Diffusing capacity for CO (DLCO) was calculated from rebreathing tracings as described by Sackner et al. (27), including the time-zero correction, as well as pulmonary blood flow (Qc) and FRC. DLCO was also corrected for day-to-day differences of estimated alveolar volume as follows: algorithms from Stam et al. (30) were used to recalculate DLCO had the alveolar volume been 50% of TLC. This recalculation in- cluded separate algorithms for supine and upright data. Alveolar volume was estimated as FRC + 1/3 rebreathing bag volume, and TLC as VC + residual volume, which was computed from anthropometric data according to Quanjer et al. (25).

One mean value per day, subject, and posture was com- puted from the repeated tests performed with the first re- breathing mixture. Membrane and capillary blood volume components of diffusing capacity could not be distinguished because of the limited number of tests with each of the two gas mixtures, in addition to the relatively low difference between their respective oxygen backgrounds (cf. 34).

Table 2. Maximal expiratory flows and volumes, lung diffusing capacity, and lung blood flow before, during, and after HDT bed rest

<table>
<thead>
<tr>
<th>Posture</th>
<th>Baseline</th>
<th>D113</th>
<th>R + 0</th>
<th>R + 3</th>
<th>R + 15</th>
<th>P Value (Posture/Time/Interaction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak flow, l (BTPS)/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>8.88 ± 0.41</td>
<td>8.95 ± 0.40</td>
<td>9.18 ± 0.34</td>
<td>8.72 ± 0.41</td>
<td>7.89 ± 0.67</td>
<td>0.57/0.20/0.83</td>
</tr>
<tr>
<td>Upright</td>
<td>8.58 ± 0.35</td>
<td>8.78 ± 0.46</td>
<td>9.15 ± 0.41</td>
<td>8.76 ± 0.55</td>
<td>7.99 ± 0.85</td>
<td></td>
</tr>
<tr>
<td>FEV1.0, liters (BTPS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>4.10 ± 0.13</td>
<td>3.77 ± 0.17</td>
<td>3.59 ± 0.11</td>
<td>3.65 ± 0.12</td>
<td>3.47 ± 0.18*</td>
<td>0.20/0.005/0.81</td>
</tr>
<tr>
<td>Upright</td>
<td>4.20 ± 0.08</td>
<td>3.85 ± 0.15</td>
<td>3.83 ± 0.14</td>
<td>3.75 ± 0.08</td>
<td>3.44 ± 0.27*</td>
<td></td>
</tr>
<tr>
<td>FEF25–75%, l (BTPS)/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>4.59 ± 0.38</td>
<td>3.6 ± 0.30*</td>
<td>3.73 ± 0.38*</td>
<td>3.62 ± 0.24*</td>
<td>4.04 ± 0.66</td>
<td>0.02/0.13/0.12</td>
</tr>
<tr>
<td>Upright</td>
<td>4.63 ± 0.35</td>
<td>4.06 ± 0.26</td>
<td>4.47 ± 0.60</td>
<td>4.52 ± 0.61</td>
<td>4.60 ± 0.79</td>
<td></td>
</tr>
<tr>
<td>VC, liters (BTPS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>5.11 ± 0.23</td>
<td>4.81 ± 0.15</td>
<td>4.35 ± 0.27*</td>
<td>3.99 ± 0.31*</td>
<td>4.24 ± 0.29*</td>
<td>0.27/0.001/0.23</td>
</tr>
<tr>
<td>Upright</td>
<td>5.05 ± 0.27</td>
<td>4.43 ± 0.26</td>
<td>4.32 ± 0.30*</td>
<td>4.32 ± 0.23*</td>
<td>3.88 ± 0.38*</td>
<td></td>
</tr>
<tr>
<td>FVC, liters (BTPS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>5.49 ± 0.19</td>
<td>5.23 ± 0.21</td>
<td>4.99 ± 0.18</td>
<td>4.89 ± 0.19</td>
<td>4.64 ± 0.35†</td>
<td>0.85/0.003/0.59</td>
</tr>
<tr>
<td>Upright</td>
<td>5.57 ± 0.20</td>
<td>5.25 ± 0.19</td>
<td>5.12 ± 0.20</td>
<td>4.92 ± 0.17</td>
<td>4.43 ± 0.41†</td>
<td></td>
</tr>
<tr>
<td>DLCO, ml (STPD)-min⁻¹-Torr⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>2.20 ± 0.24</td>
<td>1.93 ± 0.16</td>
<td>2.17 ± 0.24</td>
<td>1.99 ± 0.18</td>
<td>1.94 ± 0.23</td>
<td>0.016/0.55/0.56</td>
</tr>
<tr>
<td>Upright</td>
<td>2.87 ± 0.36</td>
<td>2.55 ± 0.35</td>
<td>2.40 ± 0.32</td>
<td>2.60 ± 0.27</td>
<td>2.69 ± 0.31</td>
<td></td>
</tr>
<tr>
<td>Volume-corrected DLCO, ml (STPD)-min⁻¹-Torr⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>21.3 ± 1.6</td>
<td>18.5 ± 1.1*</td>
<td>18.4 ± 2.1*</td>
<td>19.8 ± 1.2</td>
<td>18.9 ± 1.0</td>
<td>0.023/0.002/0.60</td>
</tr>
<tr>
<td>Upright</td>
<td>19.3 ± 1.2</td>
<td>16.9 ± 0.9</td>
<td>16.6 ± 1.2*</td>
<td>18.8 ± 0.9</td>
<td>18.3 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>Qc, l (BTPS)/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>6.95 ± 0.39</td>
<td>6.58 ± 0.18</td>
<td>6.14 ± 0.29</td>
<td>7.38 ± 0.45†</td>
<td>7.21 ± 0.33‡</td>
<td>0.0007/0.001/0.90</td>
</tr>
<tr>
<td>Upright</td>
<td>5.06 ± 0.50</td>
<td>4.55 ± 0.24</td>
<td>4.25 ± 0.22</td>
<td>5.72 ± 0.37‡</td>
<td>5.56 ± 0.19</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. HDT, head-down tilt; FEV1.0, forced expiratory volume during 1 s; FEF25–75%, maximal midexpiratory flow rate between 25 and 75% of forced vital capacity (FVC); VC, vital capacity; FRC, functional residual capacity; DLCO, diffusing capacity for CO; Qc, pulmonary blood flow; baseline, control before HDT; D113, after 113 days of HDT; R + 0/3/15, after 0/3/5 days of recovery. Statistically significant effects of posture and time as demonstrated with ANOVA are indicated with bold characters. Significant differences between experimental days as obtained with a post hoc Tukey’s test (P < 0.05) are indicated as follows: * vs. baseline; † vs. D113; ‡ vs. R + 0.

**Statistical analysis.** Data were analyzed by a MANOVA, two-way repeated-measures design ANOVA (STATISTICA 5.1; Statsoft, Tulsa, OK). Experimental design included two factors: body posture (upright or supine) and time (experimental day: baseline, D113, R + 0, R + 3, R + 15). In case of a significant effect of time, post hoc pairwise comparisons were tested for significance by using Tukey’s test. Significance was accepted at the P < 0.05 level.

When results showed no difference with time, a Friedman ANOVA analysis was repeated for each dependent variable.

**RESULTS**

Uptight FEV1.0 data before HDT ranged 87–107% of predicted values (1). All subjects could perform all tests, including those in 80° on D113 and R + 0 without signs or symptoms of orthostatic intolerance, and complete data sets were obtained for each occasion. All subjects performed breathing maneuvers as instructed. Two subjects (C and F) showed a much larger intersubject variability than did the others. Table 2 shows group mean data for each day and posture, including significances of differences with respect to time and body posture.

There was no change in PF, either with time or with posture. This pattern was consistent among all subjects but one (E), who showed a 3.5 l/s decrease between R + 3 and R + 15.

VC changed with time but did not differ between the supine and upright postures (Fig. 1). Compared with
in the supine posture was 1,700 ml higher than at any other occasion. In the remaining subjects, there was, on average, a 0.6- to 0.7-liter difference between postures throughout the study.

**D_{LCO}** (Fig. 3A) changed both with time and posture. Time courses were similar in both supine and upright measurements, and supine values were always larger than upright by $-1.5 \text{ ml} \cdot \text{min}^{-1} \cdot \text{Torr}^{-1}$. The pair-wise comparison between time points showed a 14% decrease between baseline and D113 and a 15% decrease between baseline and $R + 0$. **D_{LCO}** then increased but did not reach baseline level. Furthermore, by $R + 15$, the level was slightly less than on $R + 3$.

Volume-corrected **D_{LCO}** (Fig. 3B) also changed with time and posture, and there was no interaction effect between these two factors. The pair-wise comparison between time points showed average decreases of 20 and 15% between baseline and $R + 0$ and between baseline and $R + 15$, respectively. There was also a decreasing trend between baseline and D113 ($P = 0.07$). During the recovery period, the time course of the volume-corrected **D_{LCO}** was comparable to that of **D_{LCO}** except that volume-corrected **D_{LCO}** was significantly lower than control on $R + 15$.

**Q_{C}** changed with both time and posture, but there was no interaction effect between time and posture. Supine values were always larger than upright by $-2 \text{ l/min}$. The pair-wise comparison between time points showed a decreasing trend between baseline and $R + 0$ ($P = 0.09$), an 11% increase between D113 and $R + 3$, a 17% increase between $R + 0$ and $R + 3$, and a 15% increase between $R + 0$ and $R + 15$. Intersubject variability was lower for **Q_{C}** than for the other variables studied.

---

**Fig. 1.** Slow vital capacity (VC) in resting men ($n = 6$) before (baseline), during [day 113 (D113)], and after ($R + 0$ and $R + 15$) 120 days of head-down tilt bed rest (HDT). Values are means ± SE, and data from upright and supine tests have been pooled. *$P < 0.05$ between experimental day and baseline.

Baseline VC was decreased by 12% on day $R + 0$ and by 15 and 16% on days $R + 3$ and $R + 15$, respectively. Two subjects showed no decrease in VC on $R + 0$ compared with control values, and two others had increased values from $R + 3$ to $R + 15$.

As for VC, FVC changed with time but not with posture. The pair-wise comparison between time points showed that FVC was decreased by 16% between baseline and $R + 15$ and by 5% between D113 and $R + 15$. Also, FVC tended to decrease between baseline and $R + 3$ ($P = 0.07$). No difference was found between baseline and D113.

**FEF_{25-75%}** (Fig. 2) was the only spirometric parameter in which a difference was found between postures, with lower values in the supine posture. **FEF_{25-75%}** globally did not change with time. However, in a separate post hoc analysis, supine values were significantly decreased by $-20\%$ between baseline and D113, $R + 0$, and $R + 3$ and then increased between $R + 3$ and $R + 15$. At $R + 15$, there was no difference compared with baseline. Upright values did not change with time. Surprisingly, despite the impression that supine **FEF_{25-75%}** differed more between postures after than before HDT, there was no statistically significant interaction effect between time and posture.

**FEV_{1.0}** changed with time but not with posture. The pair-wise comparison between time points showed that **FEV_{1.0}** was decreased by 14% between baseline and $R + 15$ and tended to be lower than baseline on $R + 0$ and $R + 3$ ($P = 0.06$ and $P = 0.05$, respectively). There was a large variability among subjects: four of six had decreasing values from baseline to $R + 15$; the remaining two increased their **FEV_{1.0}** (starting from $R + 0$ for the one and from $R + 3$ for the other).

FRC changed with posture but not with time, and there was no interaction effect between time and posture. Upright values were always larger than supine values. There was generally a large intersubject variability, and in one subject ($D$) the FRC value at $R + 0$
DISCUSSION

The distinctive feature of the present experiment was its extraordinary duration. Atkov and Bednenko (2) have described even longer bed rest studies, up to 360 days, but not with the present spirometric, diffusing capacity and lung blood flow measurements. An- other feature was the measurement session on D113, a week before the end of the HDT session, in which data were not influenced by the later return to upright posture, as they probably would have been on R + 0.

The major findings in this study were post-HDT reductions in VC, forced expiratory volumes, D_{LCO}, and \( Q_C \), with no or a slow recovery of the spirometric parameters during the first 15 days after HDT in contrast to the rapid initial recovery of D_{LCO} and \( Q_C \). At the same time, there were no changes in PF during any phase of the study.

Subjects were studied in both supine and upright postures so that the impact on lung function of intrathoracic blood volume shifts caused by changes in body posture could be assessed. Thus spirometric parameters, which change with time but do not respond to shifts in body posture, are unlikely to be influenced by time-dependent changes in total and intrathoracic blood volumes. It is to be noted, however, that subjects were upright only a few minutes before measurements, so the present results from upright tests are not necessarily comparable to those of others in which an unspecified but probably longer duration of upright posture had preceded upright measurements (7, 8).

We had expected a deterioration of two aspects of lung function: 1) a reduction of respiratory muscle performance and, in particular, PF due to long-term unloading of postural muscles in the chest and abdomen (4); and 2) signs of increased tissue fluid content in apico-dorsal lung tissues, in which lung capillary hydrostatic pressures normally are lower during most of the diurnal cycle than must have been the case during the present long-term HDT. Should such changes of lung tissue fluid content have occurred to a biologically significant extent, lung diffusing capacity would have been influenced.

Although HDT is often used as a terrestrial representation of life in space, there are important differences between HDT and spaceflight. First, microgravity is accompanied by a complete unloading of postural muscles, whereas these muscles still need to work against gravity in the antero-posterior and lateral directions during HDT (e.g., when changing postures in bed). Furthermore, supine HDT leads to a much larger cranial shift of the diaphragm than does microgravity (9, 19). Thus, during respiratory movements in HDT, the diaphragm has to overcome the weight of the abdominal organs at least in supine and probably also in lateral postures. Second, spaceflight routinely includes regular and often intense physical training, which was not the case during the present HDT experiment.

As reviewed by Fortney et al. (12), a common feature to spaceflight and bed rest is an initial headward redistribution of blood in the systemic circulation and later reductions in blood and plasma volumes. Diuresis increases during the first hours of bed rest and then returns to its previous level within 24 h. Moreover, subjects undergoing slight (−4° to −8°) HDT exhibit changes in body fluid, which are greater and occur at a faster rate than in the supine 0° posture. Initial hypervolemia is followed by a decrease in plasma volume that begins after the first 6 h and is progressive during the first 3 to 6 days. Plasma volume then approaches a new steady state. Johansen et al. (15), Fortney et al. (11), and Heer et al. (13) have shown during studies that lasted up to 6 wk that, after HDT, plasma volume returns to baseline level and overshoots it in 1 to 2 wk. Fortney et al. (11) attributed this increase to an increase in aldosterone release.

![Graph of lung diffusing capacity for carbon monoxide (D_{LCO}) obtained during rebreathing in supine and upright tests.](image)

Fig. 3. A: lung diffusing capacity for carbon monoxide (D_{LCO}) obtained during rebreathing in supine and upright tests. B: D_{LCO} after correction for differences in estimated alveolar volume between test days. *P < 0.05 between experimental day and baseline.
**PF and VC.** As described by Pedersen (21) and Tzel-epis et al. (33), PF increases with high lung volumes at the start of the expiration because of increased elastic recoil and decreased upstream frictional pressure loss due to enlarged airway dimensions. Equally important, it also increases with a rise in expiratory effort because a fast acceleration of flow causes maximal flow to be reached earlier during expiration, i.e., at a higher lung volume.

No changes in PF during the experiment could be statistically demonstrated, even if the overall time course showed a tendency to decrease during and after HDT. We have found no previous HDT studies that included PF measurements. Comparisons with other conditions, in which gravity changes and alterations of the hydrostatic pressure influence lung function, may only be partly if not at all relevant. Elliott et al. (7) studied PF during 9 days of microgravity and found a transient decrease of PF during the first few days. They suggest that the initially raised intrathoracic blood volume caused a reduced degree of initial lung inflation with a secondary decrease of PF, but they could not exclude that their data were influenced by the lack of bodily support when PF maneuvers were performed in free-floating conditions.

Prefaut et al. (22) studied standing and acutely water-immersed subjects and found increased elastic recoil at large lung volumes and also increased PF. They ascribed the increase in elastic recoil to a larger intrathoracic blood volume but suggested that the increase in PF was rather a consequence of the increased hydrostatic forces compressing the thorax.

Both these studies and others comparing upright and supine resting subjects deal with acute or subacute changes, whereas, in the present study, the first data point after the initial control experiments was on D113. Judging from concomitant Qc measurements, cardiac preload and, thereby, probably thoracic blood volume were reduced during and immediately after HDT, clearly without any consequence for PF. Also the absence of upright/supine PF differences speak against thoracic blood volume as an important factor to determine PF.

We can therefore assume that PF mainly reflects muscle performance. According to our results, there are no signs of weakening of expiratory muscles in the course of a 120-day HDT, at least not to an extent that influences PF. However, it cannot be excluded that, for a HDT period even longer than the present one, signs of respiratory muscle deconditioning might become evident. Our data may thus be at variance with those of Baranov et al. (4).

VC is influenced by muscular effort (inspiratory and expiratory muscles), by lung elastic recoil, and by central blood volume through compression of lung tissues (3, 14, 17, 18, 32). Thus Hong et al. (14) showed that, during water immersion, the execution of a 5-s Val-salva maneuver after the end of a maximal inspiration, followed by an effort to inspire more, led to a ~200-ml increase in VC. This nearly compensated for the average 360-ml loss in VC due to water immersion. However, changes in VC with time in the present study are quite different from what would be expected if they were determined by central blood volume. VC decreased during HDT despite a probable decrease in central blood volume at the same time. A further argument against the influence of central blood volume on VC is that no difference was found in VC data between supine and upright postures in the present study.

The decrease in VC reported in our study has not been consistently observed in other HDT experiments (5, 28). However, Baranov et al. (4), in a review of long-term Russian spaceflights, observed that VC decreased as flight duration increased. Unfortunately, they did not make any in-flight tests and did not define how long after the flight their measurements were performed. They suggested that hypovolemia and possible lung hyperhydration (caused by an increase in intrathoracic blood volume due to the absence of hydrostatic pressures in microgravity) were the cause of the decrease in VC. However, Verbanck et al. (34) showed that, after a 10-day microgravity experiment, there was an early in-flight decrease in pulmonary tissue volume, which reached 25% late in flight. Moreover, after the 9-day recovery period, there was only a trend toward a return to normal. Their explanation was that the global loss in blood volume known to occur in microgravity counteracts the pulmonary tissue vol-ume increase that the central fluid shift might otherwise have caused.

However, these data from microgravity do not necessarily apply to HDT, in which hydrostatic pressure gradients, mostly in the antero-posterior direction, prevail in the lungs. Therefore, it cannot be assumed a priori that localized increases of lung tissue hydration do not occur during and shortly after long-term HDT.

Overall, our data suggest that VC is reduced by a mechanism characterized by a slow recovery. This speaks in favor of reduced muscle performance rather than any process associated with fluid shifts because such processes will be expected to take place to a significant degree during a 15-day recovery period. Because PF was unaffected during and after HDT, we suggest that respiratory muscle deconditioning was specific for muscles involved in VC but not in PF.

**FVC and its subdivisions.** The most likely explanation for the reductions of FVC and FEV 1.0 is that of scaling, because VC, FVC, and FEV 1.0 were roughly proportionally reduced with time, causing MEFV maneuvers to be performed at a somewhat lower volume with an associated lower elastic recoil and airway conductance. Previous short-term HDT studies showed contradictory FEV 1.0 measurements. Beckett et al. (5) observed an increase in FEV 1.0 that lasted until the end of the 2-day recovery period during an 11-day HDT, whereas Saltin et al. (28) observed no change during a 20-day HDT. We are unaware of such measurements during and after long-term HDT.

During expiration, driving pressure, as sum of the pleural pressure and lung elastic recoil, encounters frictional losses down the airways (i.e., aborally) and...
decreases until reaching atmospheric pressure at the airway opening. The point where driving pressure reaches pleural pressure is defined as the equal-pressure point (18). Downstream of the equal-pressure point, airway pressure is less than pleural pressure, which leads to airway collapse. Dynamic airway compression occurs between 25 and 75% of expired volume, thus creating an effort-independent flow restriction (18). In an alternative but not mutually excluding explanatory model, effort-independent flow is caused by a choke point, the posture of which is determined by the stiffness of the larger airways (6). Thus FEF<sub>25–75%</sub> is influenced by lung elastic recoil and airway resistance rather than muscular effort (23).

Airway resistance may potentially be influenced by intrathoracic blood volume apart from the global compression of lung tissue; an increase in the central venous pressure can cause a swelling of the bronchial mucosa (17, 19).

FEF<sub>25–75%</sub> was the only spirometric parameter that differed between postures and only after baseline. If FEF<sub>25–75%</sub> had been directly influenced by short-term and long-term changes in central blood volume, it would have been reduced in the supine posture, compared with upright, also at baseline. Then, it would have been increased during HDT and later decreased during the recovery period. As we have opposite results, we conclude that FEF<sub>25–75%</sub> changes were not primarily caused by central blood volume changes. However, the decrease in FEF<sub>25–75%</sub> in the supine posture during D113 to R + 3 might be due to a decrease in lung elastic recoil, which may only become apparent in a situation where airway resistance is increased due to a relatively larger thoracic blood volume, such as in the supine posture.

In conclusion, we consider that the observed HDT-related reduction in supine FEF<sub>25–75%</sub> results from reductions in lung elastic recoil. The cause of this change in lung tissue property requires further studies.

DL<sub>CO</sub>. The observed decrease in DL<sub>CO</sub> during HDT could, if isolated, be caused by a number of factors, such as alterations of FRC and alveolar volume (15, 29), general or localized hyperhydration of the lung tissue (30), reduced blood volume in the pulmonary capillaries (30), reduced hemoglobin concentration (10), and impaired matching between distributions of alveolar gas volume and the pulmonary capillary blood volume (24).

Because there is a strong dependence between the alveolar volume at which a DL<sub>CO</sub> test is performed and the DL<sub>CO</sub> value (15, 25, 29), we analyzed the impact of changes of FRC between experimental days. There were no systematic time-dependent trends of FRC but a considerable scatter of data, which might distort underlying trends of lung diffusing capacity. However, as shown by several investigators (15, 25, 29), a simple calculation of CO transfer coefficient (i.e., the ratio of DL<sub>CO</sub> over estimated alveolar volume) is in itself volume dependent, in fact more so than DL<sub>CO</sub>. Instead, we used data from Stam et al. (30) to recalculate DL<sub>CO</sub>, had estimated alveolar volume been 50% of TLC. The time course of the so-obtained volume-corrected DL<sub>CO</sub> differs slightly from that of the uncorrected DL<sub>CO</sub>; there was a 13–14% decrease of both upright and supine DL<sub>CO</sub> on D113 and R + 0, whereas volume-corrected DL<sub>CO</sub> tended to show a larger decrease in upright than in supine posture. Also, both DL<sub>CO</sub> and volume-corrected DL<sub>CO</sub> tended to show a partial recovery on R + 3.

Schultz et al. (29) measured DL<sub>CO</sub>, pulmonary tissue volume, and cardiac output by a rebreathing method in six subjects with a gas mixture comparable to the one we used in the present study. The recovery period was 8 days. DL<sub>CO</sub> was decreased by 5% on the sixth day of the 10-day bed-rest period. On the fifth day of the recovery period, DL<sub>CO</sub> was back to its baseline level.

To our knowledge, there are no studies of DL<sub>CO</sub> during and after long-term HDT. The consistent difference between supine and upright measurements of DL<sub>CO</sub> in the present study clearly points to the well-established relationship between pulmonary capillary blood volume and DL<sub>CO</sub>, as illustrated, for example, in the ground control data of Prisk et al. (24). In analogy, it might also be reasoned that time-dependent changes of DL<sub>CO</sub> are a function of the plasma volume reductions, which have been demonstrated to take place during long-term HDT (15). The time-course of recovery, however, appears somewhat different between DL<sub>CO</sub> and plasma volume. According to Johansen et al. (15), plasma volume recovers within a few days and possibly with an overshoot after 12–14 days. In contrast, present DL<sub>CO</sub> data show only a partial and temporary recovery, with a remaining significant reduction of volume-corrected DL<sub>CO</sub> on R + 15. It might be speculated that the slightly higher values on R + 3 than on R + 15 are a function of two parallel processes, the first determined by plasma volume and a second much slower process related to lung tissue properties.

An alternative interpretation is that the initial recovery of plasma volume is associated with hemodilution and no effective increase in the hemoglobin content in the pulmonary capillaries. This could be because the overall hemoglobin content is known to be already decreased during HDT after 2 wk (11, 12). Hemoglobin measurements during the present HDT experiment were performed by another team (unpublished data) on baseline and at D60, D120, and R + 30. Hemoglobin concentration did not differ from control at these three occasions during and after HDT. However, this absence of change on days D60 and D120 might be explained by parallel decreases in plasma volume and hemoglobin content, whereas the last measurement at R + 30 was performed too late to enable any comparison with our data. We can therefore only assume the time course of hemoglobin concentration between D120 and R + 30. Fortney et al. (11) studied plasma volume and red cell volume during and after 28 days of HDT in 10 subjects. A computation of hematocrit values from their data showed constancy during HDT followed by a decrease between the end of HDT and R + 7. This decrease had recovered to some extent by R + 14.
These results clearly show that there was a hemodilution during the first 2 wk after this 28-day HDT, and we assume that this was also the case in the present study.

Further studies with coherent measurements of plasma volume, hemoglobin concentration, and membrane and lung-capillary volume components of Dl,CO are required to fully explain the present time course of Dl,CO.

Q˙C. The most striking finding was the marked increase of both supine and upright Q˙C between R + 0 and R + 3 to levels equivalent to if not higher than control. Sundblad et al. (31), studying exercising subjects before and after 42 days of HDT, also reported a gradual increase of Q˙C on R + 2 and R + 4 but supine exercise Q˙C had not recovered fully even on R + 32. The present findings can be explained in terms of a replenishment of blood and plasma volume during the first few days of recovery, thus improving cardiac preload and causing an increment of cardiac output by the Frank-Sterling mechanism. The dissociation between the time courses of recovery of Q˙C on one hand and volume-corrected Dl,CO on the other underscores that mechanisms other than central blood volume determine the time courses of Dl,CO.

In conclusion, we have observed moderate impairments of lung function during and after long-term HDT bed rest. The preserved peak expiratory flow rate speaks against major deconditioning of respiratory muscles, whereas reductions of slow VC and FVC suggest some degree of decreased muscular performance. Spirometric parameters sensitive to alterations in lung tissue properties suggest a decrease in elastic recoil during and after long-term HDT bed rest. There are also reductions of lung diffusing capacity and lung blood flow with time courses of recovery, which can be explained by bed-rest-induced decreases in plasma and blood volumes, and a subsequent recovery of plasma volume during the 2-wk period of post-bed-rest measurements.

We thank Dr. V. Michailov [Institute of Biomedical Problems (IBMP)] for providing hemoglobin data, Dr. A. Kotov for assistance during the experiments, M. Le Gouic for invaluable support throughout all phases of the study, and the subjects for their dedicated collaboration.

The support from the European Space Agency and from IBMP in Moscow is gratefully acknowledged. This study was supported by grants from the Swedish National Space Board, Fraenckel’s Fund for Medical Research, the Swedish Medical Research Council (grant 5020), and the Centre National d’Etudes Spatiales (France).

REFERENCES