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*Chest*, September 1, 2005; 128 (3): 1339-1347.

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# Sustained microgravity reduces the human ventilatory response to hypoxia but not to hypercapnia

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**Prisk, G. Kim, Ann R. Elliott, and John B. West.** Sustained microgravity reduces the human ventilatory response to hypoxia but not to hypercapnia. *J Appl Physiol* 88: 1421–1430, 2000.—We measured the isocapnic hypoxic ventilatory response and the hypercapnic ventilatory response by using rebreathing techniques in five normal subjects (ages 37–47 yr) before, during, and after 16 days of exposure to microgravity ( $\mu\text{G}$ ). Control measurements were performed with the subjects in the standing and supine postures. In both  $\mu\text{G}$  and in the supine position, the hypoxic ventilatory response, as measured from the slope of ventilation against arterial  $\text{O}_2$  saturation, was greatly reduced, being only  $46 \pm 10\%$  ( $\mu\text{G}$ ) and  $52 \pm 11\%$  (supine) of that measured standing ( $P < 0.01$ ). During the hypercapnic ventilatory response test, the ventilation at a  $\text{PCO}_2$  of 60 Torr was not significantly different in  $\mu\text{G}$  ( $101 \pm 5\%$ ) and the supine position ( $89 \pm 3\%$ ) from that measured standing. Inspiratory occlusion pressures agreed with these results. The findings can be explained by inhibition of the hypoxic but not hypercapnic drive, possibly as a result of an increase in blood pressure in carotid baroreceptors in  $\mu\text{G}$  and the supine position.

spaceflight; carotid; inspiratory occlusion pressure; chemoreceptor; blood pressure

THERE IS REASON TO SUSPECT that the removal of gravity [weightlessness, microgravity ( $\mu\text{G}$ )] might result in changes in the control of ventilation in humans. The peripheral chemoreceptors are located in the neck region, and it is believed that  $\mu\text{G}$  alters vascular pressures in these areas, resulting in extracellular fluid engorgement, which might alter the transduction of changes in arterial blood gases. Spaceflight is known to alter the carotid baroreceptor reflex response (7), and there is some evidence for interaction between carotid baroreceptor and carotid chemoreceptor responses (11, 12, 26).

In this paper we report the results of the first measurements of the isocapnic hypoxic ventilatory response (HVR) and the hypercapnic ventilatory response (HCVR) in sustained  $\mu\text{G}$ . Using a rebreathing technique, we measured the HVR in five subjects over the course of a 16-day spaceflight and compared this with the responses before and after flight. Measurements were made on the ground with the subjects in both the standing and supine positions. The results

show that  $\mu\text{G}$  results in a large reduction of the HVR compared with the upright posture on the ground but leaves the HCVR largely unaltered.

## METHODS

**Experimental system.** We used an experimental system similar to that used for previous studies of pulmonary function in  $\mu\text{G}$  (10, 19). Briefly, airflow was measured with a linearized Fleisch no. 2 pneumotachograph (30) in the wall of a bag-in-box system and gas concentrations with a rapidly responding quadrupole spectrometer sampling at the lips of the subject, with all signals sampled at 200 Hz. Inspired gas was contained in a rebreathing bag within the bag-in-box system and was dispensed from premixed gases carried onboard.

The system was arranged to allow the subject to act as the operator for all measurements, except for those pre- and postflight measurements performed supine, when assistance was provided. Subjects were trained to maintain a constant body position while standing or sitting and in  $\mu\text{G}$ , with their hands on the valves at the level of the mouthpiece. Arterial oxygen saturation ( $\text{SaO}_2$ ) was measured by using the Vitaport II portable sleep system (Temec Instruments, Kerkrade, The Netherlands) and by using an Ohmeda Flex II fingertip probe (Ohmeda, Louisville, CO) on the ring finger of the left hand.

The mass spectrometer (gas analysis system for metabolic analysis in physiology, GASMAP) was a modified version of a rapidly responding quadrupole instrument (Marquette Electronics, Milwaukee, WI) and was calibrated immediately before and after use with known gas mixtures carried onboard. The flowmeter was calibrated by integration of the flow from strokes of a 3-liter calibration syringe. Mass spectrometer transit time was determined daily by measuring the time required for a sharp puff of gas containing  $\text{CO}_2$  to be detected by the mass spectrometer, and the data were then aligned accordingly.

For the hypoxic rebreathing test, a variable-speed fan withdrew gas from the proximal end of the rebreathing bag, passed it through a canister filled with soda lime (Puritan Bennett, Lenexa, KS), and returned the gas to the distal end of the rebreathing bag. The computer controlled the speed of the fan. The end-tidal  $\text{CO}_2$  concentration was monitored on a breath-to-breath basis, and the fan speed was set to maintain the desired end-tidal value on the basis of an algorithm incorporating both feedback and feed-forward control elements.

A valve between the subject's mouth and the rebreathing bag was under computer control and was used to occlude the breathing path to measure the inspiratory occlusion pressure. The volume signal from the bag-in-box system (on the basis of the integration of flow) was monitored continuously by the computer, and the beginning of inspiration detected when an inspiration of  $>50$  ml past the minimum volume had occurred. At this point the valve was closed for  $\sim 250$  ms. Because there was noise associated with the valve closure

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that might alert the subject, a valve was closed on every breath, but the valve that actually occluded the breathing path was only actuated on a pseudorandom basis, an average of one in four breaths. Mouth pressure resulting from the inspiratory effort against the closed valve was measured by using a differential pressure transducer (model MP-45, Validyne, Northridge, CA).

**Subjects and data-collection schedule.** Our subjects were the crew of the National Aeronautics and Space Administration Neurolab [Space Transport System (STS)-90] flight. We studied five subjects (4 men, 1 woman; average age 40 yr, range 37–44 yr; average height 182 cm, range 164–188 cm). Preflight data were collected four times in the 3 mo preceding flight at ~90, 60, 30, and 15 days before flight. Inflight, we measured the HVR and HCVR on *days 4, 6, 11, and 15* of the 16-day flight on each of the five subjects. Postflight, data were collected on the day of landing; within 3–10 h after the onset of gravity; and again on *days 1, 2, 4, 5, and 15* after landing. All preflight and postflight data were recorded both upright and supine, except on the day of landing, which allowed insufficient time for supine measurements.

In addition, we also collected HCVR data on the crew of the Life and Microgravity Spacelab (LMS) STS-78, in which we studied six subjects (5 men, 1 woman; average age 41 yr, range 38–47 yr; average height 181 cm, range 165–191 cm). One of the subjects participated in both flights. During LMS, measurements of the HCVR (but not the HVR) were made on *days 2, 4, 8, 12, and 15* of the 17-day flight. In most cases, all six subjects participated in the data-collection sessions, but there were occasional instances in which one subject was unavailable on a given day because of other duties. Postflight, data were collected on the day of landing; within 3–10 h after the onset of gravity; and again on *days 1, 2, 4, 6, and 14*. Pre- and postflight data collected from LMS were in the upright seated position only. The LMS flight took place ~20 mo before the Neurolab flight, and this allowed us to improve techniques for the experiments on Neurolab.

The subjects on Neurolab also participated in a double-blind placebo-controlled study of the effects of melatonin on sleep. Every night during the preflight and inflight testing periods, they took either 0.3 mg of melatonin or a placebo. The study design was such that we had equal numbers of data-collection points with placebo and melatonin. In all cases the drug administration was at least 10 h, and generally more than 12 h, before testing. We saw no difference between tests performed following this small amount of melatonin or placebo administration, and no separation is made between the groups.

**Test maneuvers.** The HVR was measured by using the rebreathing method of Rebeck and Campbell (24). The rebreathing bag was filled to 1 liter above the vital capacity (VC) of the subject with a gas mixture of 17%  $\text{O}_2$ -7%  $\text{CO}_2$ -balance  $\text{N}_2$ . At the end of a normal expiration, the subject turned a rotary valve to connect the breathing path to the rebreathing bag and then breathed normally. Rebreathing continued until the inspired  $\text{PO}_2$  reached 43 Torr, until 4 min had elapsed, or until the subject was unable to continue. Inspiratory occlusion pressures were only measured down to an inspired  $\text{PO}_2$  of 86 Torr because it was uncomfortable for the subject to interrupt flow at lower  $\text{PO}_2$  values. During the rebreathing period, the speed of the fan was controlled to alter the flow through the soda lime cannister. End-tidal  $\text{PCO}_2$  was controlled to  $45.6 \pm 0.4$  (SE) Torr to provide a stable control system. The average intrasubject variability of the end-tidal  $\text{PCO}_2$  was 0.6 (SE) Torr, indicating that reproducible values were achieved within each subject.

The HCVR was measured by using the rebreathing method of Read et al. (22). The rebreathing bag was filled with the VC + 1 liter or a gas mixture of 7%  $\text{CO}_2$ -60%  $\text{O}_2$ -balance  $\text{N}_2$  (for LMS, the  $\text{CO}_2$  was 6%). At the end of a normal expiration, the subject turned a rotary valve to connect the breathing path to the rebreathing bag and then breathed normally. Rebreathing continued until the  $\text{PCO}_2$  in the rebreathing system reached 70 Torr, until 4 min had elapsed, or until the subject was unable to continue. Our technique ensured that at the end of the rebreathing period, end-tidal  $\text{O}_2$  was on average >190 Torr and was never <143 Torr, eliminating the possibility of any hypoxic stimulus. Inspiratory occlusion pressures were measured on Neurolab up to a  $\text{PCO}_2$  of 54 Torr, beyond which the occlusion of the breathing path became too disturbing to the subjects.

In addition to the measurements made during forced changes in inspired gases, respiration was also measured under resting conditions on the mouthpiece. Ventilatory variables were measured while subjects breathed air during a 60-s period via a nonbreathing valve with a common dead space of 90 ml. This 1-min period of quiet breathing immediately followed a 2-min period of breathing on the mouthpiece, which ensured that the subject had become accustomed to the mouthpiece, and was not influenced by the events immediately preceding the recording period. Other than the inspiratory occlusion pressure measurements, there were no disturbances to breathing during this time.

**Data recording and analysis.** Data from each test were identified within the data stream, and the calibrations were applied. Gas data were corrected for the mass spectrometer transit time, and the flow was converted to BTPS conditions. The period of rebreathing was selected, and each breath within this period was identified from the volume signal. The inspired and end-tidal  $\text{PO}_2$  and  $\text{PCO}_2$  were measured on the basis of the points corresponding to the end of inspiration and the end of expiration.

The signal time delay for  $\text{SaO}_2$  was determined from the time between the end of the hypoxic stimulus and the beginning of the subsequent rise in  $\text{SaO}_2$ . Once this time delay was applied, the  $\text{SaO}_2$  was calculated for each breath as the average over that breath period. In cases where the  $\text{SaO}_2$  signal was absent because of motion artifact or poor signal-to-noise ratio in the pulse wave, we calculated the  $\text{SaO}_2$  by using the Kelman routines, assuming normal values for temperature and base excess (27). Comparison of the calculated  $\text{SaO}_2$  and measured  $\text{SaO}_2$  in cases when both were available showed only minor (<2%) differences in  $\text{SaO}_2$  and negligible alterations in the calculated HVR. The HVR was calculated as the linear best fit line of ventilation as a function of  $\text{SaO}_2$  between an  $\text{SaO}_2$  of 95 and 75%. To avoid errors introduced by a single large breath such as a sigh, breaths lying >2 SDs outside this line were discarded, and the line was recalculated. Sample sets of data (preflight standing and in  $\mu\text{G}$ ) from one subject show the raw data and the analysis technique (Fig. 1). The same procedure was used to calculate the response of other parameters such as tidal volume or breathing frequency to hypoxia.

The HCVR was calculated from a plot of ventilation against end-tidal  $\text{PCO}_2$ . The line was fitted to breath-by-breath ventilation as a function of end-tidal  $\text{PCO}_2$  between a  $\text{PCO}_2$  of 50 and 65 Torr by using the same technique as that used for the HVR.

The inspiratory occlusion pressure measured 100 ms after closure of the valve in the inspiratory line was taken as a measure of respiratory drive. The pressure measurement was taken 100 ms after the interruption to the flow caused by the valve closure was detected. The inspiratory occlusion pres-

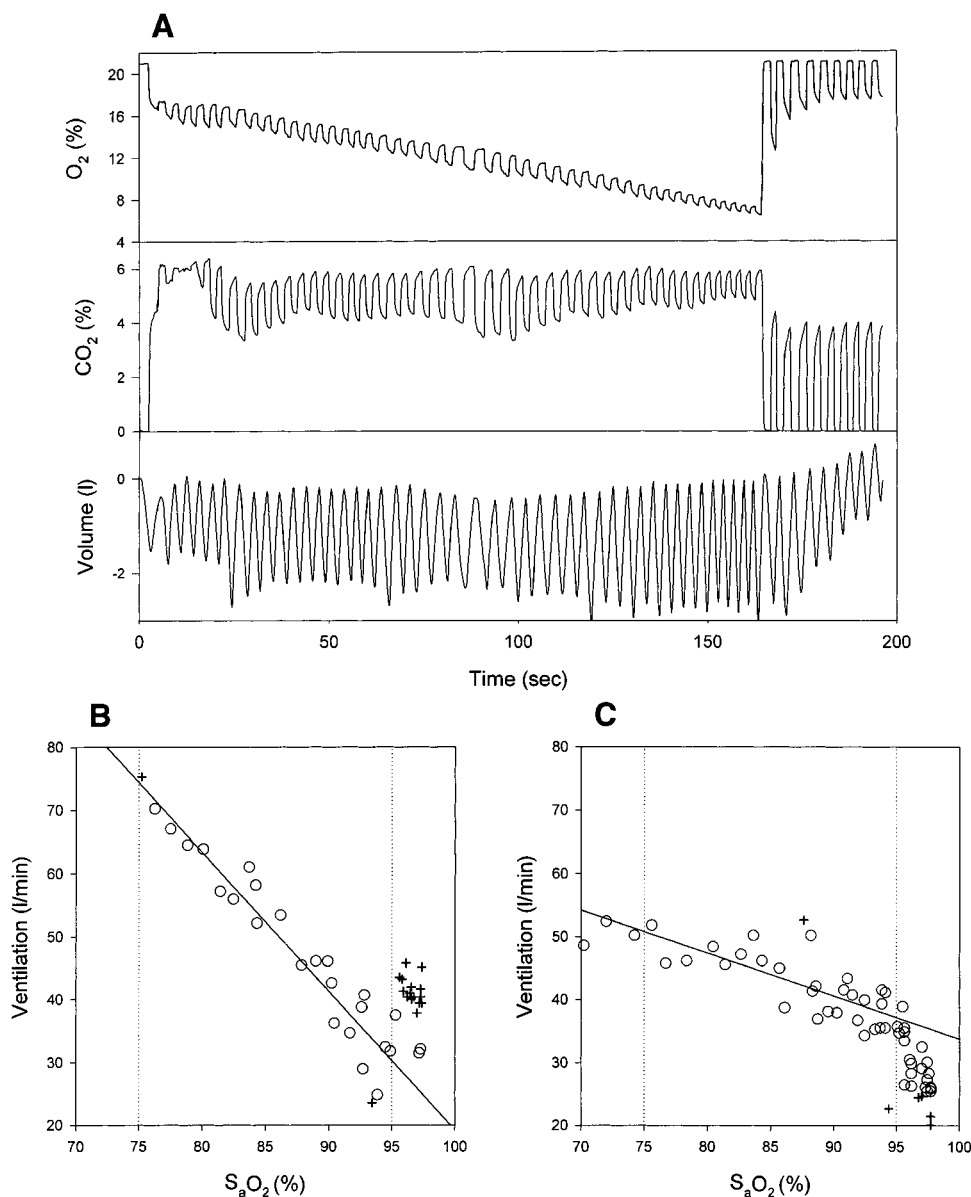


Fig. 1. *A*: raw data from measurement of hypoxic ventilatory response. Subjects rebreathed from a bag for 4 min during which time O<sub>2</sub> in the bag fell and CO<sub>2</sub> was held constant by a computer-controlled CO<sub>2</sub>-removal circuit. For 1 subject, we show hypoxic ventilatory response analysis for data collected in standing in normal gravity (*B*) and in microgravity ( $\mu\text{G}$ ; *C*). Breath-by-breath ventilation is plotted as a function of arterial O<sub>2</sub> saturation (SaO<sub>2</sub>). Line is least-squares best fit to points lying within 2 SD of the best fit to all data points (see text for details). Points marked with a "+" were excluded from the fit, as were points with an SaO<sub>2</sub> below 75 or above 95%. Slope of this line and other parameters are reported in Table 1.

sure was measured as the pressure at this time corrected for the fall in pressure baseline resulting from the inspiration itself. The baseline was determined by the linear interpolation of the pressure signal between the point before the flow occlusion and the point after the valve had opened.

**Statistical methods.** We followed the procedure used in our prior publications of pulmonary function in  $\mu\text{G}$  (19, 20). Because of slight differences in protocol and because there were no supine data collected on the LMS crew, we chose not to pool the data sets. Subjects acted as their own controls. Statistical analysis was performed by using Systat v5.0 (Systat, Evanston, IL) or Microsoft Excel (Microsoft, Redmond, WA). Data were grouped according to subject and position (standing, supine,  $\mu\text{G}$ ), and two-way analysis of variance was performed. In cases where there were significant *F* ratios, post hoc testing was performed by using the Bonferroni adjustment to determine significance levels. Simple comparisons were performed by using *t*-tests. Significance was accepted at the  $P < 0.05$  level, and the results are expressed as means  $\pm$  SE.

## RESULTS

**HVR.** Spaceflight resulted in a large and significant reduction in the HVR. Table 1 lists all of the variables that were measured.

The reduction in the HVR was a result of reductions in both the slope (Fig. 2) and the intercept of the line (Table 1) describing ventilation as a function of SaO<sub>2</sub>.  $\mu\text{G}$  and the supine position resulted in mean reductions to  $46 \pm 10$  and  $53 \pm 11\%$ , respectively, of that in preflight standing control data for the slope of the increase in ventilation with decreasing SaO<sub>2</sub>. There were concomitant reductions in the intercept of the ventilation line, with values being  $55 \pm 7\%$  in  $\mu\text{G}$  and  $59 \pm 6\%$  for the supine position. Neither the slope nor the intercept measured standing in the postflight period was significantly different from that measured preflight.

Table 1. Hypoxic ventilatory response

	Preflight		Inflight		Postflight					
	Standing 1 G	<i>n</i>	Supine 1 G	<i>n</i>	$\mu$ G	<i>n</i>	Standing 1 G	<i>n</i>	Supine 1 G	<i>n</i>
Slope of ventilatory response, $l \cdot \text{min}^{-1} \cdot \% \text{SaO}_2^{-1}$	$0.63 \pm 0.12$ (100.0 $\pm$ 9.5%)	20	$0.43 \pm 0.09^a$ (52.5 $\pm$ 11.0%)	19	$0.29 \pm 0.06^{a,c}$ (46.2 $\pm$ 9.9%)	18	$0.81 \pm 0.11^e$ (121.5 $\pm$ 14.5%)	30	$0.41 \pm 0.07^c$ (51.7 $\pm$ 8.8%)	21
Intercept of ventilatory response, l/min	$80.8 \pm 11.8$ (100.0 $\pm$ 6.3%)	20	$54.9 \pm 8.6^a$ (58.9 $\pm$ 6.4%)	19	$44.0 \pm 6.7^{a,c}$ (55.1 $\pm$ 6.9%)	18	$101.1 \pm 10.9^e$ (119.5 $\pm$ 8.4%)	30	$53.4 \pm 7.1^c$ (57.8 $\pm$ 6.5%)	21
Ventilation at $\text{SaO}_2 = 75\%$ , l/min	$33.5 \pm 3.1$ (100.0 $\pm$ 3.5%)	20	$23.0 \pm 2.0^a$ (64.5 $\pm$ 2.7%)	19	$22.5 \pm 2.4^{a,c}$ (65.0 $\pm$ 4.6%)	18	$40.7 \pm 2.8^a$ (119.0 $\pm$ 5.1%)	30	$22.9 \pm 1.8^c$ (63.8 $\pm$ 4.5%)	21
Tidal volume at $\text{SaO}_2 = 75\%$ , liters	$1.98 \pm 0.12$ (100.0 $\pm$ 2.4%)	20	$1.52 \pm 0.12^a$ (73.1 $\pm$ 2.6%)	19	$1.59 \pm 0.15^{a,c}$ (75.0 $\pm$ 3.9%)	18	$2.19 \pm 0.12^a$ (107.2 $\pm$ 2.6%)	30	$1.59 \pm 0.15^c$ (75.0 $\pm$ 3.9%)	21
Respiratory frequency at $\text{SaO}_2 = 75\%$ , breaths/min	$16.6 \pm 0.7$ (100.0 $\pm$ 2.1%)	20	$15.3 \pm 0.8^e$ (89.9 $\pm$ 3.6%)	19	$14.8 \pm 1.2^c$ (88.6 $\pm$ 7.1%)	18	$18.1 \pm 0.6^a$ (107.6 $\pm$ 3.1%)	30	$16.2 \pm 0.7^c$ (94.2 $\pm$ 3.9%)	21
End-tidal $\text{Pco}_2$ , Torr	$45.8 \pm 0.3$ (100.0 $\pm$ 0.5%)	20	$47.0 \pm 0.6^e$ (102.7 $\pm$ 1.1%)	19	$45.7 \pm 0.4^{b,d}$ (99.8 $\pm$ 0.7%)	18	$45.4 \pm 0.4^e$ (99.4 $\pm$ 0.6%)	30	$47.6 \pm 0.4^c$ (104.3 $\pm$ 0.7%)	21
Inspiratory occlusion pressure when normoxic and normocapnic, Torr	$4.3 \pm 0.2$ (100.0 $\pm$ 3.2%)	58	$4.6 \pm 0.2^e$ (95.4 $\pm$ 3.7%)	31	$4.0 \pm 0.2^e$ (91.2 $\pm$ 5.9)	47	$4.2 \pm 0.1^e$ (97.1 $\pm$ 2.2%)	87	$4.5 \pm 0.2^e$ (103.0 $\pm$ 2.5%)	51
Inspiratory occlusion pressure ( $75 < \text{PO}_2 < 85$ Torr), Torr	$6.1 \pm 0.4$ (132.5 $\pm$ 6.7%)	20	$5.1 \pm 0.3^a$ (113.3 $\pm$ 6.2%)	33	$5.7 \pm 0.3^d$ (122.7 $\pm$ 6.1%)	51	$6.1 \pm 0.2^e$ (141.7 $\pm$ 6.9%)	49	$5.1 \pm 0.2^c$ (115.4 $\pm$ 5.2%)	46

Values are means  $\pm$  SE; values within parentheses are data normalized to those measured preflight standing, except for inspiratory occlusion pressures, which are normalized to preflight standing while breathing air; *n*, no. of measurements. 1 G, normal gravity;  $\mu$ G, microgravity;  $\text{SaO}_2$ , arterial  $\text{O}_2$  saturation. <sup>a</sup> $P < 0.05$  compared with preflight standing. <sup>b</sup> $P < 0.05$  compared with preflight supine. <sup>c</sup> $P < 0.05$  compared with postflight standing. <sup>d</sup> $P < 0.05$  compared with postflight supine. <sup>e</sup> $P =$  not significant.

Both the change in slope and the intercept affect the ventilation calculated at an  $\text{SaO}_2$  of 75% (Table 1). This overall response combines the effects of a change in the slope of the HVR and a change in the intercept of such a response. Spaceflight reduced the overall HVR to  $\sim 65\%$  of that measured standing in the preflight period ( $P < 0.05$ ). There was a similar reduction in the response when subjects were placed in the supine position preflight ( $P < 0.05$ ).

Postflight, the ventilation at an  $\text{SaO}_2$  of 75% was elevated by 19% compared with preflight in the standing position ( $P < 0.05$ ) but was unaltered compared with preflight in the supine position (Table 1). There

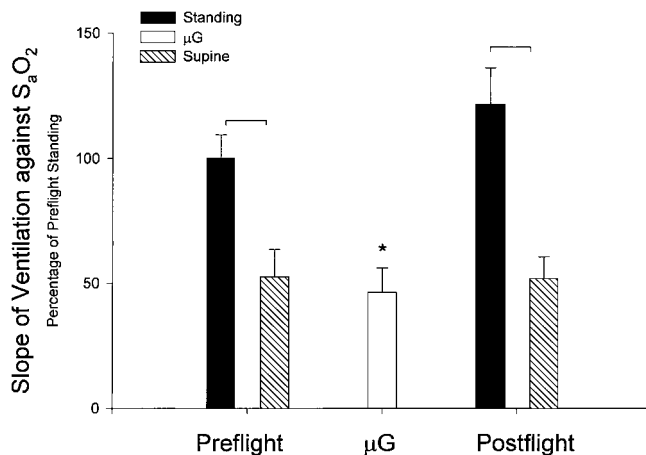


Fig. 2. Slope of ventilatory response to hypoxia calculated as rise in ventilation resulting from a decrease in  $\text{SaO}_2$ . Data are normalized to each subject's preflight standing control. Error bars, SE. Brackets between adjacent bars show  $P < 0.05$ . \* $P < 0.05$  compared with preflight study.

were similar changes in both the slope and the intercept of the response, but these changes failed to reach the level of significance. When we examined the day-to-day changes in the ventilation at an  $\text{SaO}_2$  of 75%, we found no consistent changes during the 16 days of the flight (Fig. 3). Similarly, there was no change in the response with time either standing or supine in the postflight period.

The strategy utilized to reduce the HVR was primarily one of a smaller increase in tidal volume for a given level of hypoxia (Table 1). The increase in tidal volume

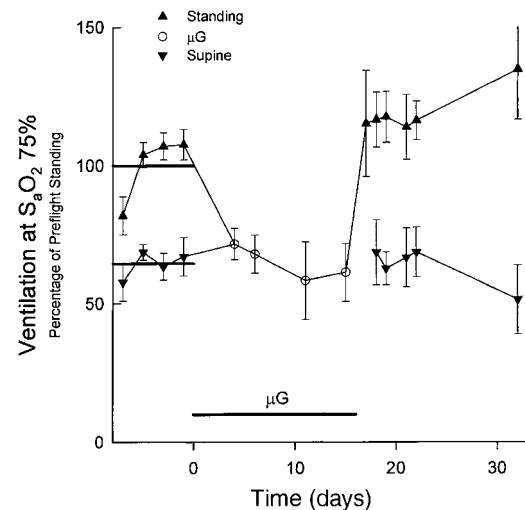


Fig. 3. Ventilation calculated at  $\text{SaO}_2$  of 75% from hypoxic ventilatory response. Heavy lines at left show average preflight control values. Note that preflight data have been given in arbitrary times and were collected in 3 mo preceding spaceflight (see text for details). Error bars, SE.

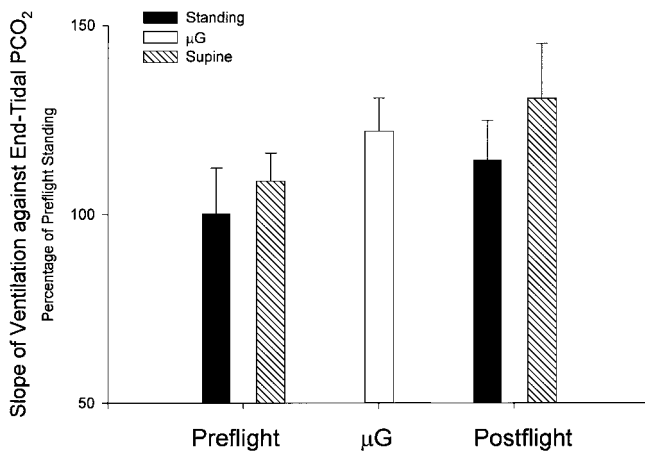


Fig. 4. Slope of ventilatory response to carbon dioxide. Data are normalized to each subject's preflight standing control. Error bars, SE.

measured at an  $\text{SaO}_2$  of 75% was reduced to  $75 \pm 4\%$  in  $\mu\text{G}$  and to  $73 \pm 3\%$  in the supine position. In contrast, the increase in respiratory frequency that occurred at an  $\text{SaO}_2$  of 75% was only slightly reduced to  $89 \pm 7\%$  in  $\mu\text{G}$  and to  $90 \pm 4\%$  in the supine position, neither of which was significantly different from control values (Table 1).

The degree to which we were able to control the end-tidal  $\text{PCO}_2$  is indicated in Table 1. End-tidal  $\text{PCO}_2$  was constant at  $\sim 46$  Torr ( $\sim 6.4\%$ ) for all measurements made standing and in  $\mu\text{G}$ . In the supine studies, end-tidal  $\text{PCO}_2$  was elevated significantly in postflight measurements (1.5 Torr), and, although not statistically significant, it was also slightly elevated in preflight supine studies.

**HCVR.** Figure 4 and Table 2 show the slope of the line of best fit of ventilation against  $\text{PCO}_2$ . There was no significant change in the slope of the response among standing, supine, and  $\mu\text{G}$ , although this did become slightly steeper in  $\mu\text{G}$  than standing and supine. Post-flight there was a persisting (although not a significant) elevation in the slope of the response. There was a corresponding small increase in the  $\text{PCO}_2$  at zero ventilation both in the supine position and  $\mu\text{G}$  (Table 2). Taken together, these changes suggest a slight steepening of the response with a concomitant shift of the line to the right. The end-tidal  $\text{PCO}_2$  measured during quiet breathing rose from 36 Torr standing preflight, to 39 Torr inflight, and to 41 Torr supine. In the LMS subjects, there were no significant changes in the slope or intercept, with the slope in  $\mu\text{G}$  being 100% of that measured standing preflight. In that group of subjects there were no changes in end-tidal  $\text{PCO}_2$ .

Table 2 and Fig. 5 show the changes in ventilation resulting from elevated  $\text{CO}_2$  by plotting the ventilation calculated from the measured response at a  $\text{PCO}_2$  of 60 Torr. This measurement combines any change in slope with any change in intercept or set point. There was no alteration in  $\text{CO}_2$  response as a result of  $\mu\text{G}$  exposure (Table 2). Similarly, there was no significant difference in the HCVR as the length of time in  $\mu\text{G}$  increased (Fig. 5). The  $\text{CO}_2$  response was slightly reduced in the supine posture, but this did not reach the level of statistical significance preflight. A similar result was obtained from the subjects in the 17-day LMS flight (Fig. 6). Although no measurements were made in the supine position for that flight, there was no difference in the ventilation at a  $\text{PCO}_2$  of 60 Torr between normal gravity (1 G) and  $\mu\text{G}$ .

Table 2. Hypercapnic ventilatory response (Neurolab data only)

	Preflight				Inflight		Postflight			
	Standing 1 G	<i>n</i>	Supine 1 G	<i>n</i>	$\mu\text{G}$	<i>n</i>	Standing 1 G	<i>n</i>	Supine 1 G	<i>n</i>
Slope of ventilatory response, $\text{l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$	$2.32 \pm 0.35$		$2.46 \pm 0.35^e$		$2.67 \pm 0.34^e$		$2.44 \pm 0.31^e$		$2.70 \pm 0.33^e$	
$\text{PCO}_2$ at a ventilation of zero, Torr	$40.3 \pm 2.3$	18	$42.9 \pm 1.5^e$	20	$43.0 \pm 1.1^c$	20	$37.6 \pm 1.8^e$	30	$43.8 \pm 1.7^c$	25
Ventilation at $\text{PCO}_2 = 60$ Torr, l/min	$41.2 \pm 4.5$	18	$35.5 \pm 4.1^e$	20	$39.7 \pm 3.6^e$	20	$42.4 \pm 3.0^e$	30	$34.2 \pm 2.7^c$	25
Tidal volume at $\text{PCO}_2 = 60$ Torr, liters	$2.26 \pm 0.15$	18	$2.03 \pm 0.13^a$	20	$2.30 \pm 0.19^{b,c}$	20	$2.31 \pm 0.12^e$	30	$1.95 \pm 0.10^c$	25
Respiratory frequency at $\text{PCO}_2 = 60$ Torr, breaths/min	$17.1 \pm 1.0$	18	$16.7 \pm 1.2^e$	20	$17.4 \pm 1.0^e$	20	$18.3 \pm 0.5^e$	30	$17.0 \pm 0.7^e$	25
Inspiratory occlusion pressure when normoxic and normocapnic, Torr	$4.3 \pm 0.2$	58	$4.6 \pm 0.2^e$	31	$4.0 \pm 0.2^e$	47	$4.2 \pm 0.1^e$	87	$4.5 \pm 0.2^e$	51
Inspiratory occlusion pressure ( $50 < \text{PCO}_2 < 65$ Torr), Torr	$4.8 \pm 0.2$	38	$4.6 \pm 0.3^e$	29	$4.6 \pm 0.2^e$	65	$4.7 \pm 0.2^e$	60	$4.5 \pm 0.2^e$	35

Values are means  $\pm$  SE; values in parentheses are data normalized to those measured preflight standing, except for inspiratory occlusion pressures which are normalized to preflight standing while breathing air; *n*, no. of measurements. <sup>a</sup> $P < 0.05$  compared with preflight standing. <sup>b</sup> $P < 0.05$  compared with preflight supine. <sup>c</sup> $P < 0.05$  compared with postflight standing. <sup>d</sup> $P < 0.05$  compared with postflight supine. <sup>e</sup> $P =$  not significant.

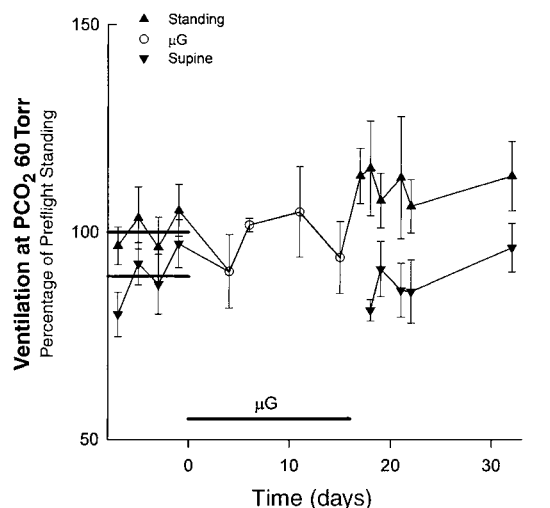


Fig. 5. Day-to-day values of ventilation calculated at a  $P_{CO_2}$  of 60 Torr from ventilatory response to carbon dioxide. Error bars, SE. Details are as for Fig. 3.

Despite slight differences in the ventilatory response and in resting gas-exchange status between flights, there were no environmental differences, with average inspired  $P_{CO_2}$  being 2.3 Torr in LMS and 2.8 Torr in Neurolab.

Table 2 shows the changes in tidal volume and respiratory frequency for the Neurolab crew. Tidal volume rose somewhat less in response to a given  $CO_2$  stimulus in the supine measurements than in the standing posture but was unaltered in  $\mu$ G. There were, however, no significant changes in the respiratory frequency at a  $P_{CO_2}$  of 60 Torr between conditions. In all conditions the minimum end-tidal  $PO_2$  reached exceeded 178 Torr, indicating that there was no stimulation of the HVR in these studies. The maximum  $P_{CO_2}$  reached at the end of the test was significantly lower both in the supine position ( $68.4 \pm 0.6\%$ ) and in  $\mu$ G ( $64.8 \pm 1.1\%$ ) compared with upright in 1 G ( $70.9 \pm 0.2\%$ ).

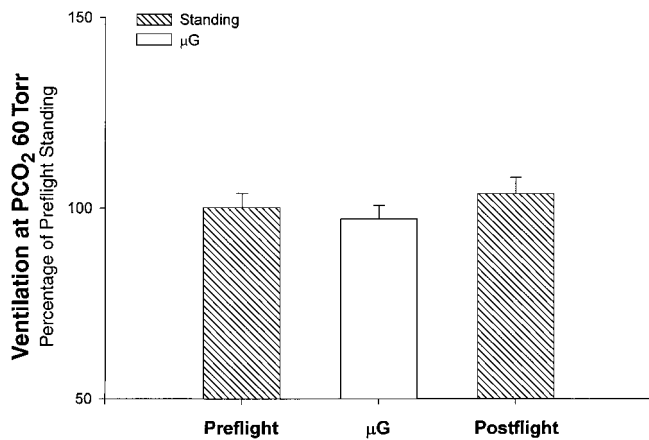


Fig. 6. Ventilation calculated at a  $P_{CO_2}$  of 60 Torr from ventilatory response to  $CO_2$  in Life and Microgravity Spacelab crew. Note that no supine data were collected in these subjects. Error bars, SE.

### Inspiratory Occlusion Pressures

The changes in inspiratory occlusion pressures were consistent with the overall changes in ventilatory response (see *HVR* and *HCVR*). Figure 7 shows the inspiratory occlusion pressures measured during air breathing and those measured during the HVR (in this case the pressures measured during breaths in which the end-tidal  $PO_2$  was between 75 and 85 Torr), and during the HCVR (end-tidal  $P_{CO_2}$  between 43 and 50 Torr). Occlusion pressures during the hypoxic test showed a marked increase above air breathing in all cases. However, the increase was significantly less in both the supine position and in  $\mu$ G than it was standing. Occlusion pressure during the measurement of the HCVR showed a modest increase above air breathing that was not different among the three conditions studied.

### DISCUSSION

*Alterations in the HVR.* The principal finding of this study is that the HVR in  $\mu$ G is greatly reduced, being only  $\sim 46\%$  of that measured standing in 1 G (Fig. 2, Table 1). This is essentially unaltered by the amount of time spent in  $\mu$ G (Fig. 3) up to the 15 days over which we were able to make measurements. On return to 1 G, the hypoxic response was slightly elevated compared with preflight control data, and this elevation persisted for at least 1 wk.

The HVR has two components: a slope, which reflects the rate at which ventilation rises with decreasing  $SA_{O_2}$ , and the intercept of this line, corresponding to the theoretical ventilation at an  $SA_{O_2}$  of zero. In the data we collected, both the slope and the intercept of the HVR showed significant reductions, with the slope being

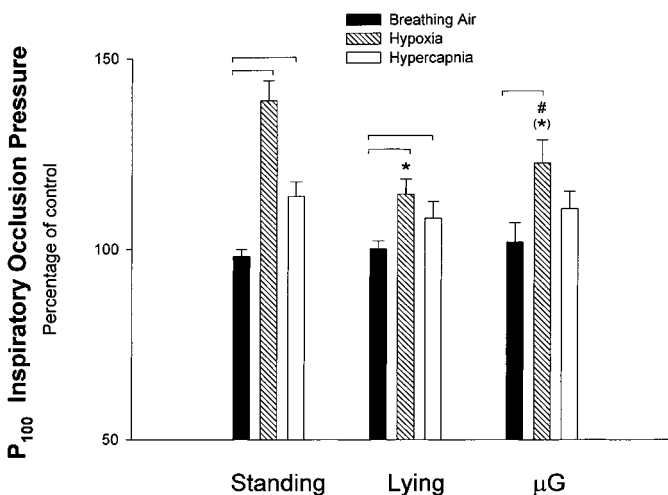


Fig. 7. Inspiratory occlusion pressure measured 100 ms after closure of a valve at beginning of inspiration ( $P_{100}$ ). Solid bars,  $P_{100}$  values during breathing of air; hatched bars,  $P_{100}$  measured during ventilatory response to hypoxia test when  $PO_2$  was between 75 and 85 Torr; open bars,  $P_{100}$  measured during ventilatory response to carbon dioxide test when  $P_{CO_2}$  was between 43 and 50 Torr. Brackets between adjacent bars indicate  $P < 0.05$ . \* $P < 0.05$  compared with preflight standing. # $P < 0.05$  compared with preflight supine. (\*) $0.10 < P < 0.05$ . Error bars, SE.

slightly more reduced than the intercept (Table 1). The degree of reduction seen in  $\mu\text{G}$  in the HVR closely matched that seen in the response measured after the subjects assumed the supine position. These measurements were generally made within 5–40 min of becoming supine.

The strategy used to generate the lower ventilations seen both in  $\mu\text{G}$  and supine are shown in Table 1. To a large extent, the differences seen in ventilation at an  $\text{SaO}_2$  of 75% result from differences in the increase in the tidal volume and not from alterations in frequency. Only postflight were there changes in respiratory frequency (a slight increase) that reached the level of significance. These changes match the strategy used to produce a lower ventilation under resting breathing conditions in  $\mu\text{G}$  (19), where frequency was largely unaltered and tidal volume decreased to reduce total ventilation compared with standing in 1 G. In the transition from the lower ventilation condition seen in normoxia to that stimulated by hypoxia, our subjects similarly elected to change tidal volume to a greater extent than frequency.

The reduction in HVR can be explained by a reduction in neural drive to the respiratory muscles. This conclusion is supported by the inspiratory occlusion pressure measurements (Fig. 7). The inspiratory occlusion pressure has been shown to provide a good indirect measure of the drive to the respiratory muscles (28). Hypoxia ( $\text{Po}_2$  between 75 and 85 Torr) resulted in a substantial rise in the inspiratory occlusion pressure in all cases, although there were marked differences in the magnitude of the increase between the different conditions tested. The greatest response was measured with the subjects standing, where there was an increase of  $\sim 40\%$  above that measured breathing air. Although there was no change in the inspiratory occlusion pressure measured during air breathing in either the supine position or in  $\mu\text{G}$ , the increase seen during hypoxia in the supine position or in  $\mu\text{G}$  was significantly less than the increase measured standing. In  $\mu\text{G}$ , the occlusion pressure rose by  $\sim 20\%$  above air breathing at the same level of hypoxia, and with the subject supine the increase was only  $\sim 15\%$  at this level of hypoxia. Such reductions suggest that the hypoxic drive is approximately halved by either the supine position or by  $\mu\text{G}$ , an observation consistent with the  $\sim 50\%$  reduction seen in the slope of the ventilatory response (Fig. 2).

*Alterations in the HCVR.* In sharp contrast to the HVR, there were no, or only small, changes in the HCVR. We collected data on two different crews of five and six subjects, each exposed to 16 or 17 days of  $\mu\text{G}$  (there was 1 crew member in common between these 2 groups). In Neurolab (Fig. 4) we also collected 1-G data in the supine posture. There was no change in the HCVR caused by  $\mu\text{G}$  in either group. The supine position did cause a slight drop in the overall response measured postflight (Table 2), but the corresponding difference measured preflight did not reach the level of statistical significance. Similarly, there was no evi-

dence for a change in the HCVR with time either inflight or postflight (Fig. 5).

There was no overall change in the HCVR as measured by the ventilation at a  $\text{PCO}_2$  of 60 Torr caused by exposure to  $\mu\text{G}$ . However, there was an indication that the slope of the response steepened somewhat both in  $\mu\text{G}$  and supine (Fig. 4), and that this was accompanied by a concomitant increase in the  $\text{PCO}_2$  at a calculated ventilation of zero (Table 2). However, only the zero intercept showed a statistically significant increase. There was also an increase in the end-tidal  $\text{PCO}_2$  of the Neurolab subjects measured during quiet breathing. The increase from 36 to 39 Torr was smaller than that seen between standing and supine (from 36 to 41 Torr) but raises the possibility of a shift in the set point of the  $\text{PCO}_2$ . Measurements made in an environmental chamber study in which the  $\text{PCO}_2$  was elevated to 1.2% (8.6 Torr) showed an early increase in the set point (6) that gradually abated. However, that study failed to show any significant alterations when the environmental  $\text{PCO}_2$  was controlled at 5.0 Torr. In the case of Neurolab, environmental  $\text{PCO}_2$  averaged  $\sim 2.3$  Torr, a level below that in the chamber studies. Furthermore, on LMS we saw no alteration in the slope and intercept of the response, and no change in resting end-tidal  $\text{PCO}_2$ , despite similar environmental levels of  $\text{CO}_2$  (2.8 Torr). Taken together, there is no convincing evidence for a change in the components of the HCVR that combine to leave ventilation at a  $\text{PCO}_2$  of 60 Torr unaltered.

The tidal volume at a  $\text{PCO}_2$  of 60 Torr was unaltered in  $\mu\text{G}$ . However, there was a small but significant reduction in the supine position (Table 2). This reduction accounted for virtually all of the difference in ventilation at a  $\text{PCO}_2$  of 60 Torr because there were virtually no changes in respiratory frequency. The absence of a change in tidal volume in  $\mu\text{G}$  is important because it indicates that when ventilation was stimulated, there was no mechanical reason per se that the increase in tidal volume was limited. Thus it is reasonable to assume that the reduction in tidal volume seen in the HVR test in  $\mu\text{G}$  (Table 1) is a result of changes in neural drive to the respiratory muscles and not a result of those muscles being at a mechanical disadvantage to respond in the absence of gravity. However, when the studies were performed supine, both the HVR and HCVR showed a reduction in tidal volume. The reduction in tidal volume was less in the case of the HCVR, but the possibility exists that a small part of the reduction in tidal volume seen in the HVR may be a direct result of the respiratory muscles being mechanically less able to respond to a given stimulus in the supine position.

The inspiratory occlusion pressure measurements support the absence of any significant change in hypercapnic drive in  $\mu\text{G}$  (Fig. 6). Although there was a modest increase in inspiratory occlusion pressure measured during mild hypercapnia ( $\text{PCO}_2$  between 43 and 50 Torr), there was no measurable difference among the three conditions studied. A  $\text{PCO}_2$  level between 43 and 50 Torr elicited an increase in inspiratory occlusion pressure above that measured breathing air of between



8 and 15% in the various conditions studied, none of which were significantly different from each other (Table 2, Fig. 7). Thus they closely match the HCVR results, which show a uniform increase in ventilation with rising  $\text{CO}_2$  between the different conditions studied.

*Potential mechanisms of changes in the HVR.* Previous studies of the effect of posture on the HVR have shown a reduction in the HVR in the supine position compared with the upright. Xie et al. (29) showed a 43% reduction in the slope of the HVR in five normal men when they were supine compared with that in the upright seated position. The control subjects in a study of Parkinson's disease had a supine HVR of  $\sim 70\%$  of that measured seated in the group aged 20–28 yr and  $\sim 57\%$  of that measured in an older group of aged 57–73 yr (25). The age of our subject population is intermediate between those groups, and our subjects showed a reduction to  $\sim 50\%$  of that measured standing both in the supine position and in  $\mu\text{G}$ .

It has long been known that cardiovascular changes directly affect respiration. In his 1945 Nobel Prize lecture, Heymans noted that "variations in arterial blood pressure exert an effect on the respiratory center . . . by a reflex mechanism involving the aortic and carotid sinus receptors." (13). In cats, hypotension increased the firing rate of aortic chemoreceptors markedly and slightly increased the neural output from carotid chemoreceptors (14, 15). However, the effects of hypotension on the carotid body firing rate was much more pronounced under hypoxic conditions, although still less than that of the aortic chemoreceptors. Similarly, in dogs, hypotension increases carotid body activity (11). This is known to occur via a central pathway through changes in peripheral chemoreceptor activation, as opposed to a direct effect on the peripheral chemoreceptors themselves, because unilateral changes in baroreceptor pressure altered chemoreceptor response on the contralateral side (11, 12). Ventilation under normoxic conditions was slightly increased by large reductions in carotid sinus blood pressure in dogs (3).

In humans there is less direct evidence for a strong coupling. However, Somers et al. (26) showed that an increase in carotid level blood pressure inhibited the ventilatory response to isocapnic hypoxia. The increase in carotid level blood pressure of  $\sim 10$  mmHg resulted in a 33% smaller increase in ventilation elicited by a hypoxic challenge of breathing 10%  $\text{O}_2$ .

The blood pressure measured at the level of the heart changes only slightly between standing and supine (8). The mean arterial blood pressure calculated from these data rose  $\sim 3$  mmHg when the subjects were supine. However, the transition from the standing position to supine in 1 G abolishes the hydrostatic difference in pressure between heart level and carotid level. Thus, in the supine position, we would expect an increase in carotid level blood pressure of 15–20 mmHg because of hydrostatic effects. Adding these two effects suggests that overall there is an increase in carotid level pressure of  $\sim 20$  mmHg.

This increase in pressure could explain the decrease in HVR we observed in the supine position. The magnitude of the decrease in HVR we saw is greater than that seen in humans by Somers et al. (26). However, in their case the degree of hypoxia they imposed was less than we used ( $\text{Sa}_{\text{O}_2}$  decreased to 83 or 84%, compared with a target minimum of 75% in this study), and they induced a change in blood pressure of only 10 mmHg compared with the  $\sim 20$  mmHg change in blood pressure at the carotid level that likely occurred here. Thus it seems likely that the greater effect we saw compared with that of Somers et al. (26) is a direct result of the lower  $\text{Sa}_{\text{O}_2}$  and hence  $\text{PO}_2$  and the larger change in carotid level blood pressure in our subjects.

Although the aortic chemoreceptors are known to be more sensitive to blood pressure changes than are the carotid chemoreceptors (14, 15), it seems unlikely that such a small change in mean arterial pressure could produce these results, given the almost absent hydrostatic gradient between the heart and the aortic chemoreceptors in the upright position in 1 G.

$\mu\text{G}$  results in only modest changes in heart-level blood pressure. Calculations based on the data of Fritsch-Yelle (8) indicate a decrease of  $\sim 4$  mmHg at heart level. In the absence of gravity, the hydrostatic gradient between heart level and the carotid region is absent. Thus, despite the slight decrease in heart level blood pressure, it is likely that carotid level blood pressure in  $\mu\text{G}$  is considerably above that in the standing posture in 1 G. Such an increase is consistent with the physical changes such as facial puffiness associated with the early period in  $\mu\text{G}$  (18).

The sustained time course of these changes is interesting. Figure 3 shows that the magnitude of the change in HVR persists throughout the flight, and, although the changes are not significant, the mean values suggest that the response may be even more reduced by longer exposure to  $\mu\text{G}$ . The blood pressure data from Fritsch-Yelle et al. (8) indicate that there is no significant change in blood pressure over the course of 5–10 days in flight. This suggests that the effect that reduces the HVR is not as a result of a rapidly adapting receptor. This is, therefore, in contrast with the results of Biscoe et al. (2), who showed that chemoreceptor activity in response to abrupt changes in carotid sinus pressure in the cat was short lived.

Blood pressure falls in the upright position in the period immediately after flight to a variable degree (7). However, by 3 days postflight, Fritsch-Yelle et al. (9) showed that the blood pressure had essentially returned to preflight levels. Despite this, our data show a persistent elevation of the HVR postflight (Fig. 1B). The reasons for this are unclear, and we cannot rule out some persisting reduction in systolic blood pressure at the carotid level in our subjects during this period. Certainly, in these subjects, there was a persisting reduction in cardiac stroke volume of  $\sim 10\%$  for the 1 wk immediately after flight, although a concomitant tachycardia maintained cardiac output (G. K. Prisk, J. M. Fine, A. R. Elliott, and J. B. West, unpublished observations). Given these conditions, the possibility exists

that carotid systolic pressure was slightly reduced compared with preflight and this may have contributed to the increase in HVR we observed in the standing posture postflight.

Some previous studies have attributed a reduction of the HVR in the supine position to greater airflow resistance and limitation of peak inspiratory pressure (1, 4). We consider this unlikely to be a large effect in these subjects as did Xie et al. (29). We previously studied forced spirometry in a similar astronaut population in both the upright and supine positions and in  $\mu\text{G}$  (5). Although there was a modest reduction in the forced VC and forced expiratory volume in 1 s in the supine posture in 1 G, and early in flight, the changes are unlikely to explain the degree of ventilation increase we saw in response to hypoxia.

Nor do our data support a reduction in inspiratory pressure due to mechanical factors. As Fig. 7 shows, inspiratory occlusion pressure breathing air was unaltered by the supine posture in 1 G or by  $\mu\text{G}$ . This would not be expected if the cause of the reduced HVR supine and in  $\mu\text{G}$  was mechanical in origin. Furthermore, there was no difference between any of the conditions studied in the inspiratory occlusion pressures during the HCVR test (Fig. 7).

*Potential mechanisms of changes in the HCVR.* Most of the HCVR can be ascribed to the central chemoreceptors. However, a significant component of the response comes from the carotid chemoreceptors (16). We reasoned that, although there might be no change of the central chemoreceptor response to  $\text{CO}_2$  as a result of exposure to  $\mu\text{G}$ , there may well be some change in the peripheral component of this response. Our data show that this is not the case. These results are consistent with those of Xie et al. (29), who show a reduction in the HVR, but not the HCVR, in the supine position compared with the upright position.

*Technical considerations.* The data we obtained showed good reproducibility (Figs. 3 and 5). The hypoxic tests were performed under slightly elevated isocapnic conditions to maintain good control of the end-tidal  $\text{PCO}_2$  levels over the course of each test and among tests. Although there was some variation between end-tidal  $\text{PCO}_2$  levels in different subjects, the variation was small in the preflight standing control data.  $\text{PCO}_2$  ranged from 45 to 47 Torr between subjects, but, in all cases, the SE within a subject was 0.7 Torr or less. Between conditions tested, end-tidal  $\text{PCO}_2$  was  $45.7 \pm 0.4$  Torr standing and in  $\mu\text{G}$  and was  $47.1 \pm 0.4$  Torr supine.

The constraints of spaceflight forced us to choose a test that could be performed rapidly. The rebreathing technique of Rebeck and Campbell (24) fulfills this criterion. However, this technique has the disadvantage that the slight elevation in  $\text{PCO}_2$  results in some stimulation of the  $\text{CO}_2$  receptors. Because of the body's capability to store  $\text{CO}_2$ , a steady state is not reached for some minutes after the elevation in  $\text{CO}_2$  in this test (23). A subsequent modification to the technique (17) holds the end-tidal  $\text{PCO}_2$  constant for 6 min before the hypoxic phase of the test is begun, allowing the body

stores of  $\text{CO}_2$  to stabilize. The constraints of spaceflight (in particular, crew time and gas storage) precluded use of this approach. However, our experimental design and the results allow us to be confident that this effect is not a serious problem in this instance. We utilized exactly the same technique to measure the HVR preflight, inflight, and postflight, so any effects relating to the time course of the  $\text{CO}_2$  rise in the body stores should be constant. In addition, there was no significant change in the HCVR among the three conditions studied (upright, supine, and  $\mu\text{G}$ ), and so any confounding influence of the slow rise in  $\text{CO}_2$  in the body stores is the same in all three groups. Finally, the change we observed in the HVR is large, and any influence of subtle changes in the interaction between the HVR and HCVR is likely to be small in comparison.

There were significant differences between conditions in the maximum level of  $\text{PCO}_2$  reached at the end of the HCVR test. In the 4 min of rebreathing during preflight testing,  $\text{PCO}_2$  rose to 71 Torr (our cutoff point) before 4 min had elapsed in 69% of tests performed standing preflight. Our subjects were able to tolerate these  $\text{CO}_2$  levels, and this is reflected by the preflight standing data, which showed a maximum  $\text{PCO}_2$  of  $\sim 71$  Torr standing. However,  $\text{CO}_2$  rose more slowly in the supine position, possibly as a result of the increase in cardiac output in that position (21). As a consequence, the maximum  $\text{CO}_2$  reached was lower because 63% of tests were terminated because they reached the 4-min time limit. In  $\mu\text{G}$ , the maximum  $\text{CO}_2$  was lower still as a consequence of a slower rise in  $\text{CO}_2$  and because 15% of the tests were terminated voluntarily by the subject compared with only  $\sim 5\%$  preflight. Because a number of the tests were terminated below 65 Torr  $\text{CO}_2$ , the upper limit of our line-fitting procedure, the possibility exists that our data are slightly skewed by different fitting ranges. However, the effect is likely small, because the ventilatory response to  $\text{CO}_2$  over the fitting range of 50–65 Torr  $\text{CO}_2$  is fairly linear. Thus we are confident that errors occasioned by differences in the line-fitting interval are small.

In summary, measurements of the HVR and HCVR were made in subjects exposed to  $\sim 2$  wk of  $\mu\text{G}$ .  $\mu\text{G}$  caused a large reduction in the HVR of similar magnitude to that seen when the subjects were in the supine position. This reduction in the response was not different between measurements made on *day 4* of the flight and measurements made on *day 15* of the flight. In sharp contrast to the HVR, there were no changes in the HCVR. Measurements of the inspiratory occlusion pressure made during the test showed no change between 1 G and  $\mu\text{G}$  during breathing of air, nor was there any difference when  $\text{CO}_2$  was elevated. However, breathing a lower oxygen mixture resulted in a much larger increase in occlusion pressure standing in 1 G than in  $\mu\text{G}$ , or in the supine position in 1 G, consistent with the measurements of the ventilatory response. The reduced occlusion pressures indicate a reduction in respiratory center output. The lack of a significant change in the hypercapnic response suggests that in  $\mu\text{G}$  there is no change in the central sensing mechanism

responsible for  $\text{CO}_2$  drive. The changes in the HVR are consistent with a reduction in chemoreceptor output, resulting from an increase in blood pressure in the carotid baroreceptors associated with both the supine position and with  $\mu\text{G}$  compared with standing in 1 G.

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