

Microgravity Reduces Sleep-disordered Breathing in Humans

ANN. R. ELLIOTT, STEVEN A. SHEA, DERK-JAN DIJK, JAMES K. WYATT, EYMARD RIEL, DAVID F. NERI, CHARLES A. CZEISLER, JOHN B. WEST, and G. KIM PRISK

Department of Medicine, University of California, San Diego, La Jolla, California; Circadian, Neuroendocrine and Sleep Disorders Section, Division of Endocrinology, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; and NASA Ames Research Center, Mountain View, California

To understand the factors that alter sleep quality in space, we studied the effect of spaceflight on sleep-disordered breathing. We analyzed 77 8-h, full polysomnographic recordings (PSGs) from five healthy subjects before spaceflight, on four occasions per subject during either a 16- or 9-d space shuttle mission and shortly after return to earth. Microgravity was associated with a 55% reduction in the apnea-hypopnea index (AHI), which decreased from a preflight value of 8.3 ± 1.6 to 3.4 ± 0.8 events/h inflight. This reduction in AHI was accompanied by a virtual elimination of snoring, which fell from $16.5 \pm 3.0\%$ of total sleep time preflight to $0.7 \pm 0.5\%$ inflight. Electroencephalogram (EEG) arousals also decreased in microgravity (by 19%), and this decrease was almost entirely a consequence of the reduction in respiratory-related arousals, which fell from 5.5 ± 1.2 arousals/h preflight to 1.8 ± 0.6 inflight. Postflight there was a return to near or slightly above preflight levels in these variables. We conclude that sleep quality during spaceflight is not degraded by sleep-disordered breathing. This is the first direct demonstration that gravity plays a dominant role in the generation of apneas, hypopneas, and snoring in healthy subjects.

Keywords: obstructive sleep apnea; airway collapse; arousals; gravitational effect

Sleep disruption and reduced sleep duration have been documented during spaceflight in both American astronauts and Russian cosmonauts, but the cause of the sleep disruptions remains unknown (1–3). Poor sleep quality in combination with the need for impeccable daytime performance has led to the usage of hypnotics at least once in as many as 50% of the astronauts during a given mission (2) and hypnotics are among the most commonly used medication during spaceflight (4). Our aim was to determine whether sleep-disordered breathing was related to the increase in sleep disruption observed during spaceflight.

Gravity significantly influences both respiratory mechanics and chemoreceptor function (5, 6). Our hypothesis was that alterations in these factors during spaceflight could have important effects on respiratory instabilities and arousal from sleep, mediated by either central or obstructive respiratory disturbances. However, conflicting factors are involved.

On the one hand, the removal of gravity might be expected to decrease any sleep-related upper airway obstruction because obstructive sleep apnea occurs more commonly when lying supine. The action of gravity on the upper airway struc-

tures is believed to be responsible for positional sleep-disordered breathing and is probably one of the primary factors in the upper airway resistance syndrome in humans (7).

On the other hand, the removal of gravity might be expected to increase any sleep-related respiratory disturbances and sleep disturbance because microgravity causes a headward shift in blood and body fluids (8) that could affect both respiratory mechanics and chemoreceptor function. For instance, increased fluid volume in the head and neck could passively reduce upper airway caliber, thereby increasing the propensity for obstructive events. Microgravity reduces the hypoxic ventilatory response by about 50% compared with the upright posture, so that the response is comparable to that measured in the supine position on the ground (6). Chemoreceptor function has been strongly implicated in the initiation of both obstructive and central periodic breathing (9) as well as the ultimate arousal from sleep caused by blood gas derangement during apneas (10, 11).

To date, only one other spaceflight experiment has attempted to examine the respiratory system during sleep. A joint Japanese–Russian experiment monitored diaphragmatic electromyogram (EMG) and sleep in one astronaut for 30 h of spaceflight (12). These investigators found a reduction in diaphragmatic EMG activity during sleep in space and attributed this effect to a reduction in upper airway resistance; however, resistance was not directly measured.

Our experiment was part of a set of experiments on two National Aeronautics and Space Administration (NASA) spaceflight missions (flight STS-90 [NeuroLab] and flight STS-95) in 1998. Our experiment is the first to perform full polysomnography, including measurements of breathing in astronauts before, during, and after spaceflight, and to focus on whether the frequency or character of any sleep-disordered breathing was altered during spaceflight. The hypercapnic and hypoxic ventilatory responses were measured during wakefulness in these subjects and have been published elsewhere (6).

METHODS

Subjects and Data Collection Schedule

Experiment protocols were approved by the Institutional Review Boards of NASA Johnson Space Center, the University of California San Diego, and the Brigham and Women's Hospital. The subjects provided written informed consent to perform all aspects of the protocol. We studied one female and four males. Four subjects flew on NeuroLab and one on STS-95. The average age of the subjects was 41.0 ± 2.7 (SD) yr, height 181 ± 13 cm, weight 79 ± 14 kg, and body mass index (BMI) 24.0 ± 1.6 kg/m². All subjects were healthy as indicated by comprehensive NASA physical examinations, reported no sleep disorders, were nonsmokers, and had FVC and FEV₁ within the predicted normal range.

A total of 77 polysomnographic recordings (PSGs) were collected (range 13–16 PSGs per subject), and included nine preflight PSGs per subject (only six for the subject on STS-95), four inflight PSGs per subject, and three postflight PSGs per subject. Each PSG period was 8 h long.

(Received in original form October 16, 2000 and in revised form April 12, 2001)

Supported by National Aeronautics and Space Administration Contracts NAS9-18764 and NAS9-19434, and National Institutes of Health Grant U01-HL53208-01.

Correspondence and requests for reprints should be addressed to G. Kim Prisk, Ph.D., Department of Medicine-0931, University of California, San Diego, 9500 Gilman Dr., La Jolla, CA 92093-0931. E-mail: kprisk@ucsd.edu

This article has an online data supplement, which is accessible from this issue's table of contents online at www.atsjournal.org

Am J Respir Crit Care Med Vol 164, pp 478–485, 2001
Internet address: www.atsjournals.org

Pre-flight PSGs were performed in batches of two to three consecutive nights on the evenings of 102–101, 73–72, and 45–44 d and 7–6–5 d prior to launch (77–76, 50–49, and 38–37 d before launch for the STS-95 subject). The four in-flight PSGs were collected during two pairs of consecutive nights between Day 3 and Day 15 of STS-90 (recording blocks were separated by ~ 1 wk) and between Day 4 and Day 8 of the STS-95 mission. Postflight sleep sessions for all subjects occurred on Day 1 (~ 36 h after landing) and Days 3 and 4 after returning to earth (i.e., on the second, fourth, and fifth sleep episodes following return to earth). During flight, the cabin atmosphere was normoxic (760 mm Hg, 21% O_2) with a slightly elevated CO_2 ($\sim 0.4\%$). All preflight and postflight PSGs were performed in Crew Quarters at the Johnson Space Center or at a local hotel (STS-95 subject only). The preflight and postflight bedtime or lights out for each subject was at $\sim 11:00$ P.M. (local time, CST) and wake-up was $\sim 7:00$ A.M. in order to ensure an 8-h sleep period. The exception to this was on the first postflight recording night when the four subjects from Neurolab requested to go to bed ~ 1 h earlier because of fatigue. During the in-flight PSGs, the subjects slept in private sleep compartments. The four-tier sleep compartments contained a sleeping bag/liner, a light, and a ventilation inlet and outlet in each of the tiers. The compartment was about 2 m long, 0.75 m high, and wide enough for one. Due to launch and landing constraints, the time for each 8-h sleep period shifted earlier each day (20 min/d during the 16-d Neurolab mission and 35 min/d during the 9-d STS-95 flight). Exact time for lights off and on for each subject was recorded on each personal sleep recorder by means of a light sensor integrated into the subject's microphone taped to his or her neck. Subjects refrained from consuming caffeine or alcohol in the 12 h preceding all PSGs.

During some sessions, the subjects were also instrumented with a continuous body temperature sensor (an ingestible pill system, CorTemp 100 sensor; HTI Technologies, St. Petersburg, FL, with a belt-worn receiver; Personal Electronics Devices, Wellesley, MA), and a wrist activity monitor (Mini-Motion Logger; Ambulatory Monitoring Inc., Ardsley, NY).

Sleep-monitoring System

The sleep monitoring system that was developed for this spaceflight experiment consisted of a portable digital sleep recorder, a custom fitted sleep cap and respiratory inductance plethysmography body suit, a cable harness, an impedance meter, and a computerized signal-quality assessment system. This system was also used for all preflight and postflight recordings using the same procedures as those used in-flight. The crew was trained extensively prior to flight. During flight, they worked in pairs to instrument themselves and verify signal quality just prior to bedtime. During preflight and postflight sessions, instrumentation was performed by technicians.

The digital sleep recorder was a Vitaport-2 (TEMEC Instruments B.V., The Netherlands). The Vitaport-2 is a $4 \times 9 \times 15$ -cm digital recording device with data storage on an 85-Mb Flash RAM card providing the capability of recording the montage used in this experiment for more than 10 h using internal batteries. The recorder was configured to acquire 16 data channels. There were four electroencephalogram (EEG) channels, O1/A2, O2/A1, C3/A2, and C4/A1 (128 Hz with a 0.33-s time constant high pass filter, 70-Hz low pass filter); two electrooculogram (EOG) channels (64 Hz, 1-s time constant high pass, 35-Hz low pass); and two EMG channels (128 Hz, 0.015-s time constant high pass, 100-Hz low pass). Additional measurements included nasal/oral air flow (three-pronged thermistor adhered to upper lip; EdenTec Corporation, Eden Prairie, MN, 32 Hz), rib cage and abdominal motion (respiratory inductance plethysmography, 32 Hz), snoring (microphone attached to the neck at the level of the larynx), light (detector incorporated into microphone on throat), arterial oxygen saturation via pulse oximetry (SA_{O_2} ; Ohmeda Flex-probe; Ohmeda Medical Inc., Columbia, MD, adhered to left ring finger), electrocardiogram (lead II, 256 Hz), and an event marker channel. There was no body position sensor in the system.

The electrophysiological head and face electrodes were integrated into an elastic lattice cap (Sleep-net; Physiometrix, Inc., N. Billerica, MA). Sleep-nets were individually tailored to each subject to ensure proper fit and reproducibility of electrode site placement. The elastic lattice of the Sleep-net positioned the C3/C4, O1/O2, and A1/A2 electrode sockets on the subject's head according to the International 10-

20 System of electrode placement. The ground reference socket was located above the nasion. The two EOG and four chin EMG sockets extended from the cap on insulated wire leads for easy placement of the collars via adhesive pads. The Sleep-net used disposable, Ag/AgCl electrodes (Hydradot; Physiometrix, Inc.) for sensing the electrophysiological signals. The skin was prepared with Nuprep (D.O. Weaver and Co., Aurora, CO). Function of each electrode was verified by impedance checking prior to each recording (maximum impedance 10 k Ω).

The remaining physiological sensors were integrated into a custom-fitted two-piece (vest plus shorts) lycra body suit (Blackbottoms; Salt Lake City, UT). The rib cage and abdominal wires for the inductance plethysmography measurements were sewn into the vest section of each suit with the chest band at the level of the nipples and the abdominal band over the umbilicus. Because the spine lengthens in microgravity, the vest section had adjustable shoulder straps and was held in place by attachment to the shorts with integrated velcro strips to ensure proper location of each band at all times. A single harness connected all leads from the subject's torso to the data recorder.

Signal quality was verified by connecting the recorder to an IBM Thinkpad computer (Model 755) that was configured with customized data acquisition and display software (13). The subjects were asked to perform a series of physiological calibrations and verify signal quality as displayed on the laptop screen. Once all signals were verified the communication link was terminated and the recording continued. The subjects were instructed to go to bed and turn the lights off at the designated bedtime to guarantee a full 8-h sleep period before scheduled wake-up time.

Data Analysis

The data recorded on the flash RAM cards were visualized on a Macintosh computer system using the Vitagraph software package (TEMEC Instruments B.V., Netherlands). All sleep and respiratory events were scored "manually" by certified polysomnographic technologists blinded to the test condition. Sleep was staged using the criteria of Rechtschaffen and Kales (14), and respiratory events were scored using the Atlas Task Force on the American Sleep Disorders Association (15). In brief, all respiratory events were at least 10 s duration; obstructive apneas required a cessation of airflow with continued respiratory effort (thoracoabdominal movement); central apneas required the absence of both airflow and thoracoabdominal movement; mixed apneas required both obstructive and central apneic characteristics; hypopneas required a reduction in either respiratory flow and/or respiratory effort with either an accompanying arousal of at least 3 s or arterial oxygen desaturation of at least 3%. Arousals of 3 s or greater in association with these respiratory events were scored using the criteria of the Atlas Task Force on the American Sleep Disorders Association (16) when they occurred within the 15 s following a respiratory event. The change in arterial oxygen saturation associated with the scored respiratory events was determined. The presence of snoring was scored "manually" on a 30-s epoch-by-epoch basis whenever the microphone signal exceeded 10% of full range for more than 50% of the 30-s epoch, and the microphone signal increased phasically with the inspiratory airflow signal during the epoch (i.e., it was not constant/ambient noise). The microphone threshold of 10% of full range was selected as the most appropriate level in which soft snoring could be detected, while avoiding "false positives" due to background noise.

Numerous indices of respiratory events were then calculated for each sleep period, including the apnea-hypopnea indices (number of respiratory events per hour of sleep) for the total sleep time and for rapid eye movement (REM) sleep (AHI_{REM}) and for non-rapid eye movement (NREM) sleep (AHI_{NREM}); the Respiratory Arousal Index (RAI, number of respiratory arousals/h of sleep) and the Snoring Index (SI = percentage of the total sleep time spent snoring). For each respiratory event, mean, maximum, minimum, and change in SA_{O_2} were measured (allowing for a 15-s delay in the pulse oximeter signal).

In addition, mean values of SA_{O_2} , respiratory rate (RR), and heart rate (HR) were calculated by averaging the 30-s epoch averages over 5-min periods separately for periods of wakefulness, slow wave sleep (SWS) at the beginning of the night ($SWS_{initial}$ = first 5-min period of Stage III or Stage IV sleep), and slow wave sleep at the end of the

night (SWS_{end} = last 5-min period of Stage III or Stage IV sleep) as an example of the differences between sleep and wakefulness. These averages were derived automatically using the Vitagraph software, whereas all other analyses noted above were manually scored.

Melatonin Administration

Part of the overall objective of the spaceflights was to determine the effectiveness of 0.3 mg of melatonin as a hypnotic for use in spaceflight. Melatonin or placebo was taken 30 min prior to scheduled bedtime for the preflight sessions at L-72 and L-45 d (L-50 and L-35, STS-95) and before all sleep episodes in flight. Administration occurred in a double-blinded manner such that melatonin or placebo was administered on alternate nights. Melatonin was not administered postflight. This small dose of melatonin had no effect on any of the measured variables when compared to placebo (e.g., two-way analyses of variance: $p = 0.18$ for preflight AHI_{TST} and 0.19 for inflight AHI_{TST}). Thus, for our purposes, statistical analyses were performed with the melatonin and placebo data combined.

Statistical Analysis of the Effect of Microgravity on Respiratory Disturbances

All data from the first pair of sleep recordings (those occurring approximately 90 d before flight) were excluded from data analysis to eliminate the effects of adaptation to the instrumentation. Descriptive statistics were performed and expressed as mean \pm SE. The apnea-hypopnea, snoring and arousal data were also expressed for each subject as a percentage of the preflight values; therefore, each subject served as his or her own control. Two-way analyses of variance were performed to compare preflight, inflight, and postflight data. Post hoc pairwise comparisons were performed using the Bonferroni adjustment. Differences were considered significant with p values less than 0.05.

RESULTS

The sleep results are the subject of a separate communication (D-J. Dijk, unpublished observations), but are briefly summarized here in order to relate the changes in respiratory disturbances to the overall quality of sleep. Total sleep time (TST, the total number of minutes the subject was asleep) averaged 408 ± 23 (mean \pm SD, $n = 5$) min preflight, which fell to 384 ± 9 min inflight (NS). Postflight TST was almost identical to that during preflight (405 ± 49 min). Sleep efficiency (TST as a percentage of lights-out time) was unchanged between preflight, inflight, and postflight ($85 \pm 5\%$, $83 \pm 2\%$, $85 \pm 9\%$, respectively). The percentage of TST spent in REM sleep was the same preflight and inflight ($24 \pm 5\%$ and $23 \pm 4\%$, respectively), but was somewhat higher postflight ($29 \pm 4\%$, NS). The percentage of TST spent in SWS was the same preflight and inflight ($15 \pm 3\%$ and $14 \pm 6\%$, respectively) but somewhat reduced postflight ($10 \pm 2\%$, NS).

Effect of Microgravity on Frequency of Apneas and Hypopneas

The average AHI_{TST} for the preflight population was 8.3 ± 1.6 events/h (Table 1). Three of the subjects had an AHI_{TST} below

TABLE 1. APNEAS, HYPOPNEAS, SNORING, AND AROUSALS DURING SLEEP

Period	AHI_{TST} (number/h)	AHI_{NREM} (number/h)	AHI_{REM} (number/h)	Snoring (%TST)*	Arousals _{RE} (number/h)
Preflight	8.3 ± 1.6	7.9 ± 1.7	9.7 ± 1.7	16.5 ± 3.0	5.5 ± 1.2
μG	$3.4 \pm 0.8^\dagger$	$2.7 \pm 0.8^\dagger$	$6.1 \pm 1.3^\ddagger$	$0.7 \pm 0.5^\ddagger$	$1.8 \pm 0.6^\ddagger$
Postflight	$9.5 \pm 2.2^\ddagger$	$8.0 \pm 2.3^\ddagger$	$12.9 \pm 2.5^\ddagger$	$18.2 \pm 3.0^\ddagger$	$6.0 \pm 1.9^\ddagger$

Definition of abbreviations: AHI = apnea-hypopnea index; arousals_{RE} = arousals associated with a respiratory event (see text for details); NREM = non-rapid eye movement sleep; μG = microgravity; REM = rapid eye movement sleep; Snoring = snoring above a predefined threshold as a percentage of TST (see text for details); TST = total sleep time.

* As a percentage of the preflight average (control) for that subject.

[†] Significantly different from preflight value.

[‡] Significantly different from inflight value.

5.0, one subject was 6.1 ± 1.1 , and the fifth subject had an AHI_{TST} of 22.7 ± 3.9 (see Table E1 in the online data supplement). AHI_{TST} for this population was primarily comprised of hypopneas with an average apnea index of 0.9 ± 0.3 , and a hypopnea index of 6.7 ± 1.2 during the preflight period (Figure 1). The AHI_{TST} for the inflight and postflight data was of similar composition. Our principal finding was that the AHI_{TST} decreased dramatically during microgravity by 55% when compared with preflight values, down to 3.4 ± 0.8 events/h. The corresponding apnea index decreased by 30% (0.3 ± 0.1 , NS) and the hypopnea index decreased by 55% (3.1 ± 0.8). On return to normal gravity postflight, the AHI_{TST} increased to 9.5 ± 2.2 , which was not statistically different from preflight. The postflight apnea index remained low (0.4 ± 0.1 , NS), but the hypopnea index (9.1 ± 2.3) was significantly greater postflight than preflight.

Effect of Microgravity on Apneas and Hypopneas in Different Stages of Sleep

During preflight, AHI_{REM} (9.7 ± 1.7) was $\sim 23\%$ greater than AHI_{NREM} (7.9 ± 1.7) (Figure 2 and Table 1). Microgravity resulted in a greater reduction in AHI_{NREM} (68%) compared with the decrease in AHI_{REM} (30%). On return to normal gravity postflight, the AHI_{NREM} returned to preflight values, but the AHI_{REM} was significantly increased by $\sim 50\%$ above preflight values. The AHI_{REM} was high for all three nights during the postflight period (12.5 ± 3.7 on the second night of recovery and 13.3 ± 3.9 and 13.0 ± 6.0 on the fourth and fifth nights, respectively).

Effect of Microgravity on Duration of Apneas and Hypopneas

The average of all the preflight apnea and hypopnea durations for the population was 32.4 ± 0.2 s. Inflight, the durations increased to 37.1 ± 0.4 s ($p < 0.05$) and remained at this level postflight (37.5 ± 0.3 s).

Effect of Microgravity on Arterial O₂ Saturation during Apneas and Hypopneas

The average Sa_{O_2} measured during a respiratory event was significantly higher during microgravity exposure ($99.6 \pm 0.1\%$) when compared with preflight ($97.1 \pm 0.1\%$) (Table 2). The average minimum in Sa_{O_2} during the respiratory events was 95.0 ± 0.1 preflight and increased to 98.4 ± 0.1 inflight. This

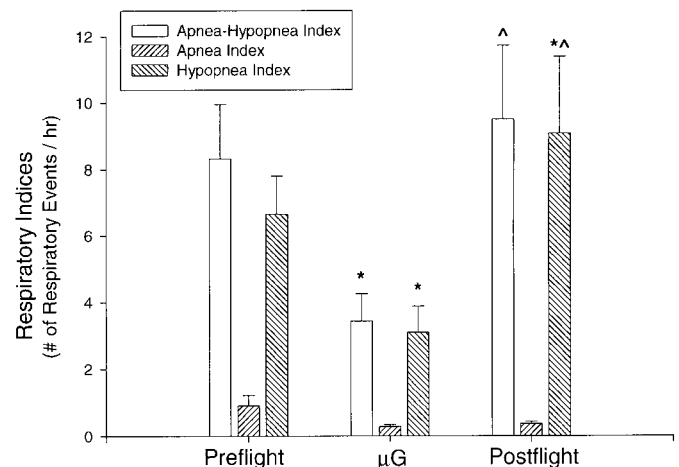


Figure 1. Respiratory indices (apnea-hypopnea index, apnea index, hypopnea index) for five subjects preflight, inflight, and postflight. *Significantly different from preflight value. **Significantly different from inflight value.

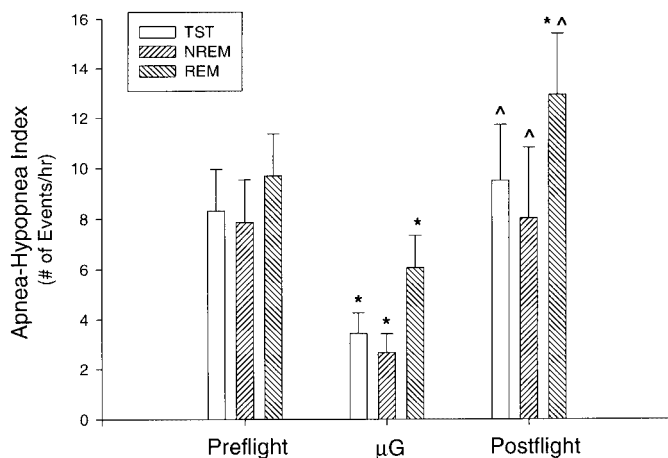


Figure 2. AHI for the total sleep time (TST), for NREM sleep time and for REM sleep time for five subjects preflight, inflight, and postflight. *Significantly different from preflight value. ^Significantly different from inflight value.

reduction in the minimum Sa_{O_2} is also associated with a reduction in the Sa_{O_2} difference between the beginning and end of a respiratory event during microgravity ($1.6 \pm 0.1\%$) as compared with preflight ($4.1 \pm 0.1\%$). Postflight, the average and minimum Sa_{O_2} were both slightly greater than preflight, and the corresponding Sa_{O_2} difference was reduced when compared with preflight. The postflight Sa_{O_2} average, minimum, and difference values were intermediate to those measured preflight and inflight.

Effect of Microgravity on Types of Apneas

When apneas were considered by type, the average number of obstructive apneas that occurred per preflight sleep period was 1.6 ± 0.7 compared with 4.4 ± 1.9 for central apneas and 1.2 ± 0.5 for mixed apneas. Inflight the number of obstructive apneas per sleep period decreased to essentially zero (0.1 ± 0.1), central apneas decreased to 1.65 ± 0.4 , and the mixed apneas decreased to 0.4 ± 0.2 events per sleep period. Obstructive apneas per postflight sleep period were 0.67 ± 0.25 , central apneas were 1.8 ± 0.4 , and mixed apneas were 0.33 ± 0.16 . None of the changes in the number of apneas was significant.

Effect of Microgravity on Snoring

The percentage of time spent snoring during the preflight sleep periods was $16.5 \pm 3.0\%$. Snoring essentially disappeared in microgravity ($0.7 \pm 0.5\%$) (Figure 3 and Table 1). Postflight the snoring returned to preflight levels ($18.2 \pm 3.0\%$). Percentage snoring was significantly correlated with AHI ($p <$

TABLE 2. ARTERIAL OXYGEN SATURATION DURING APNEAS AND HYPOPNEAS

Period	Sa_{O_2} Avg (%)	Sa_{O_2} Min (%)	Sa_{O_2} Diff (%)
Preflight	97.7 ± 0.1	95.0 ± 0.1	4.1 ± 0.1
μ G	$99.6 \pm 0.1^\dagger$	$98.4 \pm 0.1^\dagger$	$1.6 \pm 0.1^\dagger$
Postflight	$98.0 \pm 0.1^{\dagger,\ddagger}$	$96.4 \pm 0.1^{\dagger,\ddagger}$	$2.7 \pm 0.1^{\dagger,\ddagger}$

Definition of abbreviations: μ G = microgravity; Sa_{O_2} Avg = average arterial oxygen saturation during a respiratory event; Sa_{O_2} Diff = difference in arterial oxygen saturation from the beginning to the end of a respiratory event; Sa_{O_2} Min = minimum saturation observed during a respiratory event.

[†]Significantly different from preflight value.

[‡]Significantly different from inflight value.

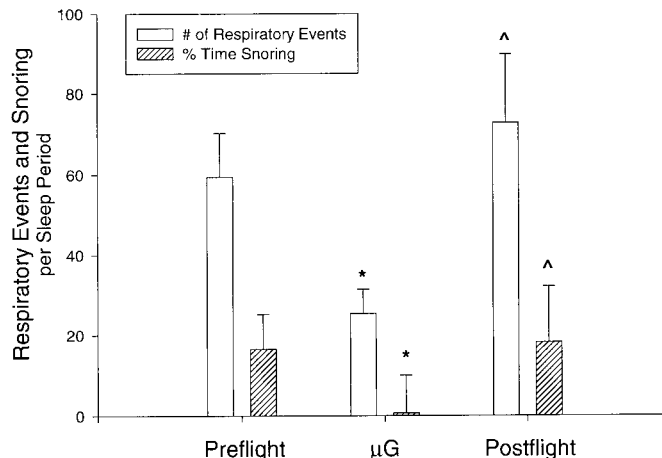


Figure 3. Relationship between the total number of respiratory events per sleep period and the percentage of time spent snoring for five subjects preflight, inflight, and postflight. *Significantly different from preflight value. ^Significantly different from inflight value.

0.05 , $r^2 = 0.31$), indicating that many of the scored hypopneas were likely obstructive rather than central hypopneas.

Arousals Associated with Apneas and Hypopneas

The number of arousals that immediately followed a scored respiratory event during the preflight sleep periods was on average 5.5 ± 1.2 arousals/h, within a total number of 18.0 ± 1.8 arousals/h (Figure 4). During microgravity, the number of respiratory arousals per hour decreased by 70% to 1.8 ± 0.6 and the total number of arousals per hour decreased by 19% to 13.4 ± 1.5 , almost all of which is a consequence of the reduction in arousals from respiratory causes (Figure 4). The most dramatic decrease in the arousal index was seen in one subject, whose inflight respiratory arousal index dropped from a preflight value of 16.3 ± 2.3 to 6.3 ± 1.1 events/h (see Table E1 in the online data supplement). This subject's total arousal index preflight was 35.7 arousals/h and significantly improved in microgravity dropping to 23.5 ± 1.5 . Postflight the respiratory arousals per hour increased to just above preflight levels

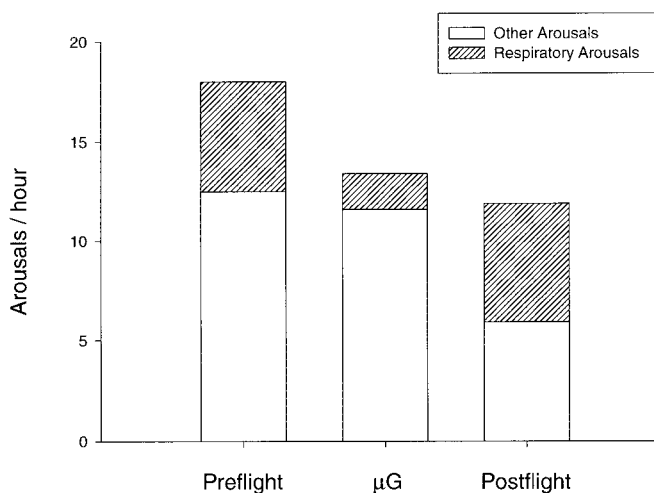


Figure 4. Arousals from respiratory and nonrespiratory causes (see text for definitions). Note that the reduction in the total number of arousals inflight is almost completely the result of the reduction in the number of respiratory arousals.

TABLE 3. Sa_O₂, RESPIRATORY RATE, AND HEART RATE DURING AWAKE CONDITION AND DURING SLOW WAVE SLEEP

Period	Sa _O ₂ (%)		Respiratory Rate (breaths/min)		Heart Rate (beats/min)	
	Awake	SWS _{initial}	Awake	SWS _{initial}	Awake	SWS _{initial}
Preflight	97.0 ± 0.1	97.1 ± 0.1	12.3 ± 0.1	10.8 ± 0.1	65.6 ± 0.5	56.5 ± 0.4
μG	98.3 ± 0.3 [†]	97.7 ± 0.3	10.5 ± 0.1 [†]	10.7 ± 0.1	61.3 ± 0.6 [†]	53.1 ± 0.7 [†]
Postflight	96.9 ± 0.2 [‡]	95.6 ± 0.2 ^{†,‡}	12.8 ± 0.2 [‡]	10.9 ± 0.1	72.8 ± 0.9 ^{†,‡}	63.1 ± 0.4 ^{†,‡}

Definition of abbreviations: μG = microgravity; SWS = slow wave sleep; awake = average of 5 min prior to the onset of sleep; SWS_{initial} = average of 5 min during the first episode of SWS of the sleep period.

[†] Significantly different from preflight value.

[‡] Significantly different from inflight value.

(6.0 ± 1.9), and the total number of arousals per hour for the sleep periods remained below preflight values (11.9 ± 0.5).

Effect of Microgravity on Arterial O₂ Saturation, Respiratory Rate, and Heart Rate

The average Sa_O₂ during awake periods just before sleep onset was 97.0 ± 0.1% preflight and increased significantly to 98.3 ± 0.3% during microgravity (Table 3). Postflight the average awake Sa_O₂ returned to preflight levels (96.9 ± 0.2%). There was no change in the average Sa_O₂ during SWS in microgravity, but postflight this was reduced slightly to 95.6 ± 0.2% compared with preflight (97.1 ± 0.1%).

Respiratory rate during the 5-min presleep wake period was 12.3 ± 0.1 breaths/min (Table 3). During microgravity, this significantly decreased to 10.5 ± 0.1, and postflight returned to preflight values (12.8 ± 0.2). The respiratory rate during slow wave sleep was 10.8 breaths/min preflight and did not change during microgravity (10.8 ± 0.1) or during postflight sleep periods (10.9 ± 0.1).

The average heart rate measured during the 5-min presleep period was 65.6 ± 0.5 beats/min preflight and significantly decreased in microgravity to 61.3 ± 0.6 (Table 3). Postflight awake, heart rate increased to 72.8 ± 0.9. The heart rate measured during slow wave sleep was 56.5 ± 0.4 beats/min preflight, decreased in microgravity to 53.1 ± 0.5, and was significantly increased to 63.1 ± 0.4 during the postflight return to normal gravity.

DISCUSSION

The most striking findings of this experiment were the dramatic reduction in the number of sleep-related breathing disturbances, the reduction in the amount of time spent snoring, and the reduced number of arousals associated with these respiratory related events during microgravity. Together these results clearly show that any sleep disruption in space is not caused by sleep-disordered breathing.

Frequencies of Apneas, Hypopneas, and Snoring

Three of the five subjects in this study had preflight apnea-hypopnea indices that were below 5.0 events/h classifying them as not having any major sleep-disordered breathing problem. Hypopneas were the primary classification of respiratory disturbances in these subjects with very few apneas (Figure 1). Even though the majority of the subjects in this study showed respiratory disturbances within the normal range, four of the five subjects showed a reduction in their AHI in space (see Table E1 in the online data supplement). The greatest reduction in the AHI of almost 60% was seen in the subject with the greatest AHI.

All five subjects in this study showed some degree of snoring from mild to moderate during preflight PSGs. Time spent snoring ranged from 2.8 to 32.6% of the total sleep time. In

microgravity, snoring was almost completely eliminated in all subjects. Importantly, the change in snoring habits of this group correlated well with the changes in the number of respiratory events per sleep period both on the ground and in space (Figure 3). The correlation between snoring and AHI suggests that the hypopneas were likely obstructive as opposed to central in nature.

Gravity and the Respiratory System

The respiratory system is greatly influenced by the force of gravity. The changes that occur in the respiratory system when the subject goes from the upright standing to the supine posture are significant. In the supine posture functional residual capacity, expiratory reserve, and tidal volumes are all reduced (5, 17). Changes in lung volume have been shown to reduce upper airway caliber (18, 19) and resistance (20–22). Functional residual capacity and expiratory reserve volumes are reduced in space but to a lesser degree than that seen in the supine posture, whereas tidal volume is reduced to a greater extent in space than supine (5).

In the supine posture, gravity also works to reduce upper airway size and to increase upper airway resistance by causing the tongue, soft palate, uvula, and epiglottis to move back toward the posterior pharyngeal wall (18, 23, 24). The tongue cross-sectional area, uvular width, and soft palate thickness all increase in the supine position resulting in a reduction in the oropharyngeal cross-sectional area (23, 25). All these anatomical changes caused by moving from the upright to supine posture result in an increase in upper airway resistance, which is likely passively related to gravity rather than changes in muscle function. It is the supine posture alone that may be one of the primary causes of the mildest form of upper airway resistance syndrome (7, 26). Spaceflight is associated with a reduction in end-expiratory lung volume (5), which would normally serve to reduce upper airway cross-sectional area (27, 28). Thus, changes in lung volume during spaceflight can likely be ruled out as a mechanism for the reduction in sleep-disordered breathing in microgravity. However, other variables such as altered control of upper airway muscles (29) and altered ventilatory control during sleep could be involved (*discussed below*).

We found that on average, the reduction in AHI was greatest in the NREM periods during which a 68% decrease in AHI was observed in microgravity. The reduction during REM periods was less, showing a significant decrease of only 30% in AHI_{REM} in microgravity. This suggests that the dominant factor causing sleep-disordered breathing during NREM sleep is the influence of gravity on the upper airway, but during REM sleep, gravity plays a lesser role. Upper airway resistance is increased during sleep (30). During REM sleep, an increase in upper airway resistance when compared with NREM sleep is observed, attributed to loss of upper airway dilator muscle

tone, specifically in the genioglossal muscle (31), although this is not a universal finding (30). Along with this reduction in dilator muscle activity, there is inhibition of other respiratory muscles including the intercostal muscles, which can alter the configuration of the rib cage and its contribution to tidal breathing (32–34). The relative dilator muscle hypotonia and the change in thoracoabdominal configuration due to inhibition of respiratory musculature are both nongravitationally dependent physiological mechanisms that contribute to the increase in upper airway resistance during REM sleep. Thus, the smaller reduction in AHI during REM than during NREM likely reflects the increased contribution of nongravitational mechanisms in the generation of upper airway resistance during REM sleep.

Takasaki and coworkers (12) compared a 30-h recording of diaphragmatic EMG activity on the ground to activity recorded for 30 h during a spaceflight in one subject in a joint Japanese–Russian mission. Full polysomnographic recordings were obtained from this subject during both recordings. On the ground, diaphragmatic EMG increased in all sleep stages (supine posture) compared with the awake state. During microgravity exposure, there was no difference between the awake state and NREM sleep, but diaphragmatic EMG remained greater in REM sleep compared with the awake and NREM sleep states. Even though there was an increase in diaphragmatic EMG during REM sleep in space, the relative EMG values in space for all sleep stages were significantly less than those on the ground. If similar changes in upper airway EMG occur in microgravity as occur in the diaphragmatic EMG, then we would expect an increase, or little change in the AHI. However, we observed a decrease in the AHI during both REM and NREM, strongly suggesting that gravity, as opposed to changes in muscle tone, plays the dominant role in increasing upper airway resistance during sleep in the healthy human subject.

Arousals

Brief arousals caused either by apneas or hypopneas contribute to fragmented sleep. Overall, we saw a significant reduction of 70% in the number of respiratory-related arousals during spaceflight in these five subjects. There was, however, virtually no change in the number of arousals resulting from nonrespiratory causes (Figure 4). Thus it appears that the microgravity environment may actually improve sleep quality to some extent, especially for the subjects with positional sleep-disordered breathing problems, obstructive sleep apnea, or upper airway resistance syndrome. Support for this is seen with the subject with the greatest AHI. This subject's respiratory-related arousal index decreased during spaceflight by 60% and sleep efficiency increased from a preflight 77% to an inflight value of 81% (D-J. Dijk, unpublished observations).

Postflight Changes

Upon return to earth, the crew complained of fatigue and on the second day of recovery (the first postflight PSG) the Neurolab crew were allowed to go to bed \sim 1 h earlier than scheduled. Although there was a small reduction in total sleep time measured on the nights of PSG recording (6.8 h preflight, 6.4 h inflight), the sleep period of the crew during spaceflight based on actigraphy data recorded on every night of the flight was only \sim 6.1 h (D-J. Dijk, unpublished observations). Thus it seems likely that the subjects were somewhat sleep deprived entering the postflight period, contributing to their fatigue. During PSGs postflight, TST was similar to preflight (6.8 h), but the percentage of REM sleep was increased (D-J. Dijk, unpublished observations). The postflight AHI_{TST} was slightly

elevated compared with preflight, AHI_{NREM} was similar to preflight values, but AHI_{REM} was 52% greater than preflight. Snoring was increased postflight indicating an increase in partial airway obstruction and airway resistance. The increase in the AHI_{REM} could be in part due to an increase in the loss of genioglossal muscle activity that is believed to be caused by sleep deprivation (35), and an increase in intercostal and accessory muscle inhibition during REM sleep (34, 36). However, these data do not suggest an aftereffect of spaceflight *per se*, but are likely a reflection of accumulated sleep loss/fatigue and circadian phase misalignment.

Arterial O₂ Saturation, Respiratory Rate, and Heart Rate

The awake and slow wave sleep oxygen saturation slightly increased during microgravity when compared with preflight values (Table 3). This increase may be due to the more uniform distribution of blood flow and ventilation and the increase in pulmonary diffusing capacity and capillary blood volume in the lung that occurs during microgravity exposure (37–39). The improved distribution of blood flow in the lung lowers the physiological deadspace by eliminating regions of high ventilation perfusion ratio, and this may improve overall gas exchange (40).

Respiratory rate while awake was decreased during microgravity when compared with both preflight and postflight (Table 3). This is in contrast to the previous measurements made in microgravity (40), which showed a \sim 10% increase in respiratory rate. However, those previous measurements were made on a mouthpiece during a pulmonary function test session, whereas the current measurements were taken with the subject resting and being passively monitored. Without the corresponding measurements of tidal volume, it is difficult to further interpret this result, although it might be considered consistent with the improvement in gas exchange (as evidenced by increased arterial oxygen saturation) also seen at the same time. Certainly the changes in respiratory rate mirror the changes in arterial oxygen saturation (Table 3).

There was a reduction in heart rate during SWS compared with awake in all three measuring periods (preflight, inflight, and postflight, Table 3). This is superimposed on a change in heart rate with a relative bradycardia inflight and a tachycardia postflight. Similar observations have been made in previous awake studies (41). The persisting tachycardia postflight while these subjects were supine may reflect the lowered circulating blood volume known to occur at this time (42).

Control of Ventilation

We had hypothesized that microgravity could alter sleep-disordered breathing by altering the control of ventilation. On the ground, it is well documented that the carotid baroreceptor and chemoreceptor function are linked (43, 44); therefore, alterations in the baroreceptors due to changes in carotid and aortic pressures could cause changes in the associated chemoreceptors. It has been shown that spaceflight reduces the carotid baroreceptor response (45). Therefore, it is likely that the peripheral chemoreceptor function could be altered by microgravity exposure.

The hypercapnic response during spaceflight did not show any consistent change whereas the hypoxic response was reduced by 46% when compared with the preflight standing response. The reduction in the hypoxic response was similar to that seen when the subject moved from the standing to the supine posture (6). The reduction in respiratory outflow was attributed to an increase in carotid vascular pressure that is experienced both during spaceflight and with the transition to the supine posture. Given that awake ventilatory control in

microgravity is not different from that measured supine in 1G, we conclude that there is probably no significant change in the control of ventilation during sleep in the microgravity environment. Thus, changes in ventilatory control during spaceflight can likely be ruled out as a mechanism for the reduction in sleep-disordered breathing in microgravity.

Limitations

The constraints of spaceflight somewhat limited our investigation. We were not able to measure either the hypoxic or hypercapnic ventilatory responses during sleep, but we were able to measure the awake responses in five of the Neurolab crew, four of whom participated in this study (6). Given the similarity of the results in microgravity compared with those measured supine on the ground, we consider a change in ventilatory control *only* during sleep in microgravity to be unlikely. Whereas the cabin atmosphere was normoxic (760 mm Hg, 21% O₂), CO₂ was slightly elevated (~ 0.4%). Although this level of chronic CO₂ exposure has little effect (46) it is possible that local level of CO₂ in the sleep compartments may have been higher. However, because we observed a reduction in arousals, this is unlikely to alter our conclusions.

We were unable to directly measure upper airway resistance during the hypopneas, nor could we determine an effect of body position on snoring and AHI during the ground portion of the study. However, the correlation between the degree of snoring and the AHI is highly suggestive of a reduction in upper airway resistance in microgravity.

Circadian aspects of the control of sleep and breathing also need to be considered in the study design. There was a daily shift of 20 min in the sleep start time (a 23 h 40 min day) for the four subjects studied during Neurolab, and of 35 min/d for the subject on STS-95. This was a consequence of the orbital dynamics of the flight and represented the minimum possible disruption we could obtain. The duration of hypopneas has been shown to increase systematically across a single night (47). If this phenomenon is due to an underlying circadian rhythm, then as subjects slept earlier each day while in space, we would expect that the circadian shift this caused (~ 5 h over the course of each flight) may have resulted in a shortening of the duration of the hypopneas measured in flight. However, we found a lengthening of events in microgravity. Thus, we doubt that a change in the timing of sleep relative to the circadian cycle caused our results. Furthermore, as the time shift was spread evenly over the course of the flights, the disruption was minimal, and core body temperature records indicated no major misalignment with respect to the light-dark cycle at both the beginning and end of the flights, suggesting that there had been no major disruption between the timing of sleep relative to the circadian cycle (D-J. Dijk, unpublished observations).

In conclusion, microgravity exposure greatly reduced the number of sleep-related apneas and hypopneas and significantly reduced snoring in these normal individuals. The results are probably due to the passive elimination of the gravitationally induced changes in the upper airway anatomical structures rather than changes in lung volume, ventilatory chemosensitivity, upper airway muscle control, or circadian timing. From this data we can infer that gravity plays a dominant role in the increase in upper airway resistance and obstruction that occurs after the transition to the supine posture and during all stages of sleep.

Acknowledgment: The authors thank the crews of STS-90 and STS-95 and the NASA and Lockheed Martin Engineering Services that supported both these missions. Specifically, they thank Jim Billups, Mel Buderer, Sherry Carter, Trevor Cooper, Steve Cunningham, Marsha Dodds, Janelle Fine, Dennis M.

Heher, Pat Kincade, Angie Lee, Raoul Ludwig, Suzanne McCollum, Wim Martens, Peter Nystrom, Carlo Peters, Carlos Reyes, Joseph M. Ronda, and Timothy Snyder.

References

1. Frost JD, Shumante WH, Salmay JG, Booher CR. Sleep monitoring: the second manned Skylab mission. *Aviat Space Environ Med* 1976;47:372-382.
2. Santy PA. Analysis of sleep on shuttle missions. *Aviat Space Environ Med* 1988;59:1094-1097.
3. Gundel A, Polyakov VV, Zulley J. The alteration of human sleep and circadian rhythms during space flight. *J Sleep Res* 1997;6:1-8.
4. Putchá L, Berens KL, Marshburn TH, Ortega HJ, Billica RD. Pharmaceutical use by U.S. astronauts on space shuttle missions. *Aviat Space Environ Med* 1999;70:705-708.
5. Elliott AR, Prisk GK, Guy HJB, West JB. Lung volumes during sustained microgravity on spacelab SLS-1. *J Appl Physiol* 1994;77:2005-2014.
6. Prisk GK, Elliott AR, West JB. Sustained microgravity reduces the human ventilatory response to hypoxia but not hypercapnia. *J Appl Physiol* 2000;88:1421-1430.
7. Oksenberg, A, Silverton DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients. *Chest* 1997;112:629-639.
8. Buckey JC Jr, Gaffney FA, Lane LD, Levine BD, Watenpaugh DE, Wright SJ, Yancy CW Jr, Meyer DM, Blomqvist CG. Central venous pressure in space. *J Appl Physiol* 1996;81:19-25.
9. Khoo MCK, Koh SS, Shin JJ, Westbrook PR, Berry RB. Ventilatory dynamics during transient arousal from NREM sleep: implications for respiratory control stability. *J Appl Physiol* 1996;80:1475-1484.
10. Berry RB, Gleeson K. Respiratory arousal from sleep: mechanisms and significance. *Sleep* 1997;20:654-675.
11. Gleeson K, Zwillich CW, White DP. The influence of increasing ventilatory effort on arousal from sleep. *Am Rev Respir Dis* 1990;142:295-300.
12. Takasaki Y, Kamio M, Okamoto Y, Yamabayashi H. Changes in diaphragmatic EMG activity during sleep in space. *Am Rev Respir Dis* 1993;148:612-617.
13. Callini G, Essig S, Heher DM, Young LR. Effectiveness of an expert system for astronaut assistance on a sleep experiment. *Aviat Space Environ Med* 2000;71:1023-1032.
14. Rechtschaffen A, Kales A, editors. A manual of standardized terminology: techniques and scoring system for sleep stages of human subjects. Los Angeles: UCLA Brain Information Service/Brain Research Institute; 1968.
15. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999;22: 667-689.
16. Atlas Task Force of the American Sleep Disorders Association. EEG arousals: scoring rules and examples. *Sleep* 1992;15:174-184.
17. Agostoni E, Hyatt RE, Macklem PT, Mead J, editors. Static behavior of the respiratory system. In: Handbook of physiology. The respiratory system. Mechanics of breathing, Sec. 3, Vol. III, pt. 1, Chapt. 9. Bethesda: American Physiological Society; 1986. p. 113-30.
18. Fouke JM, Strohl KP. Effect of position and lung volume on upper airway geometry. *J Appl Physiol* 1987;63:375-380.
19. Jan MA, Marshall I, Douglas NJ. Effect of posture on the upper airway dimensions in normal humans. *Am J Respir Crit Care Med* 1994;149: 145-148.
20. van de Graff WB. Thoracic influence on upper airway patency. *J Appl Physiol* 1988;65:2124-2131.
21. Series F, Cormier Y, Desmeules M. Influence of passive changes in lung volume on upper airways. *J Appl Physiol* 1990;68:2159-2164.
22. Anch AM, Remmers JE, Bruce H. Supraglottic airway resistance in normal subjects and patients with occlusive sleep apnea. *J Appl Physiol* 1982;53:1158-1163.
23. Yildirim N, Fitzpatrick MF, Whyte KF, Jolley R, Wrightman AJ, Douglas NJ. The effect of posture on upper airway dimensions in normal subjects and in patients with the sleep apnea-hypopnea syndrome. *Am Rev Respir Dis* 1991;144:845-847.
24. Brown IB, McLean PA, Boucher R. Changes in pharyngeal cross-sectional area with posture and application of continuous positive pressure ventilation in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1987;138:628-632.
25. Pae EK, Lowe AA, Price C, Tsuchiya M, Fleetham JA. A cephalometric and electromyographic study of upper airway structures in the upright and supine positions. *Am J Orthod Dentofacil Orthop* 1994;106:52-59.
26. Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness: the upper airway resistance syndrome. *Chest* 1993;104:781-787.

27. Rivlin J, Hoffstein V, Kalbfleisch J, McNicholas WT, Zamel N, Bryan AC. Upper airway morphology in patients with idiopathic obstructive sleep apnea. *Am Rev Respir Dis* 1984;129:355–360.
28. Hoffstein V, Zamel N, Phillipson EA. Lung volume dependence of pharyngeal cross-sectional area in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1984;130:175–178.
29. Remmers JE, DeGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol* 1978;44:931–938.
30. Hudgel DW, Martin RJ, Johnson B, Hill P. Mechanics of the respiratory system and breathing pattern during sleep in normal humans. *J Appl Physiol* 1984;56:133–137.
31. Sauerland EK, Harper RM. The human tongue during sleep: electromyographic activity of the genioglossus muscle. *Exp Neurol* 1976; 51:160–170.
32. Lopes JM, Tabachnik E, Muller NL, Levison H, Bryan AC. Total airway resistance and respiratory muscle activity during sleep. *J Appl Physiol* 1983;54:773–777.
33. Tabachnik E, Muller NL, Bryan AC, Levison H. Changes in ventilation and chest wall mechanics during sleep in normal adolescents. *J Appl Physiol* 1981;51:557–564.
34. Tusiewicz K, Moldofsky H, Bryan AC, Bryan MH. Mechanics of the rib cage and diaphragm during sleep. *J Appl Physiol* 1977;43:600–602.
35. Leiter JC, Knuth SL, Barrlet D. The effect of sleep deprivation on activity of the genioglossus muscle. *Am Rev Respir Dis* 1985;132:1242–1245.
36. Johnson M, Remmers JE. Accessory muscle activity during sleep in chronic obstructive pulmonary disease. *J Appl Physiol* 1982;57:1011–1017.
37. Prisk GK, Guy HJB, Elliott AR, West JB. Inhomogeneity of pulmonary perfusion during sustained microgravity on SLS-1. *J Appl Physiol* 1994;76:1730–1738.
38. Guy HJB, Prisk GK, Elliott AR, Deutschman RA, West JB. Inhomogeneity of pulmonary ventilation during sustained microgravity as determined by single-breath washouts. *J Appl Physiol* 1994;76:1719–1729.
39. Prisk GK, Guy HJB, Elliott AR, Deutschman RA, West JB. Pulmonary diffusing capacity, capillary blood volume and cardiac output during sustained microgravity. *J Appl Physiol* 1993;75:15–26.
40. Prisk GK, Elliott AR, Guy HJB, Kosonen JM, West JB. Pulmonary gas exchange and its determinants during sustained microgravity on Spacelabs SLS-1 and SLS-2. *J Appl Physiol* 1995;79:1290–1298.
41. Fritsch-Yelle JM, Charles JB, Jones MM, Wood ML. Microgravity decreases heart rate and arterial pressure in humans. *J Appl Physiol* 1996;80:910–914.
42. Alfrey CP, Udden MM, Leach-Huntoon C, Driscoll T, Pickett MH. Control of red blood cell mass in spaceflight. *J Appl Physiol* 1996;81:98–104.
43. Brunner MJ, Sussman MS, Greene AS, Kallman CH, Shoukas AA. Carotid sinus baroreceptor reflex control of respiration. *Circ Res* 1982; 51:624–636.
44. Somers VK, Mark AL, Abboud FM. Interaction of baroreceptor and chemoreceptor reflex control of sympathetic nerve activity in normal humans. *J Clin Invest* 1991;87:1953–1957.
45. Fritsch JM, Charles JB, Bennett BS, Jones MM, Eckberg DL. Short-duration spaceflight impairs human carotid baroreceptor-cardiac reflex responses. *J Appl Physiol* 1992;73:664–671.
46. Elliott AR, Prisk GK, Schöllman C, Hoffman U. Hypercapnic ventilatory response in humans before, during and after 23 days of low level CO₂ exposure. *Aviat Space Environ Med* 1998;69:391–396.
47. Montserrat JM, Kosmas EN, Cosio MG, Kimoff R. Mechanism of apnea lengthening across the night in obstructive sleep apnea. *Am J Respir Crit Care Med* 1996;154(4 Pt. 1):988–993.