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Influence of microgravity on astronauts' sympathetic and vagal responses to Valsalva's manoeuvre

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When astronauts return to Earth and stand, their heart rates may speed inordinately, their blood pressures may fall, and some may experience frank syncope. We studied brief autonomic and haemodynamic transients provoked by graded Valsalva manoeuvres in astronauts on Earth and in space, and tested the hypothesis that exposure to microgravity impairs sympathetic as well as vagal baroreflex responses. We recorded the electrocardiogram, finger photoplethysmographic arterial pressure, respiration and peroneal nerve muscle sympathetic activity in four healthy male astronauts (aged 38–44 years) before, during and after the 16 day Neurolab space shuttle mission. Astronauts performed two 15 s Valsalva manoeuvres at each pressure, 15 and 30 mmHg, in random order. Although no astronaut experienced presyncope after the mission, microgravity provoked major changes. For example, the average systolic pressure reduction during 30 mmHg straining was 27 mmHg pre-flight and 49 mmHg in flight. Increases in muscle sympathetic nerve activity during straining were also much greater in space than on Earth. For example, mean normalized sympathetic activity increased 445 % during 30 mmHg straining on earth and 792 % in space. However, sympathetic baroreflex gain, taken as the integrated sympathetic response divided by the maximum diastolic pressure reduction during straining, was the same in space and on Earth. In contrast, vagal baroreflex gain, particularly during arterial pressure reductions, was diminished in space. This and earlier research suggest that exposure of healthy humans to microgravity augments arterial pressure and sympathetic responses to Valsalva straining and differentially reduces vagal, but not sympathetic baroreflex gain.

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Early concerns that exposure to microgravity would lead to massive organ (particularly cardiovascular) system failure, proved unfounded; cardiovascular function remains normal in space (Michael *et al.* 1977). The most dramatic consequences of spaceflight are observed *after* space missions. With standing, heart rate increases inordinately, arterial pressure may fall (Hoffler *et al.* 1974), and some astronauts experience presyncope (Buckey *et al.* 1996). Notwithstanding comprehensive reviews (Blomqvist & Stone, 1983; Levy & Talbot, 1983; Charles *et al.* 1994; Fortney *et al.* 1996), and one prospective international study of the effects of simulated microgravity (Baisch *et al.* 1992), cardiovascular changes provoked by space travel are not understood fully. One impediment to a full understanding of the physiological changes occurring in space is the possibility that terrestrial models may not faithfully reproduce the effects of actual microgravity.

The Neurolab space shuttle mission was conceived as the National Aeronautics and Space Administration (NASA) contribution to the 1990s Decade of the Brain. This 16 day mission was conducted in 1998 and involved 26 principal investigators from six countries, who studied the neurophysiological consequences of space travel in

astronauts, mature and neonatal rats, fish, snails and crickets.

This, and the accompanying two articles (Ertl *et al.* 2002; Levine *et al.* 2002) deal with autonomic cardiovascular changes in astronauts. These articles report the first direct recordings of human muscle sympathetic nerve activity and noradrenaline kinetics in space and the first direct recordings of human muscle sympathetic nerve activity during upright tilt after space travel. Each of the three studies tested prospectively defined hypotheses that deal with different aspects of human autonomic cardiovascular regulation, as they are affected by microgravity.

Our protocol evolved from earlier research into astronauts' responses to abrupt changes of baroreceptor input. This work documented impaired vagal baroreflex responses after microgravity simulated by head-down bed rest (Convertino *et al.* 1990; Eckberg & Fritsch, 1992) and during (Fritsch & Eckberg, 1992) and after (Fritsch *et al.* 1992; Fritsch-Yelle *et al.* 1994) brief space missions. One bed rest study (Convertino *et al.* 1990) and one study performed after space missions (Fritsch *et al.* 1992) yielded significant correlations between the degree of orthostatic intolerance, as reflected by changes of arterial pressure or the occurrence of presyncope and the reduction of vagal baroreflex gain. Our Neurolab study focused on autonomic transients provoked by Valsalva straining and tested the hypothesis that exposure to microgravity impairs sympathetic as well as vagal baroreflex responses. Parts of this study have been published in abstract form (Cox, for the Autonomic Nervous System Team, 1999).

METHODS

Subjects

The three Neurolab protocols were conducted in six male astronauts aged 38–44 years, height 184–188 cm and body weight 75–89 kg. Neurolab studies conformed with the Declaration of Helsinki and were approved by NASA's Johnson Space Center Human Research Policies and Procedures Committee and the human subjects' institutional review boards at the home institutions of the principal investigators. All astronauts gave their written informed consent. Our study of Valsalva responses was conducted in four of the six astronauts. We report our results with descriptive statistics and give mean values, ranges, and when possible, individual responses. In this and the two other Neurolab articles (Ertl *et al.* 2002; Levine *et al.* 2002), individual astronauts are identified by the same numbers (numbers 1–6) and symbols.

Measurements

The surface electrocardiogram, tidal volume, mouth pressure, end-tidal carbon dioxide (CO_2) concentration, arterial pressure and muscle sympathetic nerve activity were recorded. Astronauts breathed through a mouthpiece, with their nostrils occluded by a noseclip. The mouthpiece was connected to a manually operated valve (Hans Rudolph, Kansas City, MO, USA), which astronauts closed and opened prior to and following Valsalva straining, and to a strain-gauge pressure transducer. The pressure transducer used on Earth (Model PX142, Omega Engineering, Stamford, CT, USA) was connected to the mouthpiece by ~100 cm clear polyethylene tubing. The pressure transducer used in space (Model AP121-AP-2T, Sensortec, Columbus, OH, USA) was mounted directly on the breathing assembly. We measured tidal volumes with a turbine (Interface Associates, Aliso Viejo, CA, USA), and CO_2 with a mass spectrometer (Marquette MGA1100 Mass Spectrometer, St Louis, MO, USA). We estimated finger arterial pressure with a photoplethysmograph (Finapres, Ohmeda, Englewood, CO, USA). The unit used during the Neurolab mission was adapted for use in space by TNO TPD Biomedical Instrumentation (BMI) Academic Medical Center, Amsterdam, The Netherlands, for the European Space Agency.

We recorded muscle sympathetic nerve activity as described in an earlier article (Wallin & Eckberg, 1982) and in another article of this series (Ertl *et al.* 2002). The nerve signal was amplified (total gain 70 000 to 160 000), band-pass filtered (700–2000 Hz) and integrated (time constant 0·1 s) to obtain mean voltage neurograms. Satisfactory recordings of muscle sympathetic nerve activity were defined by pulse-synchronous bursts that increased during end-expiratory apnoea or Valsalva straining and did not change during tactile or auditory stimulation.

Experimental sessions

We studied astronauts a total of six times, before, during and after the Neurolab mission. Measurements were made approximately 72 and 23 days prior to launch; on mission days 2 (early mission) and 12 or 13 (late mission); and on the first and fifth or sixth days following return to Earth. Muscle sympathetic nerve recordings were made twice, approximately 72 days prior to launch and on mission day 12 or 13. Because our study focused on sympathetic responses, we emphasize results obtained during the two microneurography sessions.

Protocol

The ordering of Neurolab autonomic function tests and the relation of autonomic testing to other Neurolab protocols are given in the Appendix. Astronauts performed Valsalva manoeuvres following 18 min of frequency-controlled breathing and tritiated noradrenaline infusion (Ertl *et al.* 2002). Each astronaut was studied in the supine position (on Earth and in space), with his lower body enclosed in a chamber fitted with a removable window to allow placement of microneurography electrodes. (The chamber was used for another study in this series (Ertl *et al.* 2002) and was open to air during Valsalva manoeuvres.)

Astronauts controlled Valsalva manoeuvres according to prompts displayed on a computer monitor. A bar gauge guided the astronaut to begin Valsalva straining from his usual tidal volume. A pressure gauge, displayed only during the period of straining, depicted the target and actual mouth pressures for each trial. Astronauts strained for 15 s, as a clock hand swept an arc of 360 deg within a circle. They performed a total of four Valsalva manoeuvres, two at each pressure, 15 and 30 mmHg, in random sequence. (There is no universally accepted standard for Valsalva manoeuvres (Eckberg & Sleight, 1992); for the Neurolab study, we chose a maximum straining level of 30 mmHg, in part to minimize the possibility that straining would dislodge the sympathetic nerve recording electrode.) Responses to the two manoeuvres at each level were averaged to obtain one 15 and one 30 mmHg response from each astronaut. Automatic finger photoplethysmograph calibration was disabled 30 s prior to and was enabled 30 s following each Valsalva manoeuvre. Data recorded during the 60 s period prior to the onset of each Valsalva manoeuvre comprised baseline measurements.

Table 1. Haemodynamic measurements

Measurement	Session (n = 4 astronauts) Pre-flight, L-72	Pre-flight, L-23	In-flight, L + 1	In-flight, L + 12/13	Post-flight, R + 1	Post-flight, R + 5/6
Systolic pressure (mmHg)	139 ± 16	131 ± 8	130 ± 8	151 ± 12	128 ± 12	130 ± 16
Diastolic pressure (mmHg)	73 ± 10	67 ± 6	63 ± 6	76 ± 6	65 ± 12	69 ± 12
R–R interval (ms)	1055 ± 114	1071 ± 100	981 ± 114	1008 ± 56	967 ± 66	1007 ± 130
Baseline muscle sympathetic nerve activity (bursts min^{-1})	13.9 ± 10.4	—	—	16.3 ± 11.0	—	—

Values are means ± S.D. L-72 = ~72 days before launch; L-23 = ~23 days before launch; L + 1 = 1 day after launch; L + 12/13 = 12 or 13 days after launch; R + 1 = 1 day after return to earth; R + 5/6 = 5 or 6 days after return to earth.

Data acquisition

During pre- and postflight sessions, all analogue signals were digitized on-line at 500 Hz per channel with Windaq software and hardware (DATAQ, Akron, OH, USA). During in-flight sessions, the electrocardiogram was digitized at 512 Hz, and all other signals were digitized at 256 Hz.

Analysis of results

We analysed our data with WinCPRS (Absolute Aliens Ay, Turku, Finland). We first detected all electrocardiographic R waves and systolic and diastolic pressures from finger photoplethysmograms. The WinCPRS program then searched for muscle sympathetic bursts with signal-to-noise ratios > 3, occurring within a 0·5 s window centred about 1.3 s each subject's R wave (one removed) – sympathetic burst latency (Fagius & Wallin, 1980). In this and the two accompanying Neurolab articles (Ertl *et al.* 2002; Levine *et al.* 2002), the computer selection of sympathetic bursts was overseen by two experienced expert microneurographers, who deleted obviously artefactual bursts and added bursts missed by the detection algorithm. All Neurolab results are based on these final determinations.

We normalized bursts by dividing the integrated areas of all bursts during each control period by the number of bursts. Each sympathetic burst occurring during Valsalva manoeuvres was divided by this normalized burst area. (For example, if a burst during straining were larger than the average control burst, the normalized area or amplitude would be greater than 1·0.)

Each period of Valsalva straining lasted nominally 15 s. We integrated all sympathetic bursts occurring during the 15 s period of straining and related the integral of sympathetic activity to the maximum fall of diastolic pressure, as measured from the highest level just after the beginning of straining (Phase 1), to its nadir. (The strength of muscle sympathetic bursts correlates closely with diastolic pressure; there is no significant correlation between muscle sympathetic nerve activity and systolic pressure; Sundlöf & Wallin, 1977.) We also expressed sympathetic responses to straining as the percentage of R–R intervals that contained sympathetic bursts and as the average normalized area per sympathetic burst.

We evaluated vagal baroreflex responses to Valsalva manoeuvres in two ways. First, we plotted 2.1 s averages of R–R intervals as functions of the 2.1 s averages of systolic pressures during the straining phase, as Lissajous figures. (We related R–R intervals to *systolic*, rather than diastolic pressure, according the time-honoured precedent established by Smyth *et al.* (1969) for estimation of vagal baroreflex gain.) Second, we plotted total R–R interval shortening during straining, or R–R interval lengthening after the release of straining, as functions of the total systolic pressure fall or rise.

Values are given as means ± S.D. or means followed by the range in parentheses throughout the text.

RESULTS

Table 1 lists mean ± S.D. arterial pressures, R–R intervals and muscle sympathetic nerve burst frequencies during the baseline periods preceding Valsalva trials. Baseline arterial pressures were similar across experimental sessions; however, average systolic pressures were higher during the late mission session than other sessions (by 12 mmHg, compared with the first pre-flight session). Baseline sympathetic nerve burst frequency was higher in space than on Earth in three of the four astronauts (13·9 (0·0–24·4) *vs.* 16·3 (6·0–26·0) bursts min^{-1}).

Valsalva manoeuvres were controlled closely by the astronauts. The durations of Valsalva straining periods were comparable ~72 days before and during the late mission session and averaged 16·3 (15·5–17·0) and 16·5 (15·6–17·8) s. The intensity of Valsalva straining was slightly greater in space than on Earth; nominal 15 mmHg strains averaged 15·2 (all 15·2) mmHg before the mission and 16·8 (15·5–18·3) mmHg during the mission. Nominal 30 mmHg strains averaged 28·7 (26·8–30·7) mmHg before the mission and 31·2 (30·8–32·4) mmHg during the mission.

Figure 1 shows representative Valsalva responses of one astronaut, recorded 72 days before the flight and on flight day 12 during the late mission session. This record documents what we consider the excellent quality of the data we obtained in space, as well as on Earth. The non-invasive photoplethysmograph produced crisp signals which clearly illustrate the classic four phases of Valsalva responses (Hamilton *et al.* 1936; Eckberg & Sleight, 1992): the rise of pressure at the onset of straining (Phase 1), the fall and partial recovery of pressure as straining continues

Table 2. Muscle sympathetic nerve activity before and during Valsalva manoeuvres

		~72 days pre-flight			Mission Day 12 or 13		
Measurement	Astronaut	Baseline	15 mmHg	30 mmHg	Baseline	15 mmHg	30 mmHg
Normalized average sympathetic burst area	1	1	1·9	2·2	1	2·0	2·7
	2	1	1·2	1·1	1	1·6	1·5
	3	1	1·4	2·2	1	2·6	2·3
	4	1	3·9	7.8	1	6·0	8·6
Mean ± s.d.		—	2·1 ± 1·2	3·3 ± 3·0	—	3·1 ± 2·0	3·8 ± 3·3
Integrated sympathetic burst area $(15\ s)^{-1}$	1	5·6	16·2	20·7	4·3	21·6	32·1
	2	7·8	13·1	12·6	8·8	22·0	22·9
	3	7·8	16·3	23·5	7·1	28·0	28·7
	4	3·6	26·9	49·0	3·8	72·6	80·6
Mean ± s.d.		6·2 ± 2·0	18·1 ± 6·0	26·4 ± 15·7	6·0 ± 2·4	36·1 ± 24·5	41·1 ± 26·6
Percentage of heart beats with a sympathetic burst	1	38·3	54·8	54·3	28·2	61·1	64·9
	2	67·6	95·6	88·0	63·2	93·1	90·9
	3	54·6	76·7	63·6	50·7	68·8	65·8
	4	22·9	46·7	37·1	26·4	72·7	51·3
Mean ± s.d.		45·8 ± 19·4	68·5 ± 22·1	60·7 ± 21·2	42·1 ± 17·9	73·9 ± 13·7	68·2 ± 16·5

(Phase 2) and the abrupt fall (Phase 3) and subsequent overshoot of pressure after release of straining (Phase 4). Changes in responses measured in this astronaut reflect the changes for the entire group. The reduction of arterial pressure and the augmentation of muscle sympathetic nerve activity during straining were substantially greater in space than on Earth. R–R interval fluxes were arguably smaller in space than on Earth.

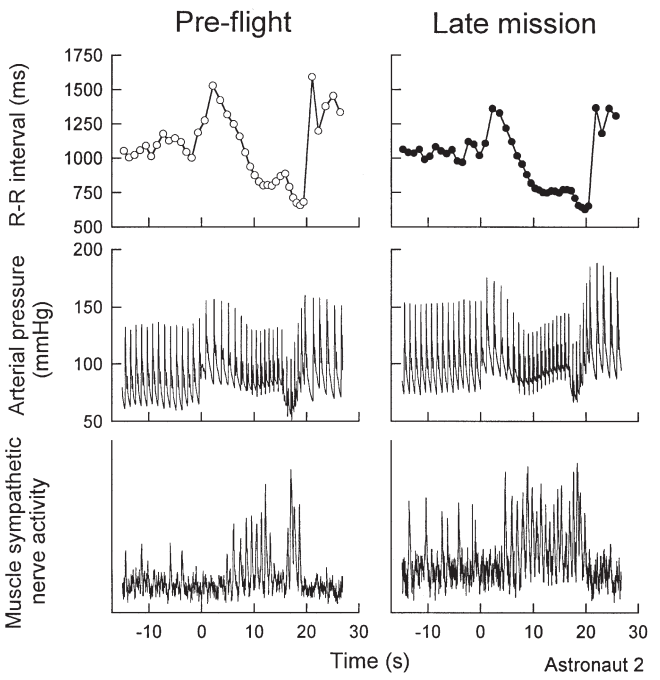

Figure 1. Valsalva manoeuvres performed 72 days before the Neurolab space shuttle mission and on mission day 12

In this and other astronauts, sympathetic responses to straining were much greater in space (right) than on Earth.

Arterial pressure

Figure 2 shows average systolic pressure responses to 15 and 30 mmHg Valsalva manoeuvres during the two microneurography sessions, from all four astronauts. (Changes in *diastolic* pressure provoked by microgravity were qualitatively similar to changes in systolic pressure.) The most striking differences are that the fall and subsequent recovery of pressure during straining and the rise of pressure after release of straining were greater in space (late mission, thick traces) than on Earth. Figure 3 depicts box plots of systolic pressure reductions (during straining) measured during all experimental sessions. Pressure reductions at both levels of straining were much greater during the late mission, than during any other session.

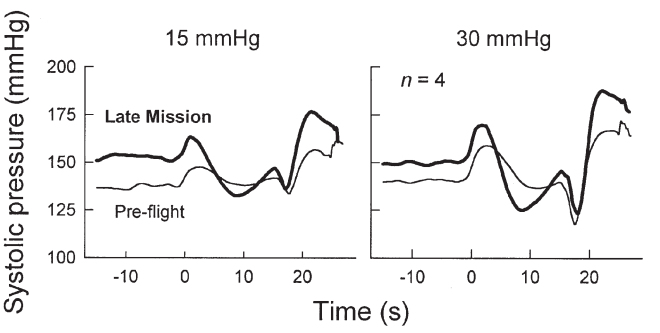

Figure 2. Average systolic pressure changes during 15 and 30 mmHg Valsalva manoeuvres for all four astronauts

All pressure changes were greater during the late mission session (thick lines) than during the first pre-flight session. Diastolic pressure changes paralleled systolic pressure changes.

Muscle sympathetic nerve activity

Table 2 lists and Fig. 4 illustrates results obtained from each astronaut during each of the two microneurography sessions. Note that the scale in Fig. 4 is larger for Astronaut 4, who had less sympathetic activity at baseline and much more sympathetic activity during straining than the other astronauts. As expected (Smith *et al.* 1996), in space and on Earth, sympathetic responses were greater during 30 than 15 mmHg Valsalva straining. As explained in Methods, we normalized sympathetic bursts during the 1 min period before each Valsalva strain and assigned the average burst area (or amplitude) a value of 1·0. The integrated sympathetic responses shown in Fig. 4 reflect changes in both burst frequency and area. Although our data are limited, it appears that increases in burst *frequency* contributed importantly to the increased sympathetic responses in space; average responses to 15 and 30 mmHg straining were 17·9 and 14·7 bursts min^{-1} greater in space than on Earth.

Figure 5 shows pre-flight (~72 days) and late mission sympathetically and vagally mediated baroreflex responses as Lissajous figures, averaged at 2.1 s intervals, for three astronauts during Valsalva straining. (Astronaut 4 was excluded because of his extremely large sympathetic responses; Fig. 4, right lower panel.) As shown in Figs 2 and 3, pressure reductions were greater in space than on Earth. Figure 5 also shows that the extent of pressure changes (horizontal planes) was greater in space (filled circles) than on Earth (open circles). Sympathetic and vagal baroreflex responses were qualitatively different. Sympathetic baroreflex control, as reflected by the slopes of the sympathetic–diastolic pressure Lissajous figures, was similar in space and on Earth. Vagal baroreflex control, as reflected by the areas inscribed by the Lissajous figures, was considerably less tight in space than on Earth.

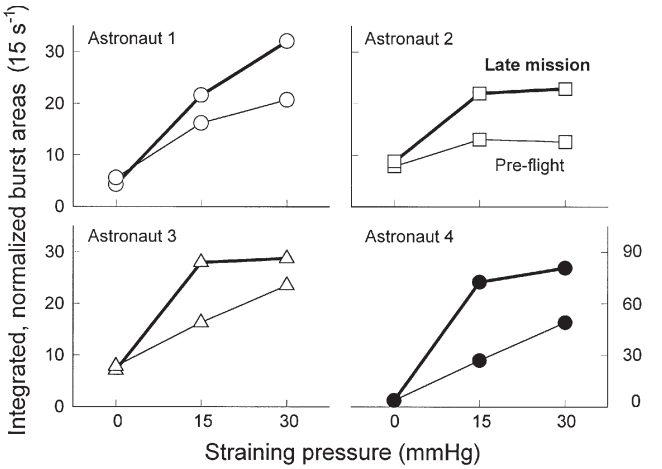

Figure 4. Average integral of muscle sympathetic nerve activity over the 15 s period of Valsalva straining

Note that the scale for Astronaut 4 is larger than that for the other three astronauts.

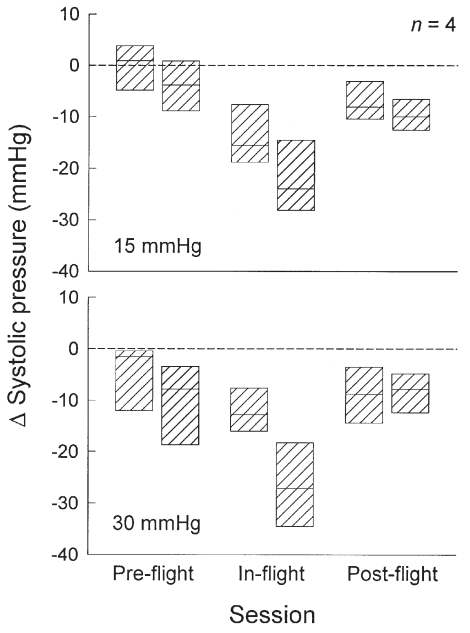

Figure 3. Box plot of systolic pressure changes for all recording sessions for all four astronauts

The top, centre and bottom lines of each box indicate the 75th, 50th and 25th percentiles, respectively, of pressure changes from baseline values before straining. The first two boxes depict measurements made ~72 and ~23 days pre-flight; the middle two sets of boxes depict measurements made on flight days 2 and 12 or 13; and the right two sets of boxes depict measurements made 1, and 5 or 6 days after return to Earth.

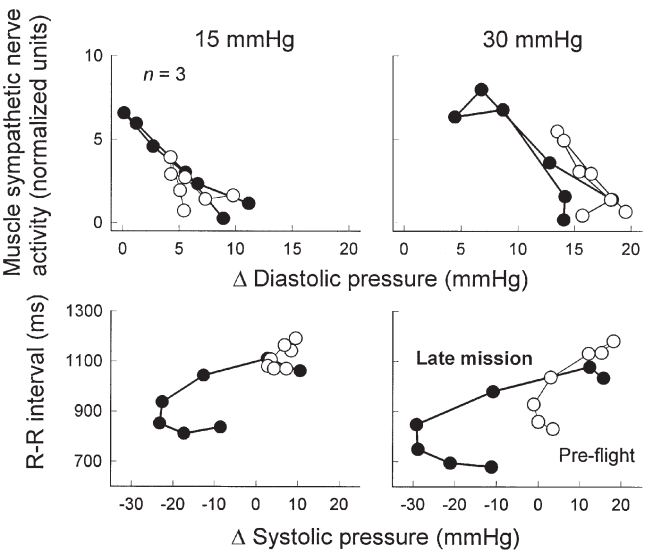

Figure 5. Average arterial pressure and muscle sympathetic nerve and R–R interval responses during Valsalva straining during the ~72 day pre-flight and the late mission sessions

Each Lissajous figure begins with the peak systolic pressure just after the beginning of straining (Phase 1) and progresses from right to left. Each data pair represents measurements averaged over 2.1 s. Astronaut 4 is not represented in these figures because of his extraordinarily large sympathetic responses.

Comparison of sympathetic and vagal baroreflex gains

As Figs 2, 3 and 5 indicate, the stimuli for increased sympathetic nerve activity and decreased or increased vagal nerve activity (which we take to be functions of diastolic and systolic pressure changes) were greater in space than on Earth. Therefore, altered autonomic responses to Valsalva manoeuvres, including especially exaggerated sympathetic responses (Figs 1 and 4), may simply reflect the fact that the stimuli are greater in space than on Earth. Figure 6 summarizes sympathetic and vagal baroreflex gains, plotted as functions of diastolic and systolic pressure changes. Sympathetic baroreflex gain (left panel) is shown as the average integrals of sympathetic nerve activity during the 15 s straining period, plotted as functions of the maximum reductions in diastolic pressure. Vagal baroreflex gain is shown as maximum R–R interval changes plotted as functions of maximum systolic pressure changes during (middle panel) and after (right panel) release of straining. In each panel, the response moves away from the zero arterial pressure change (average measurements made during the 1 min control periods before Valsalva straining); the next symbol indicates responses to 15 mmHg straining; and the symbol furthest from zero indicates responses to 30 mmHg straining.

Figure 6 encapsulates the results of our study. It suggests that augmented sympathetic baroreflex responses in space reflect merely normal responses to greater pressure reductions. Sympathetic baroreflex gain, as indicated by the slope of the stimulus–response relations, is nearly identical in space and on Earth. (Average pre-flight and in-flight gains (slopes of integrated muscle sympathetic nerve activities divided by slopes of changes of diastolic pressure) were similar, 2.74 *vs.* 2.54 arbitrary units (a.u.) $mmHg^{-1}$, and astronauts tended to have similar gains on Earth and in space. Individual gains for Astronauts 1–4 were −3.01, −0.52, −1.20 and −6.23 pre-flight and −1.83, −0.97, −1.71 and−5.66 a.u. $mmHg^{-1}$ in flight.)

DISCUSSION

Although astronauts function normally in space, many have orthostatic intolerance upon return to earth, manifested by inordinate tachycardia, hypotension and presyncope (Buckey *et al.* 1996). In this paper, one of three papers (Ertl *et al.* 2002; Levine *et al.* 2002) reporting results from the Neurolab space shuttle mission, we focused on autonomic transients provoked by Valsalva manoeuvres and tested the hypothesis that exposure to microgravity impairs sympathetic–muscle, as well as vagal–cardiac baroreflexes. Our principal new finding is that although Valsalva straining triggers much greater increases in muscle sympathetic nerve activity in space than on Earth, the stimulus, falling arterial pressure, is also greater. As a result reflex gain (sympathetic response as a function of diastolic pressure reduction) is normal. Since earlier research (Fritsch & Eckberg, 1992; Fritsch *et al.* 1992; Fritsch-Yelle *et al.* 1994) and this study (Fig. 5) document impaired vagal baroreflex responses, our results suggest that microgravity differentially affects human baroreflexes – sympathetic baroreflexes are preserved, and vagal baroreflex responses are impaired.

Physiological changes in microgravity

This research was driven by the orthostatic intolerance astronauts experience when they return to Earth. (The changes that occur are discussed in the introduction to this article and are dealt with explicitly in another article of this series; Levine *et al.* 2002.) In space, plasma volume falls (for incompletely understood reasons; Fortney *et al.* 1996; Buckey *et al.* 1996) by 16 % on the first day and remains about 10 % below pre-flight levels for the duration of short missions (Leach *et al.* 1996). By the end of brief space

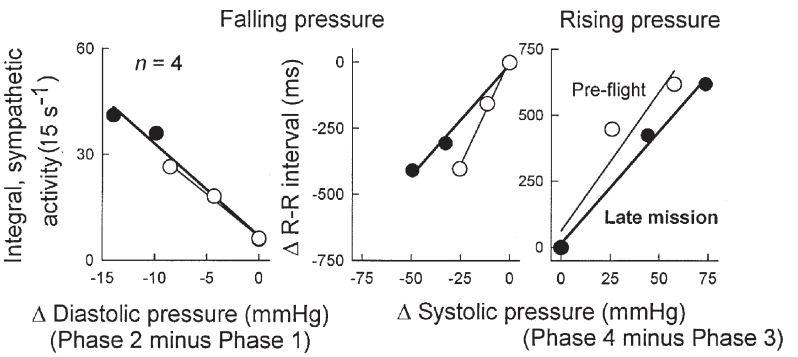

Figure 6. Average sympathetic and vagal responses plotted as functions of arterial pressure changes

Thick lines depict measurements made on flight days 12 or 13, and thin lines depict measurements made ~72 days pre-flight on Earth. In each panel, observations made during the 1 min control period before Valsalva straining are plotted at zero pressure change. The first symbol after the control value represents responses to 15 mmHg straining, and the second symbol represents responses to 30 mmHg straining. The two left panels depict responses to straining, and the right panel depicts responses after release of straining.

missions, left ventricular dimensions are *less* than they were in the supine position on Earth before the mission (Charles *et al.* 1994). Since left ventricular dimensions are less, it is likely that carotid artery and aorta dimensions are less as well. We reasoned that such dimensional changes of baroreceptive arteries, if they occur, should change arterial baroreceptor function and that such changes should alter integrated baroreflex responses.

Influence of microgravity or simulated microgravity on arterial baroreflexes

Changes in vagal baroreflex mechanisms during simulated or actual microgravity are understood better than changes in sympathetic baroreflex mechanisms. Microgravity, as simulated by head-down bed rest (Kakurin *et al.* 1976), reduces vagally mediated R–R interval responses to graded neck pressure changes (Convertino *et al.* 1990), or to spontaneous fluctuations of systolic pressure (Sigaudo *et al.* 1996). Subjects whose vagal baroreflex deteriorates after 30 days of head-down bed rest are more likely to experience orthostatic vasovagal reactions than subjects whose vagal baroreflex responses are preserved (Convertino *et al.* 1990).

Two reports document impairment of vagal baroreflex responses after space shuttle missions. In the first (Fritsch *et al.* 1992), 16 astronauts were studied with a stepwise neck pressure algorithm, which triggers a highly reproducible (Eckberg *et al.* 1992) sequence of R–R interval responses. The maximum slope and range of the sigmoidal relation between carotid distending pressures and R–R intervals were significantly less, and the resting position (operational point) of astronauts on this relation was lower after the space missions than before. Backward elimination modelling of these data indicated that impairment of orthostatic arterial pressure responses to standing after space missions is predicted best by the lowering of the astronauts' vagal baroreflex operational points and reductions of their body weight (Fritsch *et al.* 1992).

A second study (Fritsch-Yelle *et al.* 1994) also conducted in 16 astronauts, confirmed these results. This study is particularly relevant to the Neurolab results, since vagal baroreflex function also was gauged with Valsalva manoeuvres. Arterial pressure and R–R interval responses immediately after space missions were virtually identical to the responses to Valsalva manoeuvres that we measured during the Neurolab mission (Fig. 1). Systolic pressure reductions during straining and elevations after release of straining were greater on landing day than during pre-flight sessions, and R–R interval responses to these pressure changes were less.

The results of greatest relevance to the present study, which thus far have been published only in preliminary form (Fritsch & Eckberg, 1992), were obtained during two space shuttle missions. In this study of 13 astronauts, the range, maximum gain and operational point of sigmoid carotid distending pressure–R–R interval response relations were all significantly lower in space than on Earth. Results from the Neurolab mission lack the statistical power of the studies cited above. Nonetheless, they provide some indication that vagal baroreflex responses are altered in space (Fig. 5, bottom panels and Fig. 6, middle and right panels). The earlier studies, which documented impairment of vagal baroreflexes, provided a compelling rationale for study of sympathetic baroreflex responses in space. Thus, our Neurolab study tested the hypothesis that spaceflight also impairs sympathetic responses to changes of baroreceptor input.

Our results reject this hypothesis. Although sympathetic responses to Valsalva straining were greater in all astronauts in space than on Earth (Fig. 4), the arterial pressure changes that provoked the sympathetic responses were also greater (Figs 2 and 3). As a result, sympathetic baroreflex gain, as reflected by the maximum diastolic pressure reduction divided by the integrated sympathetic response (Fig. 6, left panel) was normal.

Potential mechanisms

Autonomic responses to Valsalva straining are modulated importantly by blood volume. This was illustrated convincingly by Ten Harkel *et al.* (1990, 1992), who showed that both acute reductions in central blood volume during standing, and chronic blood volume reductions after prolonged head-down bed rest, increase arterial pressure and heart rate responses to Valsalva straining. In the context of these observations, hypovolaemia in space leads acutely to greater arterial pressure reductions and increases of muscle sympathetic nerve activity during Valsalva straining, than in the supine position on earth (and chronically to increased steady-state sympathetic outflow to the important muscle vascular bed; Ertl *et al.* 2002).

We cannot be certain which sensors mediate these changes, and we do not exclude cardiac receptors (Hainsworth, 1991). However, we strongly suspect that arterial baroreceptors are importantly involved. Blombery & Korner (1982) showed that virtually all vasoconstrictor and heart rate responses in conscious rabbits to 'Valsalva-like' manoeuvres are abolished by a sinoaortic denervation procedure that leaves cardiac efferent and afferent neural pathways intact.

Moreover, the absence of changes in baseline arterial pressures and R–R intervals in no way discounts arterial baroreceptor involvement in adjustments to microgravity. Interventions which should change arterial pressure but do not, such as low levels (< 20 mmHg) of lower body suction (Zoller *et al.* 1972), provoke major reductions in thoracic aorta dimensions (Taylor *et al.* 1995) and increases in muscle sympathetic nerve activity (Victor & Leimbach, 1987). The situation in space may be analogous:

hypovolaemia is compensated for by increased sympathetic neural outflows (Ertl *et al.* 2002) and this, in turn, maintains arterial pressure at normal levels. This adjustment is so effective that, without direct recordings of sympathetic nerve activity (or baroreceptive artery dimensions), there may be no evidence of arterial baroreflex engagement.

Although we emphasize the probable contribution of hypovolaemia to autonomic adaptation in microgravity, other mechanisms are likely to contribute. Chief among these is physical exercise. In space, there is virtually no reliance on antigravity muscles for locomotion and lifting. Since skeletal muscle is highly sensitive to loading conditions, intracellular processes governing protein synthesis in antigravity muscles are transformed (Edgerton *et al.* 1995), myofibre size (Zhou *et al.* 1995) and maximum torque potential are diminished, and fatigability is increased (Day *et al.* 1995). A recent study (Kamiya *et al.* 2000) suggests that human muscle metaboreceptor modulation of muscle sympathetic nerve activity is impaired after microgravity, as simulated by head-down bed rest. Moreover, exercise, plasma volume and autonomic function are interrelated. Regular (Oscai *et al.* 1968) or acute (Green *et al.* 1984) exercise increases plasma volume, and a single bout of exercise during head-down bed rest, restores vagal baroreflex function to normal (Convertino *et al.* 1992). Another potential mechanism is cardiac atrophy (Levine *et al.* 1997), which reduces left ventricular dimensions more than hypovolaemia alone, and may alter sympathetic modulation by cardiac receptors (Hainsworth, 1991).

Figure 7 depicts average sympathetic and R–R interval responses of healthy young volunteers to brief, graded neck suction or pressure. These data, adapted from a study by Rea & Eckberg (1987), indicate that healthy young adults operate near the middle of the linear region of their vagal sigmoid arterial pressure–R–R interval relations and close to the threshold region of their reverse sigmoid arterial pressure–sympathetic response relations (both positions are indicated by open circles).

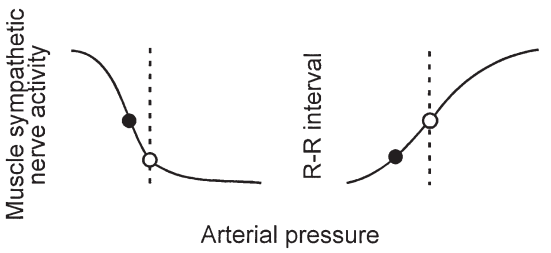

Figure 7. Mechanism proposed for baroreflex changes in space

These data depict average reverse sigmoid carotid baroreceptor–muscle sympathetic nerve, and sigmoid–R–R interval relations for a group of healthy young subjects studied earlier (Rea & Eckberg, 1987). The normal resting position (operational point) of these subjects is indicated by the open circles and vertical dashed lines. We speculate that microgravity shifts subjects leftward on both relations (filled circles).

The Neurolab data can be explained economically by positing a leftward shift of the operating position (filled circles) on the relations shown in Fig. 7. According to this speculation, chronic hypovolaemia and reduced autonomic sensory inputs from baroreceptors (and possibly other receptors) shift reverse sigmoid arterial pressure–muscle sympathetic nerve activity relations leftward and upward on the linear portion (Fig. 7, left panel). Since this shift may begin near a subject's threshold, changes in baroreceptor input provoked by the Valsalva manoeuvres used in our study may not carry them beyond the linear range; therefore, their sympathetic baroreflex gain is unchanged. Conversely, the same leftward shift of the operating position on the vagal arterial pressure–R–R interval relation (Fig. 7, right) moves subjects from the linear portion towards the threshold region. Accordingly, reductions in baroreceptor input during Valsalva straining (Fig. 5, bottom panels; Fig. 6, middle panel; Fritsch *et al.* 1992) provoke smaller reductions of R–R intervals in space than on Earth, because they carry subjects into their threshold regions. We note, however, that results from earlier space missions (Eckberg & Fritsch, 1992) point to actual impairment of vagal baroreflex relations; the range, as well as the maximum gain of sigmoidal carotid baroreceptor–cardiac reflex responses were significantly impaired in space.

Figure 7 treats vagal and sympathetic baroreflex responses as though they are independent of each other. It is clear, however, that in humans, this is not the case – sympathetic stimulation reduces vagal influences (Taylor *et al.* 2001). Therefore, increased sympathetic nerve activity and noradrenaline spillover (Ertl *et al.* 2002) may constitute an important new mechanism responsible for the degradation of vagal baroreflex responses that occurs in space (Fritsch & Eckberg, 1992).

Thus, our results suggest that there is a dichotomy between changes of sympathetic and vagal baroreflex responses in space: sympathetic responses are preserved, and vagal responses are impaired. It is of interest that normal ageing seems to provoke a similar pattern of autonomic changes, with increases of baseline muscle sympathetic nerve activity, preservation of sympathetic baroreflexes and impairment of vagal baroreflexes (Ebert *et al.* 1992). Other data from the Neurolab mission indicate that the preservation of sympathetic responses to very brief changes of baroreceptor input that we document is functionally significant. Steady-state sympathetic responses – muscle sympathetic nerve activity, plasma noradrenaline spillover and peripheral vascular resistance – to simulated orthostatic stress in space (lower body suction, Ertl *et al.* 2002); and to actual head-up tilt after space travel (Levine *et al.* 2002) are normal.

Table 3. Neurolab autonomic nervous system protocol

Activity	Experimental session		
	~ 72 days pre-flight	Mission day 12 or 13	Landing day
Instrumentation	90	85	90
Trial upright tilt		—	
Handgrip to determine maximum voluntary contractions			
Baseline cardiac outputs*		—	
Blood sampling			
Breathing protocol	25	25	25
Noradrenaline infusion	7	7	—
Valsalva manoeuvres	8	8	—
Static handgrip	10	10	10
Cold pressor	9	9	—
Lower body negative pressure	24	24	—
Upright tilt	15	—	15
Deinstrumentation	10	10	10

Instrumentation includes placement of electrodes and sensors, intravenous catheter insertion, and microneurography. Breathing protocol: uncontrolled, 5 min; random frequency, 6 min; controlled frequencies, 9 min, including hyperventilation followed by apnoea (for as long as possible). Static handgrip includes baseline measurements, 1 min; 40 % maximum voluntary contraction to fatigue, ~ 2–3 min; blood pressure cuff inflation, 2 min; and recovery, 5 min. Cold pressor includes baseline measurements, 1 min; exposure to cold, 2 min; and recovery, 5 min. Lower body negative pressure and blood draws includes baseline measurements, 10 min; and −15 and −30 mmHg, 7 min each. * Cardiac outputs were also measured before and during upright tilt. Each intervention was followed by a recovery period (1–6 min duration) to allow measurements to return to baseline levels.

Limitations

We report what we believe to be high quality (Fig. 1), state-of-the-art measurements of human autonomic function, made in the hostile environment of space. Nonetheless, our study has major limitations, which we catalogue here.

Astronauts. First, the number of subjects was small – we evaluated only the four astronauts studied with sympathetic microneurography before and during the Neurolab mission. Therefore, we present descriptive results, rather than statistical analyses.

Other Neurolab protocols. As indicated in Appendix (Table 3) Valsalva testing was performed after 18 min of controlled-frequency breathing, but before other tests of autonomic cardiovascular function, including isometric handgrip, cold pressor testing and lower body suction, which might have influenced Valsalva responses. It is unlikely that controlled-frequency breathing influenced the results we report. It is possible, however, that the Neurolab vestibular protocol (Appendix, Table 4) influenced our results. Two astronauts underwent off-axis rotation, 125 and 140 min prior to autonomic testing ~72 days before the mission, and one of these and another underwent off-axis rotation, 70 and 150 min before autonomic testing on landing day. (The autonomic tests on mission days 12 and 13 were the first to be performed on those days.) We doubt, but cannot prove, that off-axis rotation influenced autonomic responses. Shortt & Ray (1997) reported that the increased muscle sympathetic nerve activity that occurs during vestibular stimulation with head-down neck flexion returns to baseline levels in ~1 min.

Valsalva manoeuvre. We measured beat-by-beat arterial pressures indirectly. The method we used has been exhaustively vetted (Imholz *et al.* 1998) and has been shown to provide reliable estimates of changes in arterial pressure under most circumstances (including Valsalva testing, Imholz *et al.* 1988). The greater concern is with the Valsalva manoeuvre itself. Although Valsalva's manoeuvre is a time-honoured, much used method for perturbing human autonomic function (Eckberg & Sleight, 1992), it suffers from a major limitation (which is not generally recognized): *the actual stimulus is not measured*. As mentioned, arterial baroreceptors appear to be prepotent in mediating sympathetic and vagal responses to Valsalva straining (Blombery & Korner, 1982). However, arterial baroreceptors sense distortion, not pressure (Angell James, 1971), and we measured distortion of neither carotid nor aortic baroreceptive areas. It is likely that the transient changes in finger photoplethysmographic arterial pressure we measured paralleled changes in carotid arterial pressure and dimensions. However, we have no information on changes in aortic dimensions.

Table 4. Neurolab protocols that preceded autonomic testing

	Astronaut					
Protocol	1	2	3	4	5	6
~72 days pre-flight						
Off-axis rotation	—	—	Yes (140)	Yes (125)	—	—
Virtual Environment Generator	—	—	—	Yes	—	
Pulmonary function	—	—	—	—	—	
Landing Day						
Off-axis rotation	Yes (150)	—	—	Yes (70)	—	—
Virtual Environment Generator	Yes	—	—	Yes	—	—
Pulmonary function	Yes	—	—	Yes	—	—
Ball catch	Yes	—	—	—	—	

Off-axis rotation was performed during 19 min sessions, with astronauts seated in a centrifuge developed by the European Space Agency. In-flight centrifugation was performed on the days before autonomic testing, days 12 and 13, but not on the same days. The position of astronauts during off-axis rotation was such that during portions of the testing, pressures in the carotid arteries and aorta were increased. Numbers in parentheses indicate the time (min) between off-axis rotation and autonomic testing. The virtual environment generator is a head-mounted display that shows computer-generated virtual reality scenes to test astronauts' perceptions. Studies of pulmonary function involved measurements of respiratory gas compositions and flow rates, and rib cage and abdominal motions. In the ball catching experiment, astronauts caught a light-weight ball propelled downward, while their arm movements and arm electrical activity were recorded.

Smith *et al.* (1996) obtained transoesophageal echograms to measure ascending thoracic aortic cross-sectional areas during Valsalva straining. They showed that aortic dimensions decline throughout the period of straining. Since finger, and presumably carotid, artery pressures and dimensions increase during the earliest seconds of straining, baroreceptor inputs are transiently changing in opposite directions – carotid baroreceptor firing is increasing and aortic baroreceptor firing is decreasing. Moreover, even during the late stages of straining, carotid pressure and presumably dimensions, may remain above baseline levels (as shown in Fig. 1, Preflight). However, it is likely that during this time, inputs from carotid and aortic baroreceptors are changing in parallel (and that therefore, there is no central conflict). Muscle sympathetic nerve activity is much more responsive to the direction of (diastolic) arterial pressure change than to its absolute level (Sundlöf & Wallin, 1977).

In conclusion, we studied sympathetic and vagal transients provoked by Valsalva straining in four astronauts before and during the Neurolab space shuttle mission. We propose that exposure to microgravity chronically shifts astronauts' positions on their arterial pressure–sympathetic and arterial pressure–vagal response relations (Fig. 7) to the left. Although we do not exclude other mechanisms, including particularly atrophy of antigravity and cardiac muscle, this postulated shift can be explained economically as a consequence of hypovolaemia in space, itself a chronic adjustment provoked by microgravity.

APPENDIX

Arguably, the most precious commodity in space research is astronauts' time. The autonomic nervous system team developed (at Vanderbilt University's Center for Space Physiology and Medicine, and the Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas) a fixed protocol to fit within the severe time constraints imposed by NASA mission planners for research during the space mission. Table 3 gives the sequence of autonomic tests during the critical microneurography sessions, ~72 days before the mission, on flight days 12 or 13, and on landing day. Table 4 also indicates the relation between autonomic function tests and other Neurolab protocols conducted by other research groups. Each article in this series (Cox *et al.* 2002; Ertl *et al.* 2002) discusses potential influences of preceding research in limitations sections.

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