

The Human Sympathetic Nervous System Response to Spaceflight

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ABSTRACT

The sympathetic nervous system is an important part of the autonomic (or automatic) nervous system. When an individual stands up, the sympathetic nervous system speeds the heart and constricts blood vessels to prevent a drop in blood pressure. A significant number of astronauts experience a drop in blood pressure when standing for prolonged periods after they return from spaceflight. Difficulty maintaining blood pressure with standing is also a daily problem for many patients. Indirect evidence available before the Neurolab mission suggested the problem in astronauts while in space might be due partially to reduced sympathetic nervous system activity. The purpose of this experiment was to identify whether sympathetic activity was reduced during spaceflight. Sympathetic nervous system activity can be determined in part by measuring heart rate, nerve activity going to blood vessels, and the release of the hormone norepinephrine into the blood. Norepinephrine is a neurotransmitter discharged from active sympathetic nerve terminals, so its rate of release can serve as a marker of sympathetic nervous system action. In addition to standard cardiovascular measurements (heart rate, blood pressure), we determined sympathetic nerve activity as well as norepinephrine release and clearance on four crewmembers on the Neurolab mission. Contrary to our expectation, the results demonstrated that the astronauts had mildly elevated resting sympathetic nervous system activity in space. Sympathetic nervous system responses to stresses that simulated the cardiovascular effects of standing (lower body negative pressure) were brisk both during and after spaceflight. We concluded that, in the astronauts tested, the activity and response of the sympathetic nervous system to cardiovascular stresses appeared intact and mildly elevated both during and after spaceflight. These changes returned to normal within a few days.

INTRODUCTION

Many human physiological responses are controlled by the nervous system without any conscious effort by the individual. For example, when people are startled, their skin prickles. When they are excited, their eyes dilate; and when they are frightened, blood is directed to their muscles and shunted away from the digestive tract to prepare for fighting or running away. These examples are part of the autonomic (or automatic) nervous system's almost immediate response and adjustment to everyday occurrences. The two branches of the autonomic nervous system that control these adjustments are

the sympathetic nervous system, which usually controls alerting responses, and the parasympathetic nervous system, which usually controls resting and relaxing responses.

Automatic autonomic nervous system adjustments are essential for standing. During standing, gravity causes about 700 mL of blood and body fluids to move from the chest into the legs and trunk. Autonomic reflexes increase heart rate and constrict blood vessels in many areas, thereby increasing resistance to blood flow in less essential regions. Blood pressure would fall if these autonomic adjustments did not occur. Instead, blood pressure is maintained, allowing humans to remain conscious while standing upright. These adjustments

also keep blood pressure relatively constant under varied everyday conditions.

Blood pressure is sensed by pressure receptors in the blood vessels of the carotid sinus in the neck, in the aortic arch, and in the heart. The pressure receptors are called baroreceptors. When blood pressure is high, the baroreceptors inhibit sympathetic nerve activity from the brain, which allows a relative relaxation of blood vessels. When these receptors sense low blood pressure, the outgoing (or efferent), sympathetic activity increases and causes blood vessels to constrict. These reflex reactions are called baroreflexes. When the sympathetic nerves are activated, they release the hormone norepinephrine into the blood. Norepinephrine is a neurotransmitter discharged from active sympathetic nerve terminals, so its rate of release can serve as a marker of sympathetic nervous system activity.

When astronauts return from a spaceflight and experience gravitational forces on Earth again, they may have difficulty standing (Buckey, 1996). Their bodies' adaptations to spaceflight (such as a reduction in blood volume) can result in elevated heart rates and the feeling that they are about to faint. If these symptoms were severe during landing or in an emergency after landing, this could present a risk to the astronauts. Therefore, an understanding of this problem is important to NASA.

The inability to tolerate an upright position is called orthostatic intolerance (OI). Spaceflight-induced OI results from factors such as reduced blood volume and possibly autonomic nervous system dysfunction produced by a prolonged reduction of sympathetic nervous system activity while in space (Robertson, 1994).

There are several reasons why microgravity might reduce sympathetic nervous system activity in space. When body fluids are no longer pulled towards the legs by gravity and therefore remain in the central part of the body (Watenpaugh, 1995), this might stretch pressure receptors in the heart and inhibit sympathetic activation. The absence of the regular baroreflex-mediated sympathetic stimulation, which occurs on Earth with frequent body position changes and subsequent fluid shifts, might lead to temporary baroreflex dysfunction in space and exaggerated but insufficient sympathetic responses when astronauts are reexposed to Earth's gravity (Vernikos, 1996).

An early study (Leach, 1983) of sympathetic activity in space suggested that sympathetic nervous system activity was reduced in astronauts. This study showed that norepinephrine levels in blood were decreased in flight compared to preflight measurements. The level of norepinephrine in blood, however, is not always an accurate marker of sympathetic nervous system activity. The blood level of norepinephrine represents a balance between the norepinephrine entering the blood and the clearance of norepinephrine from the blood. A more useful measure of sympathetic nervous system activity therefore is how much norepinephrine is actually entering the bloodstream, not just the blood level.

Subsequent studies of norepinephrine levels in space have shown either no change or an increase in norepinephrine levels. To resolve whether sympathetic nervous system activity was in fact reduced in space, we conducted a study that would

measure the actual release (or spillover) of norepinephrine into the bloodstream. In addition, we measured sympathetic nerve activity directly using microneurography (see technical report by Ertl et al. in this publication). Measurement of sympathetic nerve activity with microneurography enables direct on-line monitoring of sympathetic nervous system function, is remarkably stable in individual subjects over time, and yields measurements that correlate well with norepinephrine spillover. With this combination of measurements, we could determine definitively whether reduced or increased sympathetic activity occurred during spaceflight.

METHODS

The experiment required a way to provide a standardized stress to the cardiovascular system both in space and on Earth. With standing, blood leaves the chest and moves to the lower body. Standing, however, could not be used as a cardiovascular stress in space, since the astronauts are experiencing weightlessness. Instead, suction was applied to the lower body of supine astronauts with their hips and legs sealed in a chamber just above the pelvis. The suction moves blood from the chest to the lower body, in a way that is very similar to what occurs with standing. This suction (or lower body negative pressure (LBNP)) was used preflight, in flight, and postflight as the cardiovascular stress.

The LBNP chamber used on Earth was made of rigid plastic, and the LBNP chamber used in space was made of collapsible airtight fabric. Both had windows to allow leg access for microneurography. After seven minutes of resting baseline recording, suction was applied at -15 and -30 mmHg for seven minutes each. The simulated gravitational stress of LBNP at these levels is somewhat less than standing in an upright posture on Earth, and it is considered by NASA to be a safe stress for astronauts in space. Data were collected in space during the third to fifth minute of each seven-minute period, and blood was drawn at the end of each segment. Data were collected by computer and analyzed on Earth. The blood samples were processed in space and analyzed in our laboratory on Earth.

Heart rate was measured by electrocardiogram. Adhesive electrodes were placed on the chest to monitor the heart's pulse and electrical activity. Blood pressure was monitored continuously using finger arterial pressure by placing a small pressure cuff on a finger. Muscle sympathetic nerve activity (MSNA) was recorded by microneurography (see technical report by Ertl et al. in this publication). Briefly, the tip of a $200\text{-}\mu\text{m}$ tungsten microelectrode was introduced into the peroneal nerve behind the knee and placed among C-fibers carrying the sympathetic nervous system signals to the small blood vessels supplying the leg muscles. To provide another measure of sympathetic nervous system activation, plasma norepinephrine spillover and clearance were measured before, during, and after the Neurolab flight. This technique used a tracer dose of radioactive norepinephrine, which was infused into an arm vein. Blood samples were taken from the opposite arm during the experiment. Analysis of these samples provided

the kinetics of norepinephrine appearance and disappearance from the circulation. Use of this methodology helps us understand the divergent results from norepinephrine measurements determined in previous spaceflight experiments. The amount of radioactive norepinephrine was so small that it did not change norepinephrine levels in the plasma or affect the astronaut's heart or circulation (Ertl, 2002). These measurements were made at rest in a supine posture and after seven minutes of LBNP at -15 and -30 mmHg on Earth and in space.

RESULTS

We indicated the number of subjects for each measurement on the graphs. Not all astronauts were studied with all protocols because of NASA regulations and technical difficulties.

While the average heart rate of four astronauts at rest in the LBNP was similar preflight and inflight (56 ± 4 beats per minute), heart rate during -30 mmHg LBNP was greater in

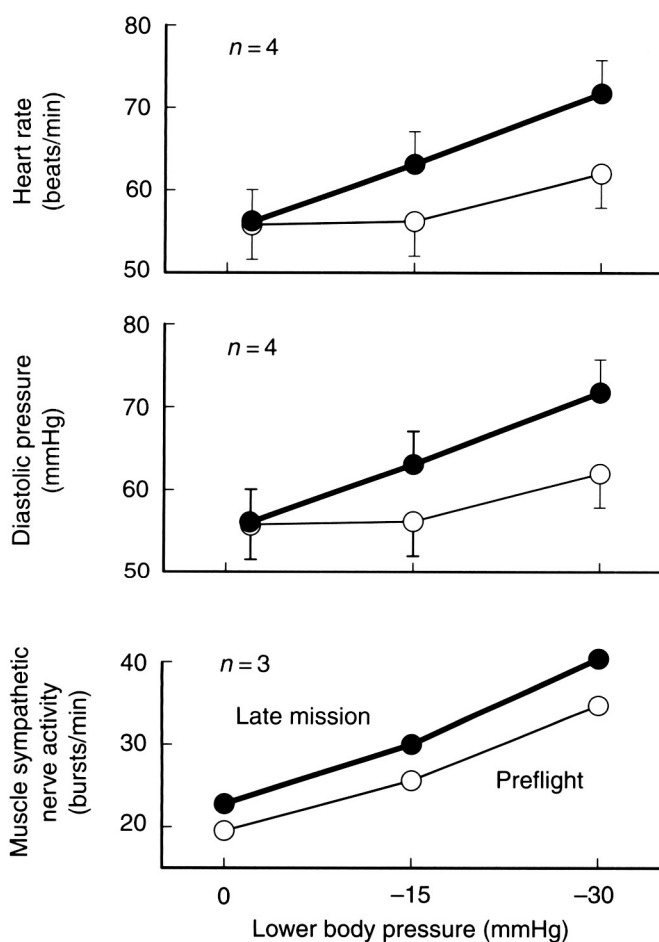


Figure 1. Hemodynamic responses to LBNP. Although average baseline heart rates and diastolic pressures were similar during preflight and inflight sessions, increments during graded LBNP were greater in space. All three astronauts had more muscle sympathetic bursts per minute before and during LBNP in space than on Earth. (From Ertl, 2002, with permission; reproduced from *The Journal of Physiology*.)

space (72 ± 4 beats per minute) than before spaceflight (62 ± 4 beats per minute). In Figure 1, the steeper slope of the heart rate response to LBNP during spaceflight indicates a greater response to LBNP in space compared to Earth. Average blood pressures did not change significantly during LBNP in any session. Figure 2 depicts MSNA in one astronaut, recorded 73 days preflight and 13 days inflight. This subject's MSNA prior to LBNP increased from 15 bursts per minute preflight to 20 bursts per minute inflight. The astronaut's MSNA further increased during -15 and -30 mmHg LBNP, and these increases also were greater during inflight than preflight sessions (19 vs. 32, and 39 vs. 48 bursts per minute). Average MSNA, in bursts per minute, before and during spaceflight for three astronauts is depicted in Figure 1, bottom panel. The average activity for the three astronauts was slightly elevated both at rest and during LBNP in space compared to on Earth.

Plasma norepinephrine and norepinephrine kinetics

In the same three astronauts who underwent sympathetic microneurography, baseline plasma norepinephrine concentrations were higher inflight than preflight (range of increases: 35–169%, Figure 3). Average norepinephrine clearance and spillover were also elevated in space from preflight values. In five astronauts, plasma norepinephrine concentrations and whole body norepinephrine spillover and clearance were significantly higher one day after landing as compared to preflight levels. These values all returned to preflight levels by day five or six.

DISCUSSION

Our study provided the first comprehensive analysis of human sympathetic nervous system function during spaceflight. In space, baseline sympathetic neural outflow, whether measured by plasma norepinephrine spillover or MSNA, was slightly increased and sympathetic responses to LBNP were exaggerated. The astronauts we studied responded normally to the simulated orthostatic stress of LBNP, and they also maintained their blood pressures.

Baseline sympathetic outflow

In three astronauts, microgravity moderately increased the number of sympathetic bursts per minute in baseline MSNA. These limited data agree with most studies measuring sympathetic microneurography during the simulated microgravity of head-down bed rest on Earth. The data show, however, that we need to reject our hypothesis that spaceflight reduces sympathetic neural outflow. The finding of increased levels of MSNA during the Neurolab mission suggests that the significantly increased levels of sympathetic nerve activity recorded in five astronauts after the Neurolab mission (see science report by Levine et al. in this publication) is not an artifact resulting from uncontrollable stresses on landing day.

The changes in astronauts' sympathetic nerve activity were mirrored by the norepinephrine data. The same three astronauts had elevated plasma norepinephrine levels as

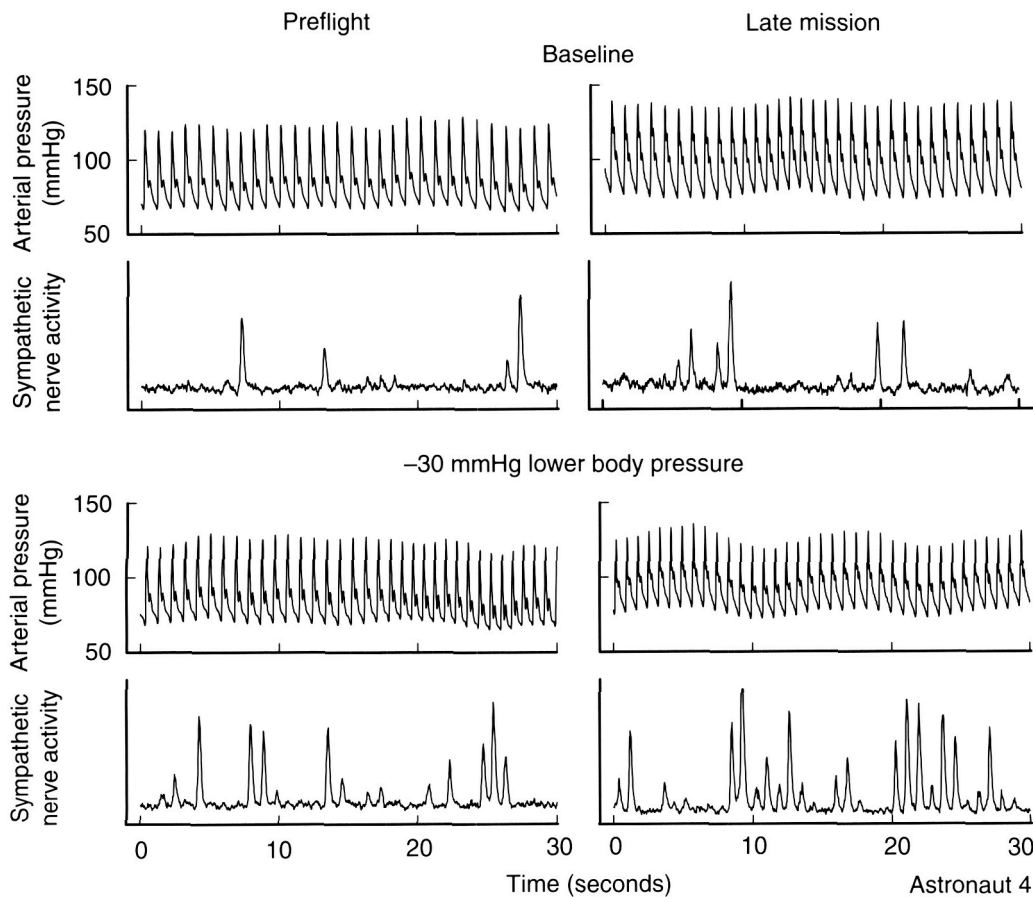


Figure 2. Recordings before and during 30-mmHg LBNP from one astronaut. This and the other two astronauts had greater sympathetic responses to LBNP in space than on Earth. (From Ertl, 2002, with permission; reproduced from *The Journal of Physiology*.)

compared to values obtained in the supine position on Earth (Figure 3). As mentioned earlier, however, elevations of plasma norepinephrine concentrations may reflect reduced clearance as well as increased spillover. We found that norepinephrine clearance is increased in space, a change that should reduce, not increase, plasma norepinephrine levels. One implication of increased norepinephrine clearance is that plasma norepinephrine levels in space underestimate increases of sympathetic nervous activity. In Neurolab astronauts, plasma norepinephrine spillover was increased more than was norepinephrine clearance; and, therefore, plasma norepinephrine levels were higher (Figure 3), not lower, in space.

All of the measurements of sympathetic activity in astronauts—muscle sympathetic nerve activity, plasma norepinephrine concentrations, and norepinephrine spillover—indicate that spaceflight increases baseline sympathetic neural outflow. This finding may explain increases of calf vascular resistance documented in astronauts during brief space missions. Following the Neurolab mission, we continued studies of norepinephrine kinetics in five astronauts, and found that norepinephrine spillover remains elevated for at least one to two days after spaceflight. We were reassured by the agreement between norepinephrine kinetics measurements made five days postflight and those made preflight.

LBNP

LBNP in space further increased MSNA, and these exaggerated increases of MSNA were paralleled by exaggerated increases of norepinephrine spillover. The greater sympathetic responses to LBNP in space than on Earth (where recordings also were made in the supine position) compensated for the LBNP-induced reduction of the already reduced central blood volume and contributed to maintenance of arterial pressure at preflight levels. We also found no support for our hypothesis that sympathetic responses to simulated orthostatic stress in space are impaired. The finding of normal sympathetic responses to steady-state LBNP is consistent with the findings of other Neurolab protocols, which documented normal sympathetic responses to abrupt reductions of baroreceptor input during Valsalva straining in space (see science report by Cox et al. in this publication), and normal sympathetic and hemodynamic responses to upright tilt after spaceflight (see science report by Levine et al. in this publication).

Autonomic mechanisms in space

Cardiovascular measurements confirmed results from earlier studies conducted during simulated or actual spaceflight. We found exaggerated heart rate and arterial pressure increases

during LBNP, as has been seen in other studies (Ertl, 2002). Such large responses to LBNP begin after only two days of spaceflight, by which time intravascular volume has declined by 14–17%. Greater increases in heart rate may reflect increased sympathetic stimulation of the heart, increased withdrawal of vagal restraint (Cox, 2002), or a combination of these factors. Exaggerated responses to LBNP might also be mediated by cardiac muscle atrophy (Levine, 2002).

Several mechanisms might explain increased norepinephrine clearance in space. Flow in the vascular bed of the lungs is altered by microgravity, and the lungs are importantly involved in norepinephrine spillover and clearance. Headward redistribution of fluid might also alter blood flow, capillary exchange, and how norepinephrine is disposed in other vascular beds. If such gravitational shifts alter norepinephrine kinetics in space, it is unclear what mechanism sustained the changes during the first postflight measurements.

Limitations

The principal limitations of our study are shared by most research conducted on humans in space: the small numbers of subjects, and the limited time available for individual research protocols. We were able to record MSNA in only three astronauts. However, we also characterized sympathetic activity with plasma norepinephrine concentrations and norepinephrine spillover in the same three astronauts. All indexes of sympathetic function changed in parallel. Further, we were able to obtain complete sets of norepinephrine kinetic data in five subjects before the Neurolab mission, and after landing. These measurements documented elevations of plasma norepinephrine concentrations and norepinephrine spillover one day after landing—measurements that were similar to those recorded about four days earlier in space in three of the five astronauts.

There were severe time constraints for all of the Neurolab protocols, including ours. Nonetheless, we believe that we allowed sufficient time for tritiated norepinephrine to reach a steady-state level for baseline measurements, and that the seven-minute stages of LBNP also were adequate for our purposes. The diet and fluid intakes of Neurolab astronauts were similar to those of astronauts on earlier NASA missions and were not controlled. Since we studied short-duration spaceflight, we do not know if sympathetic mechanisms would have undergone further adaptation had spaceflight been extended. As detailed in the Appendix of Cox et al. (Cox, 2002), our studies followed other protocols.

In conclusion, we studied the influence of spaceflight on sympathetic control mechanisms by measuring plasma norepinephrine concentrations, whole body norepinephrine spillover and clearance, and peroneal nerve muscle sympathetic activity on Earth and in space. In space, baseline sympathetic neural outflow (however it is measured) is increased moderately, and sympathetic responses to LBNP are exaggerated. The consequence of these changes is that in spite of a reduced blood volume, the astronauts we studied responded normally to simulated orthostatic stress (and to upright tilt on landing day), and were able to maintain their blood pressures at normal levels.

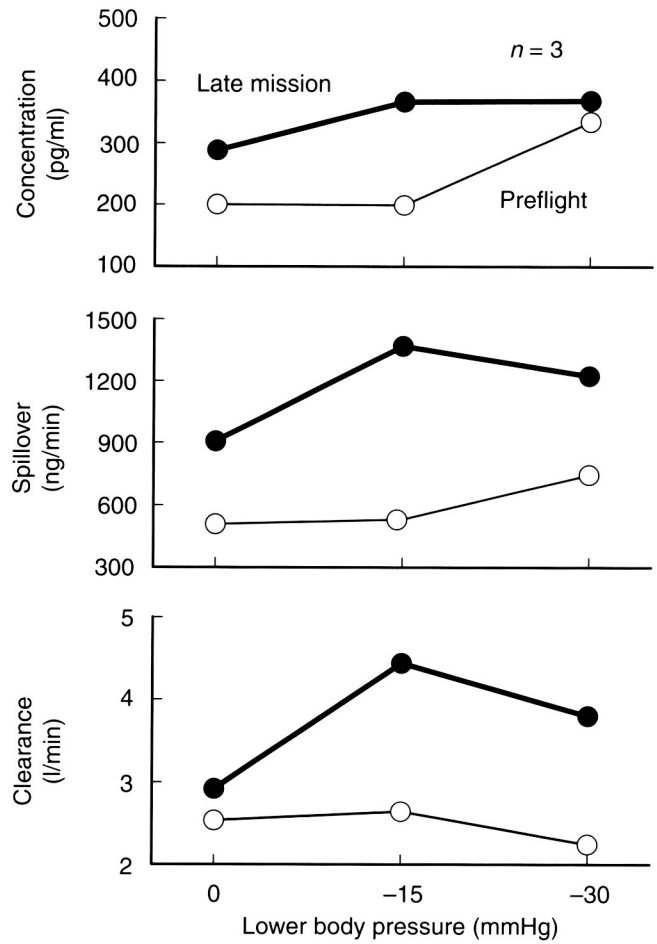


Figure 3. Average norepinephrine data from three astronauts. These data are from the same three subjects whose microneurography responses were depicted in Figure 1, bottom panel. (From Ertl, 2002, with permission; reproduced from *The Journal of Physiology*.)

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