Neural Control of the Cardiovascular System in Space

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ABSTRACT

During the acute transition from lying supine to standing upright, a large volume of blood suddenly moves from the chest into the legs. To prevent fainting, the blood pressure control system senses this change immediately, and rapidly adjusts flow (by increasing heart rate) and resistance to flow (by constricting the blood vessels) to restore blood pressure and maintain brain blood flow. If this system is inadequate, the brain has a "backup plan." Blood vessels in the brain can adjust their diameter to keep blood flow constant. If blood pressure drops, the brain blood vessels dilate; if blood pressure increases, the brain blood vessels constrict. This process, which is called "autoregulation," allows the brain to maintain a steady stream of oxygen, even when blood pressure changes. We examined what changes in the blood pressure control system or cerebral autoregulation contribute to the blood pressure control problems seen after spaceflight. We asked: (1) does the adaptation to spaceflight cause an adaptation in the blood pressure control system that impairs the ability of the system to constrict blood vessels on return to Earth?; (2) if such a defect exists, could we pinpoint the neural pathways involved?; and (3) does cerebral autoregulation become abnormal during spaceflight, impairing the body's ability to maintain constant brain blood flow when standing upright on Earth? We stressed the blood pressure control system using lower body negative pressure, upright tilt, handgrip exercise, and cold stimulation of the hand. Standard cardiovascular parameters were measured along with sympathetic nerve activity (the nerve activity causing blood vessels to constrict) and brain blood flow.

We confirmed that the primary cardiovascular effect of spaceflight was a postflight reduction in upright stroke volume (the amount of blood the heart pumps per beat). Heart rate increased appropriately for the reduction in stroke volume, thereby showing that changes in heart rate regulation alone cannot be responsible for orthostatic hypotension after spaceflight. All of the astronauts in our study had an increase in sympathetic nerve activity during upright tilting on Earth postflight. This increase was well calibrated for the reduction in stroke volume induced by the upright posture. The results obtained from stimulating the sympathetic nervous system using handgrip exercise or cold stress were also entirely normal during and after spaceflight. No astronaut had reduced cerebral blood flow during upright tilt, and cerebral autoregulation was normal or even enhanced inflight. These experiments show that the cardiovascular adaptation to spaceflight does not lead to a defect in the regulation of blood vessel constriction via sympathetic nerve activity. In addition, cerebral autoregulation is well-maintained. It is possible that despite the increased sympathetic nerve activity, blood vessels did not respond with a greater degree of constriction than occurred preflight, possibly uncovering a limit of "vasoconstrictor reserve."

INTRODUCTION

The Challenge of Upright Posture

One of the unique features distinguishing humans from quadrupeds is the requirement for standing upright. Teleologically, this upright posture frees the hands to perform complex tasks and, therefore, is considered an essential component of human evolution. By placing the brain above the heart, however, the upright posture presents a complex problem for the blood pressure control system.

During the acute transition from supine to upright posture, a large volume of blood suddenly moves out of the chest and into the lower body. Large gravitationally induced pressure gradients (hundreds of mmHg) force blood away from the brain. Within seconds, the cardiovascular control system must sense this change, and then rapidly adjust flow (by increasing heart rate) and resistance (by constricting the blood vessels) within the circulation to restore an adequate blood pressure and maintain blood flow to the brain. If this process fails, fainting or "syncope" will occur—a medical problem affecting millions of Americans, and accounting for nearly 2% of all emergency room visits in the United States.

The Control System—The Autonomic Nervous System

A complex network of nerves called the autonomic nervous system mediates this rapid response. This system contains two main branches—the sympathetic and the parasympathetic pathways. A good analogy for how this system works would be the environmental control system in a room. A thermostat set at a specific temperature serves as the target. If the temperature drops too low, the heater comes on and raises the temperature; similarly if it gets too hot, the air conditioner kicks in and brings the temperature down. If all components are working well (sensors, heater, air conditioner), the temperature stays relatively constant. A similar process occurs in the human body. Pressure sensors, called "baroreceptors," are located in key areas such as the carotid arteries at the base of the brain, the aortic arch, and the heart itself. If the pressure gets too low, the "heater" or sympathetic nervous system speeds the heart and constricts the blood vessels; if the pressure gets too high, the "heater" turns off, relaxing the blood vessels. The parasympathetic nervous system or "air conditioner" then acts to slow the heart rate and reduce the blood flow.

Cerebral Autoregulation

If this system is not working perfectly, the brain has a "backup plan." Over a relatively large range of pressures, the blood vessels of the brain can adjust their own diameter to keep blood flow constant. If blood pressure drops, the blood vessels dilate; if blood pressure increases, the blood vessels constrict. This process, which is called "autoregulation," allows the brain to maintain a steady stream of oxygen and nutrients, even when blood pressure changes during the activities of daily life.

Cerebral autoregulation is a dynamic process that is frequency dependent. In other words, the ability of local vascular control mechanisms to buffer changes in arterial pressure and keep cerebral blood flow (CBF) constant may be more or less effective, depending on the time period or frequency at which changes in blood pressure occur. Previous work in our laboratory has described the cerebral circulation as a "high pass filter." In other words, when blood pressure changes rapidly, or with "high" frequency (>0.20 Hz, or faster than every five seconds), the autoregulatory process can't keep up and blood flow changes along with pressure. In contrast, at lower frequencies (<0.07 Hz, or slower than every 13 seconds), autoregulation is more effective and the changes in blood pressure can be buffered or filtered. This allows the maintenance of stable brain blood flow despite changes in blood pressure.

The brain has such a high metabolic rate that if its blood flow is interrupted even for a few seconds, normal neuronal function is disrupted and syncope will occur. Ultimately, syncope occurs because of a reduction in CBF sufficient to cause loss of consciousness. Usually, the fall in CBF is secondary to a dramatic drop in blood pressure, which overwhelms the capacity of cerebral autoregulation to maintain a constant flow. In some patients with recurrent syncope, however, cerebral autoregulation may be compromised. This may result in a fall in CBF during standing or sitting, even with relatively minor changes in blood pressure.

The Problem: Syncope after Spaceflight

Because gravity plays such a critical role in determining the pressure and distribution of blood flow within the circulation, the absence of gravity, such as occurs in spaceflight, affords a unique environment in which to examine these control systems. Moreover, in the earliest days of the crewed space program, the clinical importance of this issue became evident. When astronauts returned to Earth and tried to stand up, it was found that many of them couldn't—they experienced lightheadedness, dizziness, and fainting. This problem is called "orthostatic intolerance."

This problem was a topic of intense investigation during the first American and European dedicated space life sciences (SLS) missions: SLS-1, SLS-2, and Spacelab-D2. In the SLS studies, our research group made a number of important observations (Buckey, 1996): (a) about two-thirds of astronauts could not stand for 10 minutes after returning from even a short (one–two weeks) spaceflight; (b) the hearts of all of the astronauts pumped less blood in the upright position (reduced "stroke volume") after spaceflight; (c) all of the astronauts had an increase in heart rate on standing, to compensate for the reduced stroke volume; (d) in contrast to this augmented heart rate, those astronauts with the least ability to tolerate standing after spaceflight were unable to constrict their blood vessels to a greater degree than they were before flight; and, thus, they were unable to compensate for the reduced stroke volume. A similar finding was made subsequently by NASA investigators (Fritsch-Yelle, 1996), who confirmed this problem in a larger number of astronauts. They also found that the concentrations in the blood of norepinephrine (the neurotransmitter released by the sympathetic nervous system) were lower in those astronauts

with the most impaired orthostatic tolerance. These data suggested that spaceflight could be leading to a possible defect in the sympathetic nervous system that impaired the ability to constrict the blood vessels. Finally, (e) some astronauts could not remain standing, even though their blood pressure appeared to be normal. This finding raised the possibility that spaceflight could also impair autoregulation in the brain, leading to abnormal cerebral blood flow, even with adequate autonomic neural control of blood pressure.

These then were the questions we wanted to address with our Neurolab experiments: (1) does the adaptation to spaceflight cause a unique adaptation in the autonomic nervous system that would impair the ability to increase sympathetic activity and constrict blood vessels when gravitational gradients are restored on return to Earth?; (2) if such a defect could be found, could we pinpoint the specific afferent (the sensors sending signals from the body to the brain) or efferent (the sympathetic signals to the blood vessels themselves) neural pathways that were involved?; and (3) is there an abnormality of cerebral autoregulation that develops during spaceflight and impairs the ability to maintain CBF constantly in the upright position on Earth, even if blood pressure is well maintained?

METHODS

To answer these questions, we needed to be able to quantify precisely the sympathetic responses of the autonomic nervous system, as well as systemic and cerebral blood flow, in the context of an experimental protocol that perturbed multiple components of the blood pressure control system. Our experimental setup is shown in Figure 1.

The subject lay supine in a clear plastic box, which allowed the application of LBNP (see science report by Ertl et al. in this publication). This procedure moves blood from the chest to the lower body, as standing does, and stresses the cardiovascular control system. Beat-by-beat, arterial pressure was measured in the finger using photoplethysmography (Finapres, Ohmeda, Madison, WI); it also was measured intermittently in the brachial artery using a blood pressure cuff (SunTech, Raleigh, NC). Heart rate was measured with an ECG, and cardiac output was measured with the foreign gas C_2H_2 rebreathing technique. Sympathetic nerve activity was measured directly with high resolution, using microelectrodes placed in the efferent sympathetic nerves as the nerves passed by the knee using the microneurographic technique. Ertl et al. provide details of this technique in a technical report (see technical report by Ertl et. al. in this publication). A small, removable window in the LBNP box allowed access for microneurography, both supine and during upright tilt as shown in Figure 2.

The study of CBF in humans aboard the Space Shuttle required a technique that was safe, noninvasive, and allowed repeatable estimates of changes in flow on a beat-to-beat

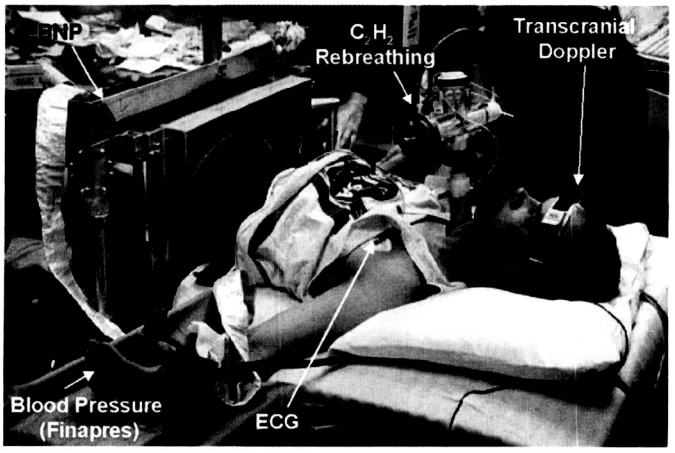

Figure 1. Alternate payload specialist Alexander Dunlap is shown during a preflight lower body negative pressure (LBNP) testing session. The head strap holds the transcranial Doppler device that makes the brain blood flow measurements in place. Acetylene (C_2H_2) rebreathing is used to measure cardiac output. The finger blood pressure device and electrocardiogram (ECG) electrodes are also shown.

Figure 2. This figure shows the test apparatus in Figure 1 tilted upright for the 60-degree upright tilt measurements. Microneurography is being performed through the side window in the LBNP device.

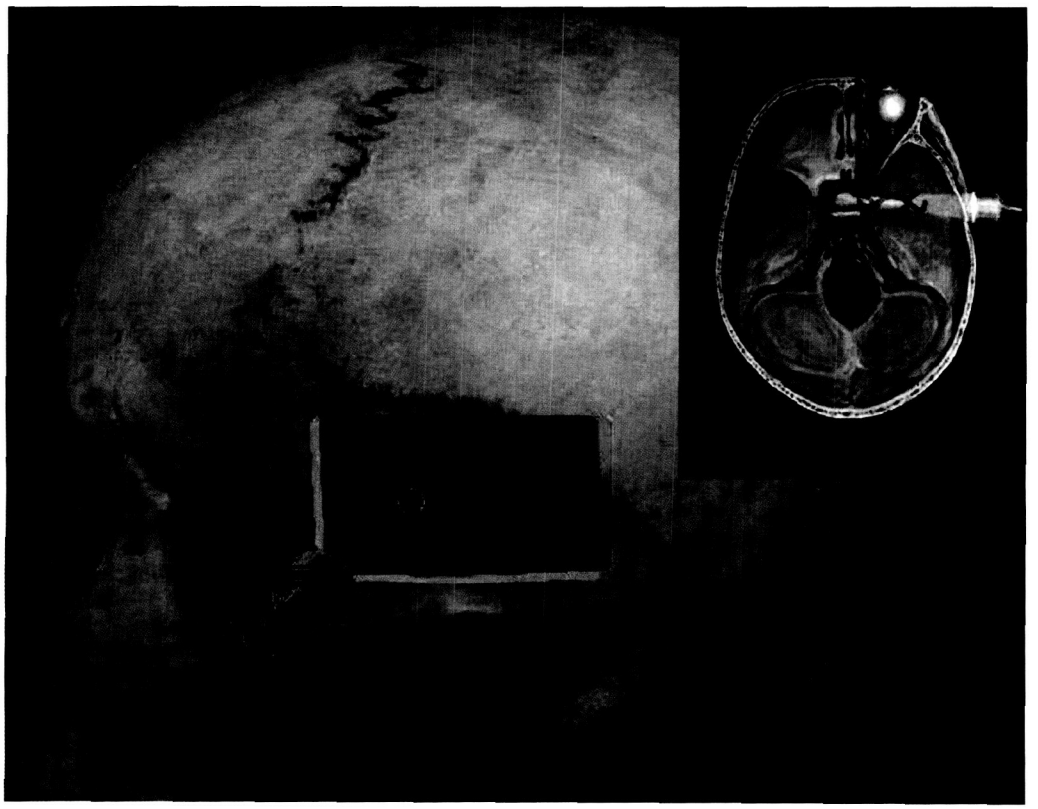

Figure 3. Transcranial Doppler. The middle cerebral arteries head toward the ears. The Doppler ultrasound travels through the skull and is partially reflected back by the blood flowing in the artery. The velocity of blood flow in the middle cerebral artery can be calculated from the reflected ultrasound. Used courtesy of Rune Aaslid.

basis. To meet these requirements, we used the transcranial Doppler technique that takes advantage of the ability of ultrasound to penetrate the skull at relatively low frequencies (2 mHz). This technique measures flow in the middle cerebral artery (Figure 3).

Because of its safety, ease of use, and ability to monitor rapid changes in CBF from velocity, transcranial Doppler has become a standard clinical tool for evaluating diseases of the cerebral circulation. By recording dynamic changes in cerebral blood flow velocity simultaneously with beat-by-beat changes in arterial blood pressure, we were able to use special mathematical techniques, called "spectral analysis," to evaluate the dynamic relationship between pressure and flow, known as "dynamic cerebral autoregulation."

By calculating the mathematical relationship between pressure and velocity, called the "transfer function," we were able to measure the strength of association (coherence) and the magnitude of association (gain) between blood pressure and cerebral blood flow at multiple frequencies. These served as indices of cerebral autoregulation. By these criteria, a high coherence means that pressure and velocity vary together very closely, implying relatively weak autoregulation. If coherence is low, the signals are independent of each other, suggesting that autoregulation is working well. In addition, when coherence is sufficiently high, the gain can be calculated. Under such circumstances, even with a high coherence, if gain is small, large changes in blood pressure lead to only small changes in CBF, implying effective autoregulation. Similarly, a large gain implies that large changes in pressure lead to similarly large changes in flow, and to relatively poor autoregulation.

An additional problem had to be overcome to measure CBF reliably—how to place the Doppler probe in exactly the same position both inflight and on the ground, with a technique that could be learned easily by nonexpert astronaut operators. To solve this problem, we used a polymer employed by dentists to take impressions of teeth. From this we made a mold of the lateral portion of the skull and ear that could hold the probe.

Protocol

We developed a protocol involving various stimuli that stressed different aspects of the blood pressure control system. The details of some of these, such as LBNP and the Valsalva maneuver, are described in detail in the science reports by Ertl et al. and Cox et al. in this publication. In this section, we will focus on three specific challenges: orthostatic stress, handgrip exercise, and cold stimulation.

To examine autonomic neural control in the upright posture, we studied our six astronaut subjects first lying flat, and then tilted upright to 60 degrees. The head-to-foot gravitational stress is equivalent to the sine of the tilt angle (90 degrees or standing upright=100% of Gz, the gravitational force directed toward the feet; 180 degrees or lying flat=0% of Gz). Therefore, 60 degrees allowed us to achieve nearly 90% of the Gz force, but still allowed the subjects to be lying quietly for careful study. Tilt studies were performed approximately two months before flight (with microneurography), two weeks before flight (without microneurography), and on landing day (with microneurography). During flight, orthostatic stress was produced using LBNP.

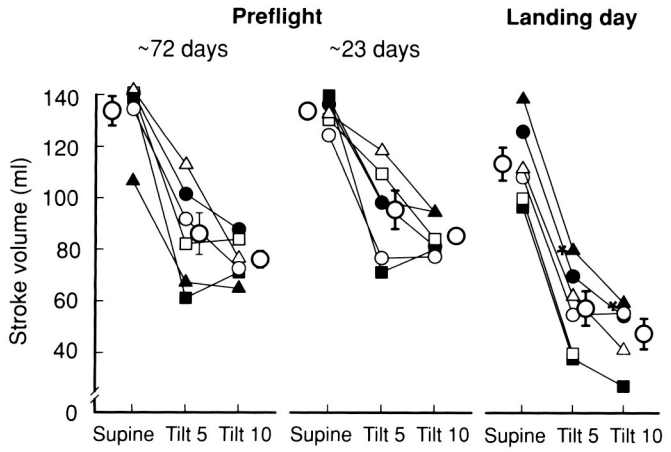

Figure 4. Stroke volume responses to 60-degree upright tilt. The graph shows average and individual stroke volumes in the supine position and after five and 10 minutes of 60-degree head-up tilt. Each astronaut is represented by a different symbol. An asterisk (*) shows a change that was significant ($p<0.05$) compared to the same time preflight. On landing day, supine stroke volumes were lower, and early and late stroke volume reductions during tilt were greater. (From Levine, 2002, with permission; reproduced from *The Journal of Physiology.*)

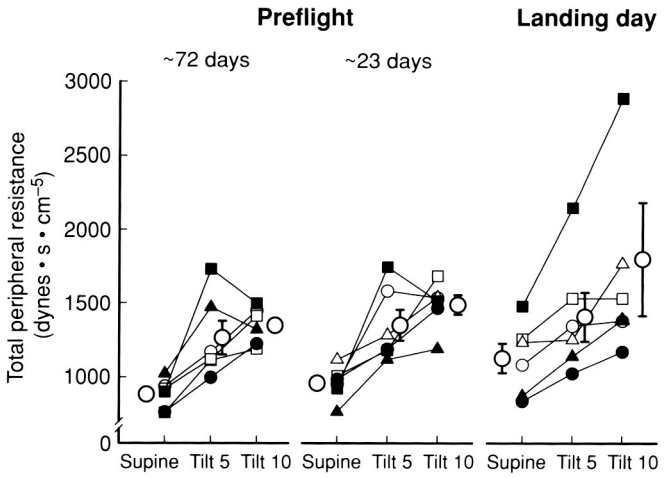

Figure 6. Calculated total peripheral resistance responses to 60-degree head-up tilt. Total peripheral resistance increased significantly when the crewmembers were tilted from supine to 60-degree upright positions both pre- and postflight. These increases were not significantly different on landing day. (From Levine, 2002, with permission; reproduced from *The Journal of Physiology.*)

The sympathetic nervous system is the primary mediator by which the cardiovascular response to exercise is controlled. During exercise, heart rate and blood pressure increase, and both cardiac output and muscle blood flow also increase to provide exercising muscle with the fuel for muscle contraction. This process is remarkably tightly regulated, and the study of the "exercise pressor reflex" is one of the classic tools in autonomic physiology. The control of the cardiovascular response to exercise involves the initiation of the reflex response from higher-order centers in the brain (so-called "central command"), plus feedback signals from muscle, which sends information regarding the fatigue level or metabolic state ("metaboreceptors") and the strength ("mechanoreceptors") of muscle contraction. Because spaceflight also leads to muscle atrophy, some investigators have wondered whether signals generated from skeletal muscle could be impaired, leading to abnormal sympathetic nerve activity.

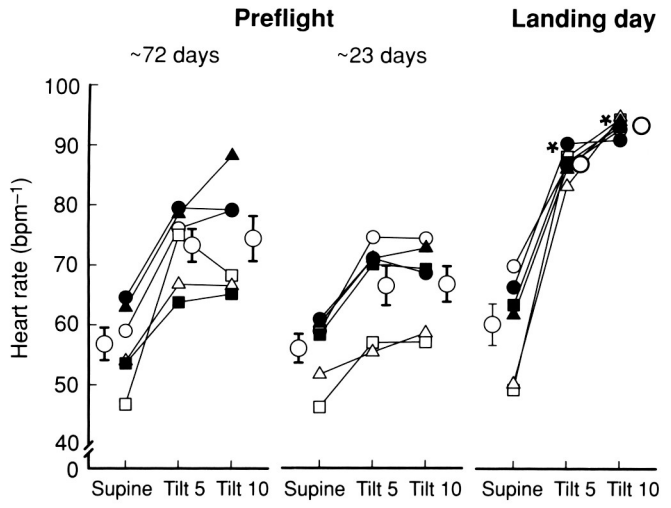

Figure 5. Heart rate responses to 60-degree head-up tilt. Heart rate increased to a significantly greater level during tilting after landing as compared to preflight. (From Levine, 2002, with permission; reproduced from *The Journal of Physiology.*)

In 1937, an ingenious strategy was developed to isolate these signals during handgrip exercise. The investigators had their subjects squeeze a handgrip device at 30% of their maximal force, while recording heart rate and blood pressure (and more recently, by other investigators, sympathetic nerve activity). After two minutes, they inflated a cuff on the upper arm to very high levels (300 mmHg) designed to occlude blood flow to the limb and prevent the washout of metabolites within skeletal muscle that were stimulating muscle metaboreceptors. This is also called "post exercise circulatory arrest." After the cuff was inflated, the subjects stopped exercising. At that point, central command had ceased (there was no more effort to contract) and the muscle was relaxed, but the metaboreceptors were still being stimulated. This approach demonstrated that most of the increase in heart rate during such exercise was mediated by central command from the brain (McCloskey, 1972). However, virtually all of the increase in sympathetic nerve activity, and about half of the increase in blood pressure, was mediated from peripheral metaboreceptors.

In the Neurolab investigations, we used this protocol to determine: (a) if the pathways from the brain through the sympathetic nervous system were intact; (b) if they could be activated appropriately by exercising skeletal muscle; and (c)

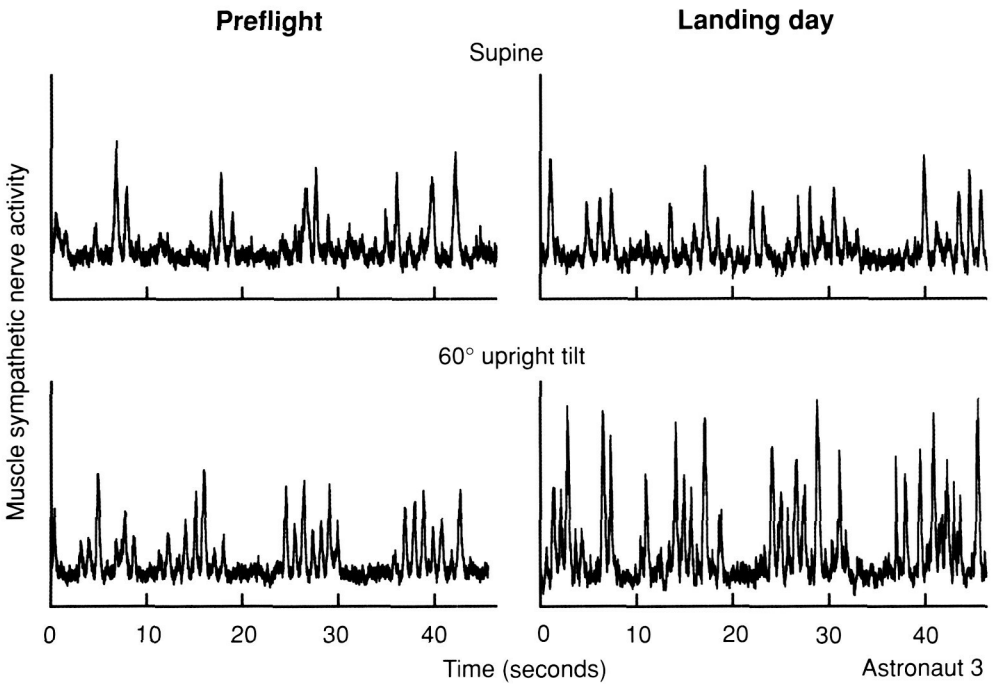

Figure 7. Muscle sympathetic nerve responses of one astronaut. Sympathetic nerve activity increased from the supine to upright-tilt positions both pre- and postflight. The activity was greater postflight compared to preflight levels in both the supine and upright-tilt positions. (From Levine, 2002, with permission; reproduced from *The Journal of Physiology.*)

if they would raise the blood pressure similar to before spaceflight. We modified the classic protocol by continuing the handgrip exercise to fatigue to try to get the maximal possible stimulus to sympathetic activation possible, and to control for possible changes in muscle strength during spaceflight (Seals 1993). Handgrip studies were performed approximately two months before flight (with microneurography), two weeks before flight (without microneurography), towards the end of the flight on day 12 or 13, and on landing day (both with microneurography).

Finally, to make sure that the sympathetic nervous system could be activated by a stimulus that we didn't think would change during spaceflight, we chose to use another classic test, the "cold pressor" test, where the subject's hand is placed in ice water for two minutes. This test stimulates peripheral "nociceptors" and increases sympathetic nerve activity (thereby raising blood pressure) by a completely different set of afferent pathways. The test thus served as a control to make sure that the central and efferent pathways were intact and functioning normally. If orthostatic or handgrip responses were abnormal but cold pressor responses were normal, we could isolate the defect to the afferent, or sensing, side of the control system. If all three were abnormal, the defect would more likely be in the brain or the efferent sympathetic neural pathways. Since a bucket of ice would not be practical to use on the Space Shuttle, we used a specially designed mitt filled with a gel that allowed us to deliver a cold stimulus to the hand. Cold pressor tests were performed preflight and inflight along with the handgrip studies, but could not be performed on landing day because of time restrictions.

RESULTS

Hemodynamic measurements were performed on all six crewmembers during all pre- and postflight data collection sessions. Microneurographic recordings were performed on five of these six subjects. During flight, neither the commander nor the pilot was available for study, so only four subjects completed all the inflight experiments.

Stroke volumes (the amount of blood pumped with each heartbeat, Figure 4) in the supine position and stroke volume

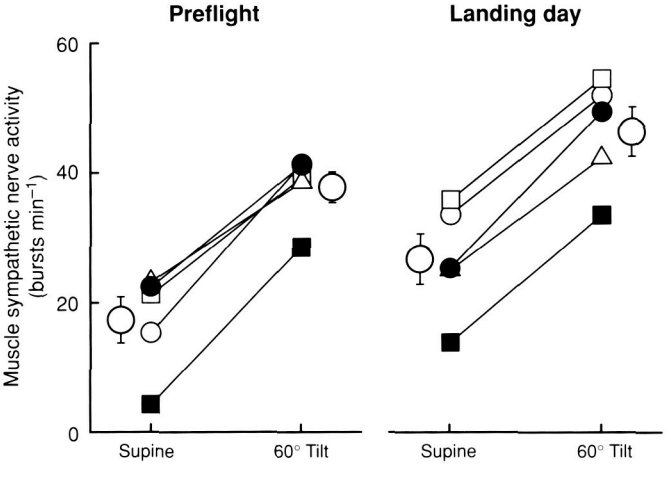

Figure 8. Muscle sympathetic nerve burst frequencies for all astronauts. Supine sympathetic nerve activity was significantly greater postflight. The increase in sympathetic nerve activity with tilting was comparable pre- and postflight, but carried sympathetic nerve activity to higher levels postflight. (From Levine, 2002, with permission; reproduced from *The Journal of Physiology.*)

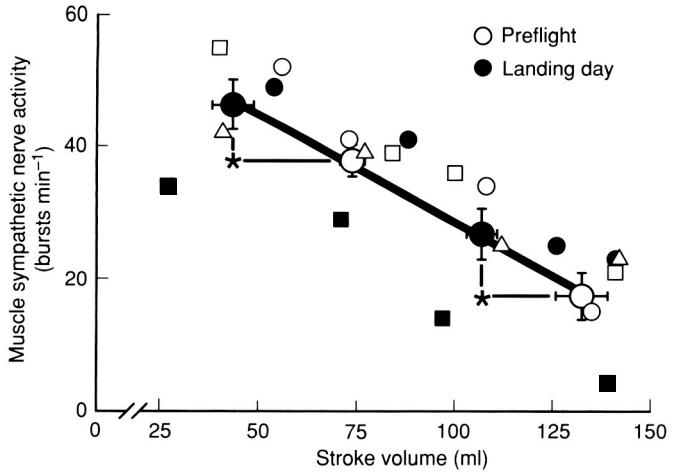

Figure 9. Muscle sympathetic nerve burst frequency plotted as a function of left ventricular stroke volume. The relationship between stroke volume and sympathetic nerve activity was similar both pre- and postflight. (From Levine, 2002, with permission; reproduced from the *Journal of Physiology.*)

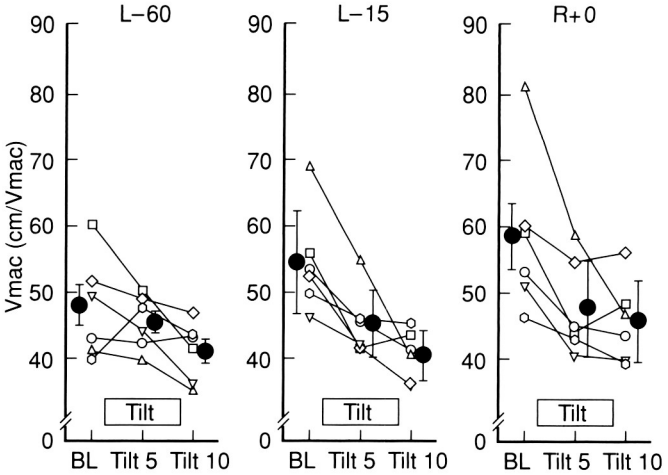

Figure 10. Cerebral blood flow responses to tilting. CBF fell slightly with tilt, but the change did not differ between pre- and postflight testing.

reductions during 60-degree upright tilt were remarkably similar during the two preflight sessions. Preflight stroke volumes decreased by about 40% after five minutes, and by 50% after 10 minutes of 60-degree upright tilt. On landing day, stroke volumes during supine rest were lower ($p<0.05$), and early and late stroke volume reductions during 60-degree upright tilt were greater than on either preflight day. Stroke volumes during postflight tilting were lower than those measured during either preflight session in all subjects ($p<0.01$).

Heart rate (Figure 5) during supine rest and heart rate increases during 60-degree upright tilt were similar in the two preflight sessions. The greater decreases of stroke volume registered during postflight tilting (Figure 4) were associated with greater increases of heart rate ($p<0.01$, compared with preflight levels). As a result, cardiac outputs, or the amount of blood pumped per minute (heart rate × stroke volume), during tilting were comparable during pre- and postflight sessions. Pre- and postflight cardiac outputs averaged 7.8+0.3 vs. 7.3+0.6 ($p=0.54$) in the supine position, and 5.6+0.3 vs. 4.9+0.6 ($p=0.37$) at 10-minute tilt.

Total peripheral resistance during supine rest and total peripheral resistance increases during 60-degree upright tilt (Figure 6) were similar during the preflight sessions. Peripheral resistance in the supine position was insignificantly greater on landing day than during preflight sessions. In contrast to the much greater increases of heart rate that occurred during tilting on landing day (Figure 5), increases of total peripheral resistance with tilting were not greater than those measured preflight ($p=0.32$). Thus, on landing day, greater stroke volume reductions were not matched by greater increases of total peripheral resistance. On landing day, five of the six astronauts had total peripheral resistance increases during tilting similar to those measured preflight. (In two astronauts, peripheral resistance increases were slightly greater; and in three astronauts, peripheral resistance increases were slightly smaller.) Only one subject, a high-performance jet pilot, experienced a substantially greater increase of total peripheral resistance during tilting on landing day than during the preflight sessions (Figure 6, right panel, filled squares).

The net result of reduced stroke volumes, increased heart rates, and unchanged total peripheral resistances was that arterial pressures were preserved. There were no significant differences between supine and tilting measurements, or among measurements made during preflight and landing day sessions. Diastolic pressure increased significantly from supine levels during tilting

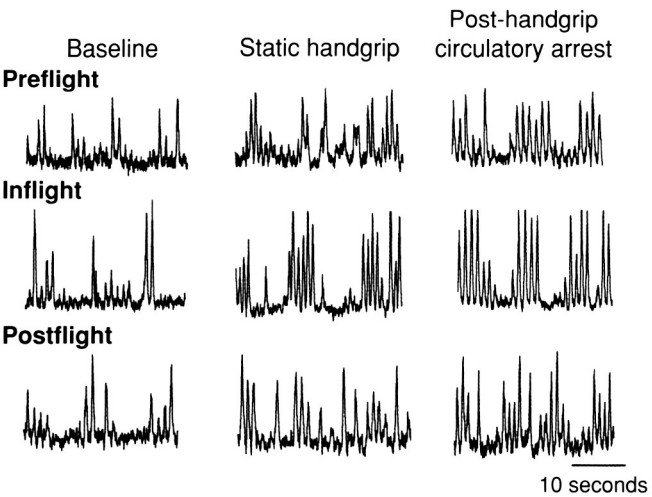

Figure 11. Muscle sympathetic nerve activity (MSNA) during handgrip. Sympathetic nerve activity was higher postflight in all subjects before static handgrip. Handgrip exercise produced the same peak increases in MSNA both during and after spaceflight. (From Fu, 2002, with permission; reproduced from *The Journal of Physiology.*)

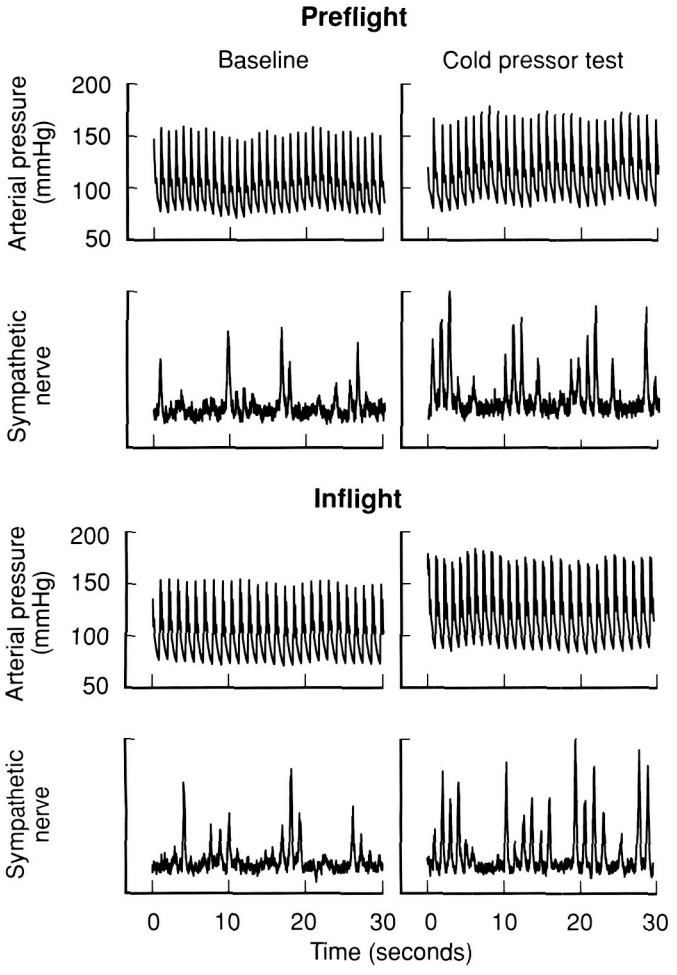

Figure 12. Sympathetic nerve recordings from one crewmember during the cold pressor test. All subjects showed similar increases in MSNA and blood pressure during the cold pressor test preflight and inflight. This confirms the integrity of reflexes that increase in sympathetic nerve activity in response to cold stimulation. (From Fu, 2002, with permission; reproduced from *the Journal of Physiology.*)

($p<0.05$) in both preflight and landing day trials, with no significant differences among them. Postflight, most individual recordings showed large respiratory oscillations of arterial pressure during tilting that were not observed preflight. Systolic pressure standard deviations, used as indexes of this variability, did not change significantly from supine to tilting preflight (7.3+1.2 vs. 8.2+1.6 mmHg, $p=0.11$), but they increased significantly, by >50%, on landing day (6.7+0.8 vs. 10.1+2.1 mmHg, $p<0.01$). Increases of systolic pressure standard deviations during tilting on landing day were significantly greater than those measured during preflight sessions ($p<0.001$).

Sympathetic neural responses – Figure 7 shows muscle sympathetic nerve activity of a representative crewmember. Preflight recordings (left) document typical pulse-synchronous sympathetic bursting during supine rest and increased burst frequency during tilting. The postflight supine recording (upper right panel) is scaled so that its mean burst height is equivalent to the mean preflight burst height. The vertical scale is the same in postflight supine and upright recordings, and faithfully indicates the changes of burst amplitude that occurred with tilting. Figure 7 shows increases of sympathetic nerve activity when the subject changed from supine to upright-tilt positions, both pre- and postflight, and higher levels of sympathetic nerve activity postflight compared to preflight levels in both supine and upright-tilt positions.

Figure 8 depicts individual and mean measurements of muscle sympathetic nerve burst frequency from all subjects. Increases of muscle sympathetic nerve activity provoked by 60-degree upright tilt were remarkably consistent among astronauts during both pre- and postflight sessions. However, supine muscle sympathetic nerve burst frequency was significantly greater in postflight than in preflight sessions ($p<0.05$). Therefore, increases of muscle sympathetic nerve activity with tilting, which were comparable both pre- and postflight, carried muscle sympathetic nerve burst frequency to higher levels postflight.

As noted above, steady-state arterial pressures were similar in supine and tilted positions, both before and after spaceflight. Therefore, arterial pressure measurements provided no evidence for the changes of baroreceptor activity, which must have occurred during pre- and postflight tilting, and postflight hypovolemia (dehydration). Left ventricular stroke volumes, on the other hand, did change as expected. Figure 9 depicts average and individual pre- and postflight muscle sympathetic nerve activity as a function of left ventricular stroke volume. Linear regression coefficients were extremely high, both for individual astronauts ($R^2=0.91–1.00$) and mean data (heavy line, $R^2=0.99$, $p<0.01$).

Stroke volumes were largest, and muscle sympathetic nerve activities were smallest, during preflight supine rest (Figure 9, extreme right). Stroke volumes and muscle sympathetic nerve activities during postflight supine rest fell about halfway between preflight supine and upright values. Stroke volumes were lowest, and muscle sympathetic nerve activity was highest, during postflight tilting (Figure 9, extreme left).

CBF responses to tilting are shown in Figure 10. There was a small, but statistically significant decrease in CBF in the tilted position that did not differ during both preflight sessions. Inflight, CBF was well maintained during low-level LBNP. In fact, small decreases in CBF velocity, which had been observed during LBNP of –30 mmHg during both preflight sessions, were not observed inflight. On landing day, this response was similar to preflight. No astronaut had a reduction in CBF despite maintenance of arterial pressure. In keeping with this preservation of CBF velocity during LBNP or tilting, spectral analysis showed that coherence between blood pressure and CBF velocity was unchanged at all frequencies. Moreover, the gain between pressure and flow at low frequencies, where autoregulation is most effective, was decreased significantly by 26% (FD6–FD7), 23% (FD12–FD13), and 27% (on landing day) as compared with the preflight value of 1.11 cm/s/mmHg ($p<0.05$). In other words, smaller oscillations in CBF occurred for a given change in blood pressure, which is suggestive of improved rather than impaired autoregulation.

Clinical outcome in response to tilt – All subjects completed the entire protocol, and were able to remain upright at 60 degrees for 10 minutes both before and after spaceflight.

Handgrip responses – Microneurograms representing sympathetic nerve activity at baseline, during fatiguing handgrip exercise, and during post-handgrip circulatory arrest, from one astronaut are shown in Figure 11.

For all subjects, the contraction-induced rises in heart rate were similar among preflight, inflight, and postflight conditions. MSNA was higher postflight in all subjects before static handgrip (26±4 postflight vs. 15±4 bursts min^{-1} preflight, p=0.017). The contraction-evoked peak increases in MSNA were not different before, during, or after spaceflight (41±4, 38±5, and 46±6 bursts min^{-1}, respectively, all p>0.05). MSNA during post-handgrip circulatory arrest was higher postflight than it was preflight or inflight (41±1 postflight vs. 33±3 preflight and 30±5 bursts min^{-1} inflight, p=0.038 and 0.036, respectively). These data demonstrate that fatiguing handgrip exercise elicits the same peak increases in MSNA, blood pressure, and heart rate during and after 16 days in space, with no evidence for impairment in central command or reflex stimulation of peripheral mechano- or metaboreceptors.

Cold pressor test – Sympathetic nerve recordings from one representative subject before and during spaceflight are shown in Figure 12. For all subjects, similar increases in MSNA and blood pressure during the cold pressor test were observed preflight and inflight, thereby confirming the integrity of peripherally stimulated reflex increases in sympathetic nerve activity and vasomotor responsiveness. Together, both handgrip and cold pressor data confirm that stimulation of muscle or other nociceptive afferent receptors and their reflex responses are not impaired by short-duration spaceflight.

DISCUSSION

Blood Pressure Control in the Upright Position: A Problem with Stroke Volume

This experiment demonstrated a number of important findings —some expected, and others unexpected. As has been demonstrated previously, we confirmed that the key cardiovascular adaptation to spaceflight was a reduction in upright stroke volume. The astronauts lost blood volume while in space (i.e., they became effectively "dehydrated"), and their hearts may have become smaller and less distensible (Levine, 1997; Perhonen, 2001a; Perhonen, 2001b). So when crewmembers stood up after being in space, less blood was left in their hearts to pump compared to preflight. In this case, the heart behaves somewhat like a rubber band—the more it stretches, the more it snaps back during pumping. Similarly, the less it stretches, the less blood it can pump. This reduction in upright stroke volume appears to be the primary specific effect of gravity (or its prolonged absence) on the cardiovascular system.

When thinking about the processes regulating blood pressure, it may be helpful to consider the circulation as an electrical circuit that obeys a form of Ohm's law (V=IR, or voltage=current×resistance), where blood pressure is the "voltage," blood flow is the "current," and total peripheral resistance (TPR) is the "resistance." In this model, BP=Qc×TPR, or blood pressure = cardiac output (blood flow in liters/min)×total peripheral resistance. Since cardiac output=heart rate (beats/min)×stroke volume (mL/beat), the blood pressure can be thought of as the "triple product" of heart rate×stroke volume×total peripheral resistance (Levine, 1991). During changes in gravitational stress, such as moving from the supine to the upright position, stroke volume changes acutely, with less blood pumped per beat into the arterial tree and less pulsatile distension of arterial baroreceptors. The cardiovascular control system responds to this challenge by increasing the heart rate and/or the TPR. A useful analogy might be a firefighter trying to get water to the roof of a house that is on fire. The problem is that gravity is pulling the water to the ground (akin to a low stroke volume). The firefighter can then either turn the pump up faster (similar to increasing the heart rate), or the firefighter can place a finger over the end of the hose (similar to constricting the blood vessels and raising the peripheral resistance).

Reflex Responses to Upright Posture

If after spaceflight stroke volume was reduced by gravity pulling blood into the feet, how did the cardiovascular control system respond to this challenge? Although some investigators have demonstrated alterations in the baroreflex control of heart rate during or after spaceflight (see science report by Cox et al., in this publication), heart rate increased appropriately for the reduction in stroke volume in every astronaut. Thus, a low heart rate, by itself, cannot be responsible for the orthostatic hypotension observed after spaceflight.

Previous work has focused attention on the sympathetic nervous system and regulation of the vascular resistance as a potential mediator of postflight orthostatic intolerance. During SLS-1, SLS-2, and Spacelab-D2, Buckey and colleagues (Buckey, 1996) demonstrated that approximately two-thirds of the astronauts studied could not stand quietly for 10 minutes following spaceflight of one to two weeks, whereas they could all complete the test before flight. Afterwards, those astronauts with the best orthostatic tolerance were able to raise their vascular resistance to greater levels than they were preflight, thus compensating well for the reduction in stroke volume. However, the astronauts with the poorest orthostatic tolerance couldn't increase the vascular resistance during standing more than they did preflight.

Subsequently, Fritsch-Yelle et al. (Fritsch-Yelle, 1996) studied a larger number of astronauts and showed that in this series, about 25% of the astronauts couldn't stand quietly for 10 minutes. These investigators also measured plasma levels of norepinephrine, the neurotransmitter released from the sympathetic nerve endings that causes blood vessels to constrict. Fritsch-Yelle et al. found that the astronauts with the worst orthostatic tolerance had lower levels of norepinephrine in their blood than those who tolerated standing best. However, there were two important caveats to these studies. First, the more tolerant astronauts had their blood drawn while they were still standing, and the sympathetic nervous system was still highly activated. Because they were feeling faint, the less-tolerant

astronauts had their blood drawn only after they were placed in a supine position. Since the autonomic nervous system responds very rapidly to changes in body position, this protocol could have biased the results toward lower values in the less-tolerant astronauts. Second, most of the time people who faint do so because the cardiovascular reflexes "make a mistake"—that is, the sympathetic nervous system withdraws, so that the blood vessels are no longer constricted (similar to taking the finger off the end of the hose in the firefighter example). Such a sympathetic withdrawal or fainting reaction could reduce the levels of norepinephrine and the peripheral resistance in orthostatically intolerant astronauts, even if it had increased appropriately at the beginning of the stand.

These experiments set the stage for the Neurolab studies of the sympathetic nervous system in the upright posture after spaceflight. Both studies raised the possibility that the cardiovascular adaptation to spaceflight might result in a defect in the sympathetic nervous system that would prevent astronauts from increasing sympathetic activity in the upright position, impairing their ability to raise vascular resistance and compensate for the reduction in upright stroke volume. However, the results from Neurolab were surprising, yet convincing. All of the astronauts studied in these experiments had an increase in sympathetic nerve activity during upright tilting on Earth after two weeks of spaceflight. Moreover, this increase in sympathetic nerve activity was perfectly well calibrated for the reduction in stroke volume induced by the upright posture (Figure 9). Finally, the results from stimulating the sympathetic nervous system by other pathways—handgrip exercise (stimulating muscle metaboreceptors) or cold stress (stimulating peripheral nociceptors)—were also entirely normal during and after spaceflight. From these experiments, we can say convincingly that the cardiovascular adaptation to spaceflight does NOT lead to a defect in the autonomic regulation of sympathetic nerve activity.

Cerebral Autoregulation

But, what about the brain? Even though blood pressure was well-regulated in these studies, was there evidence that cerebral autoregulation was impaired? Ground-based experiments in support of these studies suggested that this might be the case, and animal studies have confirmed changes in the cerebral blood vessels with simulated microgravity. In the Neurolab experiments, however, CBF was precisely regulated under all conditions. There was no evidence of reduced CBF during upright tilt in any astronaut. Moreover, during the inflight experiments using LBNP, the greater orthostatic stress inflight was accompanied by normal or even enhanced cerebral autoregulation, thereby preserving CBF. Using sophisticated frequency domain measures of autoregulation, we were unable to demonstrate impaired cerebral autoregulation at any frequency. Rather at the lower frequencies, cerebral autoregulation appeared to be improved, not impaired, during and immediately following spaceflight. The mechanism of this improvement is speculative, but it may result from hypertrophy of cerebral blood vessels due to a persistent central fluid shift.

Orthostatic Intolerance After Spaceflight

So, if the neural control system is not impaired and cerebral autoregulation is preserved, why then do some astronauts faint after spaceflight? Unfortunately, we cannot answer that question definitively. One of the problems with interpreting our experiment in this regard was that no astronaut had frank orthostatic intolerance during testing on landing day. We suspect that at least some of this problem may have been related to the specific experimental conditions. Astronauts were only tilted to 60 degrees upright to allow microneurography, instead of standing fully upright as in previous experiments. Moreover, our subject numbers were small, raising the possibility of sampling bias. However, all evidence points to the fact that the Neurolab crew behaved similarly and had a similar cardiovascular adaptation to spaceflight as did other, previously evaluated astronauts. Their upright stroke volumes were very low, and their heart rates were high. Their mean blood pressures were stable when tilted upright, but we observed prominent oscillations in blood pressure around this mean. This is typical of other astronauts, and indicative of individuals whose blood pressure control system is being severely challenged. Thus we suspect, but cannot prove that, even if we had studied a much larger group of astronauts, the results would have been the same. Failure to augment sympathetic nerve activity properly is not likely to be an important mechanism in this condition.

Some additional insight may be gained from examining the changes in total peripheral resistance after flight. Despite the increased sympathetic nerve activity, most astronauts did not increase their vascular resistance to a greater degree than they did preflight. This observation suggests that these may be a limited "vasomotor reserve" in many individuals, such that more sympathetic nerve activity does not necessarily result in greater vascular resistance. To continue our firefighter analogy—the finger may be already compressed over the edge of the hose as tightly as it can be, and squeezing tighter won't help anymore. Some investigators have suggested that such a limited vasomotor reserve may be responsible for some patients who have orthostatic intolerance in everyday life. Thus, the examination of astronauts who lose the ability to tolerate gravity, after brief periods without gravity in space, may provide important insights into patients with orthostatic intolerance on Earth.

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