Influence of Microgravity on Arterial Baroreflex Responses Triggered by Valsalva’s Maneuver

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ABSTRACT

When astronauts return to Earth and stand upright, their heart rates may speed inordinately, their blood pressures may fall, and some returning astronauts may even faint. Since physiological adjustments to standing are mediated importantly by pressure-regulating reflexes (baroreflexes), we studied involuntary (or autonomic) nerve and blood pressure responses of astronauts to four, 15-second periods of 15- and 30-mmHg straining (Valsalva’s maneuver). We measured the electrocardiogram, finger blood pressure, respiration, and muscle sympathetic nerve activity in four healthy male astronauts before and during the 16-day Neurolab Space Shuttle mission. We found that although microgravity provoked major autonomic changes, no astronaut experienced fainting symptoms after the mission. Blood pressure fell more during straining in space than on Earth (the average reduction of systolic pressure with 30-mmHg straining was 49 mmHg during and 27 mmHg before the mission). However, the increases of muscle sympathetic nerve activity that were triggered by straining were also larger in space than on Earth. As a result, the gain of the sympathetic baroreflex, taken as the total sympathetic nerve response divided by the maximum pressure reduction during straining, was the same in space as on Earth. In contrast, heart rate changes, which are mediated by changes of vagus nerve activity, were smaller in space. This and earlier research suggest that exposure to microgravity augments blood pressure and sympathetic adjustments to Valsalva straining and differentially reduces vagal, but not sympathetic baroreflex responsiveness. The changes that we documented can be explained economically as a consequence of the blood volume reduction that occurs in space.
INTRODUCTION

All terrestrial life forms have to contend with gravity. Some of gravity’s effects are readily observed. Others are not apparent but, nonetheless, important. For example, in animals, gravity pulls blood toward the Earth. Such effects are posture-specific: they are maximal during upright standing and minimal during recumbency. When humans stand upright, the shift of blood to the lower body could cause blood pressure to fall markedly. People are usually unaware of gravitational pull because their blood pressure-regulating reflexes (baroreflexes) respond to the challenge by increasing their heart rates and blood vessel tone. Such adjustments are involuntary, and are made by the autonomic nervous system.

At the beginning of the space exploration era, scientists were concerned that microgravity would overwhelm the circulatory system. Their concern proved unfounded. Cardiovascular function is normal in space despite the major gravitational changes that occur. Interestingly, the most dramatic consequences of spaceflight are observed after, not during space missions, when astronauts stand upright. In many astronauts, standing causes their hearts to beat very rapidly and their blood pressures to fall. In some returning astronauts, these changes are quite pronounced—some feel lightheaded, as if they are going to pass out, a condition known as pre-syncope; and some actually faint (syncope). Eventually (within days), symptoms during standing disappear, and astronauts re-adapt to living on Earth. Presumably, these symptoms have their origins in physiological changes occurring during spaceflight.

Mechanisms responsible for the cardiovascular changes that take place in microgravity are not understood fully (Blomqvist, 1983; Fortney, 1996). However, many sophisticated measurements have been made in astronauts, and much is known. Published research indicates clearly that human cardiovascular function in space is not fixed, and that measurements made during the earliest days of space missions are very different than those made later. For example, there is an immediate shift of fluids from the lowest parts of the body toward the head. These changes are responsible for astronauts’ “moon faces” and “bird legs” in space. Associated with the early headward fluid and blood shifts, heart chamber sizes increase. However, after the first few days of spaceflight, blood volume declines by about 10% from measurements made on Earth. Heart chambers shrink and are smaller than they were (in the supine position) before space travel. As might be expected, the body takes note of these changes and makes adjustments, by altering autonomic nerve traffic to vital organs.

The autonomic nervous system

Autonomic nerve traffic from the central nervous system is carried by the left and right vagus nerves and by many sympathetic nerves. The principal cardiovascular target of the vagus (or parasympathetic) branch of the autonomic nervous system is the pacemaker of the heart, the sinus node. Increases of vagus nerve traffic increase concentrations of the neurotransmitter, acetylcholine, at the sinus node and slow the heart rate. Conversely, reductions of vagus nerve traffic allow more acetylcholine to be taken back into the vagus nerve endings, and the heart rate speeds. The vagus nerve does not control blood pressure directly, but it does modulate blood pressure by changing heart rate.

Sympathetic nerves directly influence both the cardiac pacemaker and the blood pressure. Sympathetic nerve traffic tends to fluctuate reciprocally with vagus nerve traffic; and the effects of the sympathetic neurotransmitter, norepinephrine, tend to be opposite those of the parasympathetic neurotransmitter, acetylcholine. Increases of sympathetic nerve traffic to the sinus node speed the heart; and increases of sympathetic nerve traffic to the small resistance blood vessels, the arterioles, constrict their muscular walls and increase blood pressure.

Traffic carried over the two branches of the autonomic nervous system is modulated according to signals coming to the brain from sensors located throughout the body. Arterial baroreceptors are particularly important mediators of responses to standing. Baroreceptors are nerves with stretch-sensitive endings located in the walls of the carotid arteries in the neck, and in the aorta, (the largest artery in the body) in the chest. Consider how the baroreflex responds to a simple challenge—standing. Within a few seconds of standing, blood pressure falls. Reductions of pressure within arteries reduce the stretch of the artery walls, and the arteries shrink. Shrinkage of the carotid arteries and aorta reduces the stretch on baroreceptive nerves, and they reduce their level of firing. Reduced baroreceptor traffic is sensed in an area of the brain stem known as the solitary tract nucleus. The information that arrives in the solitary tract nucleus—that baroreceptor traffic has fallen off—is carried by a bucket brigade of intermediary neurons that connect, or synapse, with each other, and eventually arrives at the motor neurons that are responsible for vagus and sympathetic nerve firing.

The reduction of baroreceptor nerve traffic is interpreted, appropriately enough, as a reduction of blood pressure. The vagus and sympathetic motor neurons respond in opposite ways to the change of baroreceptor traffic, which they both see. Vagus firing declines, less acetylcholine is released at the sinus node, and the heart rate speeds. This faster heart rate translates into more strokes of blood being ejected into the circulation per minute, and this helps to restore blood pressure toward usual levels. Sympathetic motor neurons take the opposite tack. Sympathetic nerve traffic increases, and this speeds the heart and constricts the blood vessels. The sympathetic changes complement the faster heart rate that results from reduced vagus nerve traffic. Both sets of responses tend to restore blood pressure toward usual levels. The two systems work together seamlessly, and the person who stands may not even be aware that the circulation has been challenged.

Autonomic responses to space travel

Prior to the Neurolab mission, research in astronauts focused on the vagus limb of baroreflex responses. There was a practical reason for this: changes of vagus nerve traffic to the sinus node can be inferred from changes of heart rate measured from the electrocardiogram, which can be recorded safely anywhere.
In the earlier research, baroreceptor input to the brain was changed by a mechanical device that tricked the baroreflex. As we mentioned, the carotid arteries have neurons embedded in their walls that sense the degree of distension. When pressure inside a carotid artery increases, the artery stretches, the level of neuron firing increases, and a reflex adjustment is made. As would be predicted, the carotid arteries stretch when pressures inside them increase. The carotid arteries also stretch when pressures outside them decrease. Astronauts' baroreflexes were tricked by applying a vacuum to the neck collars that they were wearing. Thus, the usual pressure inside the carotid arteries pushed against a vacuum outside the arteries. This caused the carotid arteries to stretch, the baroreceptor nerves to increase firing, and the heart rate to slow. Thus, in earlier research, scientists merely recorded the degree of heart rate slowing with the electrocardiogram, and related the slowing to the neck pressure of the moment. The conclusion from this research was that in space, vagal baroreflex function is impaired. For the same degree of neck pressure reduction, the heart rate slowing is less during (Fritsch, 1992b) or immediately after spaceflight (Fritsch, 1992a; Fritsch-Yelle, 1994) than it was before spaceflight.

Does this mean that since vagal baroreflexes are impaired in space, sympathetic baroreflex responses are also impaired? This was the question asked and answered during the Neurolab mission. The challenge was to measure sympathetic nerve traffic. As mentioned, changes of vagus nerve traffic can be inferred from changes of the period between heartbeats on the electrocardiogram. However, there is no comparable indirect way to measure sympathetic nerve traffic. To have an indication of the heartbeat-by-heartbeat changes of sympathetic nerve traffic, it is necessary to measure sympathetic nerve electrical activity directly. Sympathetic microneurography was developed in the 1970's by two Swedish neurologists, Hagbarth and Vallbo, who fashioned minute needles, inserted the needles through the skin into their own nerves, and led off and amplified the electrical activity that was present in those nerves. This method is described in the technical report in this volume by Ertl et al.

For Neurolab research, we perturbed the baroreflex system simply, by asking astronauts to perform Valsalva's maneuver (Smith, 1996). The Italian scientist, Antonio Maria Valsalva, published a book on anatomy in 1704, The Human Ear. Buried in that Latin text is one phrase that has, for almost three centuries, maintained Valsalva's position in the firmament of medical science: "... inflation of the middle ear by closing the mouth and nostrils and blowing, so as to puff out the cheeks." Valsalva's maneuver is nothing more than straining against a closed airway, as would occur when lifting a heavy book. This is done, however, in a highly controlled manner.

METHODS

Valsalva's maneuver

Astronauts' workdays during the Neurolab mission were filled to overflowing. Therefore, it was necessary that each task be presented simply and clearly. As with any kind of scientific experiment, it was important that whatever the astronauts were asked to do, they must do it precisely and reproducibly. Therefore, we developed a computer program that guided astronauts through their Valsalva maneuvers. One screen that the astronauts saw (on laptop computers positioned in front of them) is shown in Figure 1.

Over a period of eight minutes, astronauts strained four times in precisely controlled ways. Before each period of straining, they breathed through a mouthpiece, in synchrony with a tone that sounded every four seconds, to a depth shown by the "gas gauge" displayed in Figure 1, right. Then, on cue from the computer, they were asked to strain and to increase the pressure in their mouthpieces to match the height of the gauge on the left. They performed four Valsalva maneuvers and strained to a level of either 15 or 30 millimeters of mercury (mmHg) in a random order that was chosen by the computer. The "clock," shown in the center of Figure 1, appeared as soon as astronauts began straining. As they strained, they watched a "second hand," shown as a blue wedge, fill the circle, rotating clockwise. The second hand made one complete revolution in 15 seconds. As soon as the second hand had reached 12 o'clock, the astronaut stopped straining and resumed breathing as before.

Thus, before and during the Neurolab mission, each of four astronauts strained four times to intensities of either 15 or 30 mmHg (two each), for 15 seconds, in random order. Figure 2 shows one astronaut holding a mouthpiece as he prepares to perform Valsalva maneuvers. This astronaut is barely discernible because of the wealth of equipment surrounding him. A second astronaut, who is readily seen, is watching over the experiment. The astronaut who is to perform the Valsalva maneuvers is lying supine, with his lower body enclosed in an airtight chamber that was used for a different experiment. The laptop computer that guided him during actual measurements is not shown. Figure 2 gives some indication that although it is a simple matter for astronauts to strain four times for 15 seconds each, preparations for such challenges during the Neurolab mission were complicated indeed.
Figure 2. The view from inside the Space Shuttle, as one astronaut prepares to perform Valsalva maneuvers during the Neurolab mission.

Although we studied six astronauts on six occasions before, during, and after the Neurolab mission, this chapter focuses on results from the four astronauts who were studied during the two sessions that featured sympathetic microneurography, about 72 days prior to the Neurolab launch, and on the 12th or 13th day of the mission.

Measurements

Our measurements included electrocardiograms (signals reflecting the heart's electrical activity, recorded from electrodes attached to the skin and amplified), beat-by-beat finger blood pressure, the depth of each breath, mouthpiece pressure (to indicate the force of Valsalva straining), and muscle sympathetic nerve activity.

Vagal traffic travels to the heart in right and left vagus nerves. These nerves emerge from the brain stem and travel in the neck to the chest. The sympathetic nerves are unlike the vagus nerves, in that they do not come from the brain (they emerge from many levels of the spinal cord) and they are not discrete nerves. Rather, sympathetic nerve fibers join other nerves and thus become parts of multifunctional superhighways with traffic traveling in both directions—out to body structures, and back to the central nervous system. An example of such a nerve is the peroneal nerve, the one used for Neurolab recordings, which travels from behind the knee and down the lateral side of the leg. Within this nerve are motor neurons that cause leg muscles to contract on demand, and several types of sensory nerves that apprise the central nervous system of the state of muscle contraction. Also within the peroneal nerve are sympathetic nerve fibers that travel to those same muscles and regulate their blood flow. Since muscle is over 40% of adult body mass, sympathetic nerves to muscle arterioles are very important.

The technical report by Ertl et al. in this volume describes the technique of sympathetic microneurography in detail. Briefly, electrical shocks are applied just posterior and lateral to a knee to locate the peroneal nerve. When the shock is applied directly over the nerve, the foot twitches. A mark is placed on the skin at this location, and the electrode that was used to deliver the shocks is moved to a different location, where the process is repeated. After several repetitions, a track of dots on the skin traces the path of the nerve. Then, a fine needle, 0.5 mm in diameter, is stuck through the skin and aimed directly toward the nerve. (A ground needle is also inserted nearby, just beneath the skin.) The electrical activity from the nerve electrode is amplified. The astronaut inserting the needle listens to this amplified signal with headphones. When the uninsulated tip of the needle touches a nerve fiber, a highly characteristic barrage of nerve firing is heard (it sounds like a dive bomber). The astronaut then makes very fine adjustments until he or she hears sounds typical of muscle sympathetic nerve activity: episodic bursts of firing, at the same frequency as the heart, that wax and wane with breathing.

RESULTS

Valsalva responses

Figure 3 shows the responses of one astronaut to Valsalva maneuvers performed 72 days before, and on day 12 of the Neurolab mission. The classic blood pressure responses to 30-mmHg Valsalva straining (Smith, 1996) are illustrated in the middle panels. At the beginning of straining (time zero), blood pressure rises, secondary to displacement of blood from the...
abdomen and chest to the rest of the body. Then, as straining continues and pressure increases in the abdomen and chest are maintained, finger blood pressure falls. [Blood moves throughout the circulation simply according to pressure gradients—blood (or fluid in any other hydraulic system) moves from higher to lower pressure areas. During straining, less blood reaches the heart because pressure in the limbs is lower than pressure in the abdomen and chest.] Then, as straining continues, compensatory mechanisms kick in, and pressure begins to return to normal.

After the astronaut stops straining (at 15 seconds), there is an abrupt further reduction of pressure. This occurs because vein pressure has been increasing as blood has dammed up in the limbs during straining. When the astronaut takes his or her first breath (and thereby creates a negative pressure in the chest), increased quantities of blood suddenly move from the limbs to the chest and heart. Finally, as the astronaut resumes normal breathing, blood pressure rises to levels higher than those measured before straining (middle panels, right).

As our discussion suggests, some of the blood pressure transients shown in the middle panels of Figure 3 result simply from hydraulic forces—they are mechanical. However, other of the blood pressure changes result from neural activity. The bottom panels of Figure 3 show how Valsalva straining influences sympathetic nerve activity. Notice that before straining (left of time zero), sympathetic activity increased episodically as small vertical spikes or "bursts." The quantity and quality of the sympathetic bursts changed when the astronaut began straining. First, sympathetic traffic was turned off, between zero and about five seconds; this is seen particularly well in the tracing made in space (bottom, right). Sympathetic silence reflected simply a baroreflex response to the very brief increase of blood pressure that occurred at the beginning of straining. (When blood pressure rises, sympathetic activity is silenced as baroreflex mechanisms work to return blood pressure to normal.) Then, as blood pressure fell, the size and number of sympathetic bursts increased. This also represents a baroreflex response: sympathetic bursts come out to restore blood pressure to usual levels. Note that the increased sympathetic nerve activity, brought out by straining, reversed the downward blood pressure trend; and, even though straining continued (between about five and 10 seconds), blood pressure began to return toward the usual levels. This is particularly evident in space (right middle panel).

The sudden reduction of blood pressure after the end of Valsalva straining (at about 15 seconds) and the consequent increase of sympathetic nerve activity also illustrate (quite remarkably) the elegance of baroreflex sympathetic responses. This is shown particularly well in the preflight recording (bottom, left). The very brief blood pressure reduction was answered by an equally brief increase of sympathetic nerve activity. Finally, at the very end of the responses, blood pressure rose (middle panels, right). The terminal rise of blood pressure reflects both the constriction of arterioles in the body, secondary to the preceding bursts of sympathetic nerve activity, and the greater return of blood to the heart. After straining, more blood is being pumped by the heart than during straining, and the blood is being pumped into a constricted vascular bed. Baroreflex physiology also can be seen after Valsalva straining; i.e., when pressure is high, sympathetic neurons fall silent.

The top panels of Figure 3 show changes of the period between heartbeats. (The R wave of the electrocardiogram is the tall, narrow spike that indicates the spread of electricity through the main pumping chambers of the heart. The interval between each heartbeat, the \( R-R \) interval, is used as an indirect index of the amount of vagus nerve traffic traveling to the heart.) Thus, at the beginning of straining, blood pressure rises and \( R-R \) intervals increase (the heart rate slows) as vagus nerve traffic to the heart increases. The \( R-R \) interval responses throughout all stages of the Valsalva maneuver elegantly reflect baroreflex physiology. Notice how changes of \( R-R \) intervals move exactly in parallel to changes of blood pressure.

**Valsalva responses on Earth and in space**

Did spaceflight alter astronauts' responses to Valsalva maneuvers? For one answer to this question, compare recordings made before (left) with those made during the Neurolab mission (right) in Figure 3. It is arguable whether or not the vagally mediated \( R-R \) interval changes (top panels) were less in space than on Earth. However, it seems clear that the sympathetic nerve responses (bottom panels) were different in space. Before straining (to the left of zero second), sympathetic bursts were more numerous in space. During straining, sympathetic bursts were also more numerous in space than on Earth.
Figure 4. Average systolic pressure changes during 15- and 30-mmHg Valsalva maneuvers for all four astronauts. Systolic blood pressure changes were greater during the late mission session (dark lines) than during the first preflight session. Diastolic pressure changes (not shown) paralleled systolic pressure changes. (From Cox, 2002, with permission; reproduced from *The Journal of Physiology*.)

Why were the sympathetic responses in this and the other astronauts so much greater in space than on Earth? Figure 3 provides a clue: the reductions of blood pressure that triggered the increases of sympathetic activity (middle panels) also may have been greater. To test this possibility, we averaged all blood pressure responses to both levels of Valsalva straining in all four astronauts. Figure 4 shows that systolic pressure (the upper number given with blood pressure readings) reductions during, and increases after, straining were greater in space (heavy lines) than on Earth. One might conclude from this that the greater sympathetic outpouring in response to Valsalva straining meant simply that the baroreflex was doing its job: the blood pressure challenge was greater and, therefore, the sympathetic response also was greater.

As mentioned, astronauts performed Valsalva maneuvers six times, before, during, and after the Neurolab mission. Average measurements from the four astronauts give an excellent notion of how space travel alters blood pressure responses to straining. Figure 5 shows a box plot of changes ($\Delta$) of systolic pressure during all recording sessions. (The top, center, and bottom lines of each box indicate the 75th, 50th, and 25th percentiles of pressure changes from baseline values before straining.) The reduction of pressure during straining was clearly greatest during the second inflight session. Our study was not designed to explore why pressure falls more during straining in space than on Earth. No doubt it was due importantly to the reduction of blood volume that astronauts experience when they travel into space.

Figure 6 shows total nerve activity for all four astronauts, before (zero straining pressure) and during 15- and 30-mmHg Valsalva maneuvers. (Note that the scale is larger for Astronaut 4 than for the other astronauts; this astronaut had particularly large sympathetic responses to Valsalva straining.) We did not perform statistical analyses because there were only four subjects. However, the fact that all astronauts changed in the same way suggests strongly that sympathetic responses to blood pressure reductions are greater in space than on Earth.

Figure 5. Box plot of systolic pressure changes for all recording sessions for all four astronauts. The top, center, and bottom lines of each box indicate the 75th, 50th, and 25th percentiles of pressure changes from baseline values before straining. (From Cox, 2002, with permission; reproduced from *The Journal of Physiology*.)

Did spaceflight really change sympathetic nerve responses? Or, was the sympathetic response greater simply because the pressure changes were greater? To answer these questions, we related astronauts’ responses to the stimuli that provoked those.
We studied the pressure-regulating reflexes that enable people rapidly than before they went into space, and their blood pressures may fall. Some astronauts may even faint (Buckey, 1996). Responses to pressure reductions in space are stimulus-response relations. The data in this chapter reject our hypothesis: sympathetic baroreflex responses are normal in space. Therefore, it appears that microgravity differentially affects human baroreflexes—vagal baroreflex responses are impaired, and sympathetic baroreflex responses are preserved.

**Sympathetic baroreflexes in space**

In our study, we focused on autonomic transients provoked by Valsalva maneuvers. Our principal new finding is that although Valsalva straining triggers much greater increases of muscle sympathetic nerve activity in space than on Earth, the stimulus, falling blood pressure, is also greater. As a result, reflex gain (the sympathetic response plotted as a function of the diastolic pressure reduction, Figure 7, left panel) is normal. Ours is one of three studies involving sympathetic microneurograms obtained from Neurolab astronauts. The results of the three studies, which employed different research provocations and tested different hypotheses, are remarkably congruent. Ertl and coworkers (see science report by Ertl et al. in this publication) showed that muscle sympathetic nerve and plasma norepinephrine spillover responses to lower body suction (used to simulate the effects of standing in space) are similar in space and on Earth. Levine and his colleagues (see science report by Levine et al. in this publication) showed that sympathetic nerve responses to actual upright tilt on landing day after the Neurolab mission were the same as before the mission.

**Potential mechanisms**

Autonomic responses to Valsalva straining are determined importantly by blood volume. Both acute reductions of central blood volume, such as those provoked by standing on Earth, and those that occur after prolonged head-down bed rest increase arterial pressure and heart rate responses to Valsalva straining. Therefore, the blood volume reduction that occurs 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.

As mentioned earlier in this chapter, reflex adjustments occur as responses to changes of information carried to the brain by sensors distributed throughout the body. We are not certain which sensors mediated these changes we report. However, as we suggest, we strongly suspect that arterial baroreflexes were involved. Blombery and Korner (Blombery, 1982) studied what they called “Valsalva-like” maneuvers in conscious rabbits, and showed that nearly all vascular and heart rate responses are abolished by cutting the nerves leading from baroreceptive arteries.

Absence of changes of baseline arterial pressures and R-R intervals (we measured similar baseline blood pressures and R-R intervals in space and on Earth) does not discount arterial baroreceptor participation in the adjustments made by astronauts to...
However, it is likely that the changes of finger blood pressure measured.

Eckberg, 1992), is deceptively simple. Although Valsalva’s maneuver is time-sure, and we did not measure baroreceptive artery dimensions. Limitation of our study is the Valsalva maneuver itself, which

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These data suggest that healthy young adults work near the middle of the linear region of their vagal blood pressure-R-R interval relations (right)—and close to the threshold of their time and emotional energy to make this research project successful. We also thank James E. Ames, Virginia Commonwealth University, and a large cadre of scientists and engineers, including particularly Hasan Rahman and Suzanne McCollum at Lyndon B. Johnson Space Center. This research was supported by National Aeronautics and Space Administration contracts NAS0-19541 and NAG2-48, and a grant from the National Heart, Lung, and Blood Institute, U01HL-56417. The research was also supported by a grant from Helsingin Sanomat, Finland.

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