Effect of spaceflight on the subcutaneous vеноarteriolar reflex in the human lower leg

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The reduction in subcutaneous blood flow was measured by the 133Xe washout technique just proximal to the ankle joint in dependent lower legs of eight supine astronauts, where the knee joint was passively bent by 90°. The measurements were conducted before spaceflight and 3–6 h on landing following 4–6.5 mo in space. Activation of the vеноarteriolar reflex reduced subcutaneous blood flow by 37 ± 9% (P = 0.016) before flight and by 64 ± 8% (P < 0.001) following landing with no statistical significant difference between the two reductions (P = 0.062). Therefore, our results show that the vеноarteriolar reflex is not attenuated by weightlessness and therefore does not need the everyday stimulus of gravity to maintain efficiency.

Throughout evolution of mankind, gravity has constantly stressed and shaped the autonomic nervous control of the cardiovascular system. As an example, gravity drags blood and fluid into the legs in upright humans. To protect the dependent tissues against accumulation of blood and formation of edema, a local vascular reflex is activated by the hydrostatic distension of the venules, which through local axon reflexes elicits contraction of the adjacent arterioles. In this way, blood flow is diminished and capillary pressures reduced. The mechanism is termed the vеноarteriolar reflex and is continuously activated by gravity during everyday life.

Wilson et al. (17) showed that 14 days of 6° head-down-tilted bed rest attenuated the cutaneous vеноarteriolar response to local venous stasis in the lower legs by some 16%, whereas it was unaffected in the forearm. The authors explained this difference between arms and legs by the fact that the lower legs usually are exposed to much higher hydrostatic pressures in the upright posture so that bed rest would have a more pronounced effect.

The mechanisms as to how the vеноarteriolar reflex could be attenuated in the lower leg during bed rest are not known. Zhang (18) has thoroughly reviewed how hindlimb unloading and tail suspension in rats decrease the contractility of resistance vessels. Therefore, it is possible that when the smooth muscle cells in the arterioles of the dependent regions of the body are not chronically stretched by the gravity-induced hydrostatic pressure gradients, their contractile responsiveness decreases. Furthermore, the density of perivascular adrenergic and peptidergic nerve fibers to arteries and arterioles in hindlimb muscle are decreased during hindlimb unloading, whereas hyperinnervation occurs around the main cerebral arteries (18). All of these effects are reversed on cessation of hindlimb unloading. Collectively, these observations indicate that arterial smooth muscle cells and perivascular adrenergic and peptidergic innervation are sensitive to changes in local transmural pressures and that long-term weightlessness attenuates the contractile responses of arteriolar resistance vessels to hydrostatic stimuli.

In this study, we therefore tested whether the subcutaneous vеноarteriolar reflex in the lower legs would be attenuated in astronauts following weightlessness for between 4 and 6.5 mo on the International Space Station (ISS). Thus we speculated that, after long-term spaceflight, blood flow would not decrease to the same extent as before flight in the lower leg when subjected to an orthostatic stimulus. If confirmed, it would indicate that the vеноarteriolar reflex depends on the everyday activation by gravity to maintain efficiency and that degeneration of autonomic nerves poses a health problem in astronauts during long-term travels in space. An attenuation of the vеноarteriolar reflex could also be one of several mechanisms of postflight orthostatic hypotension (3, 10, 17).

Methods

The investigation was conducted according to the principles in the Declaration of Helsinki and approved by the ethics review boards at NASA and the Ethics Committee of Copenhagen, Denmark (01–123/97). Eight healthy male astronauts (age 39–52 yr) were investigated after obtaining written, informed consent based on careful explanation of the experiment and the possible consequences. They were investigated 23–65 days before spaceflight and 3–6 h on landing following either 128 (n = 3), 184 (n = 2), or 195 (n = 3) days on board the ISS.

Onboard the ISS, the astronauts followed a countermeasure program, where for some 2.5 h/day for six or seven times per week, they performed dynamic exercise on a bicycle ergometer and/or on a treadmill and isometric exercise with resistive devices. The important notion in this case concerning our study is that these interventions do not have an impact on the weightlessness-induced lack of hydrostatic pressure gradients in the circulation. Therefore, the vеноarteriolar reflex could not have been activated by the countermeasures.

Experimental protocol. Each subject was investigated once pre-flight and once postflight and placed in the horizontal supine position throughout each experiment, during which relative changes in subcutaneous blood flow were measured 5 cm proximal to the ankle joint on...
the lateral side of the leg by the radioactive Xenon (\(^{133}\)Xe) wash-out technique. After 30 min of supine rest, the blood flow measurements were commenced with the lower leg maintained horizontal for 7 min (baseline). This was followed by another 7 min of lowering it by removing the support from knee to foot and thus passively bending the knee joint 90° (venoarteriolar reflex activation). Finally, the lower leg was passively bent back to horizontal and placed on a support, where the measurements were continued for yet another 7 min (recovery).

Ambient conditions were on all occasions controlled by air conditioning, and the temperature was very similar during the experiments before and after flight (24–25°C). Blood pressure was measured by the golden standard Korotkoff technique by auscultation in a brachial artery of the supine subjects after at least 30 min of rest and heart rate by palpating the radial artery for 1 min.

Subcutaneous blood flow. Subcutaneous blood flow was measured by the \(^{133}\)Xe wash-out technique, which is a method to determine relative changes in blood flow as described in detail previously (7–9). A residue of \(^{133}\)Xe (80 μCi) in isotonic sterile saline (0.1–0.2 ml, Iso-Tex Diagnostics, Houston, TX) was injected into the subcutaneous tissue 25 min before the measurements were commenced. The blood flow measurements were performed by continuous registration of the radioactive \(^{133}\)Xe counts by a Cadmium Telluride detector covered by a mylar membrane and attached directly to the skin over the injection point of maximum radioactivity. Count values were stored in an electronic memory box and, after completion of the experiment, loaded into a computer for analysis. The slope of the logarithmically transformed count values against time reflected the wash-out rate of \(^{133}\)Xe and thus the magnitude of blood flow. The relative reduction in blood flow during the whole 7-min period of vasoconstrictor activation was calculated by dividing the slope of the \(^{133}\)Xe wash-out rate during leg lowering with the average of the wash-out slopes of the 7-min horizontal baseline and 7-min horizontal recovery periods, subtracting it from 1 and multiplying it by 100%.

Statistical analysis. Values are reported as means ± SE of the eight subjects. The reduction in blood flow during lowering of the leg was tested for statistical significance by Student’s paired t-test after testing for normal distribution of the data, which was also the case when comparing the reduction in blood flow before spaceflight with that of after. Differences between mean values were considered statistical significant when \(P < 0.05\) (SigmaStat 2.03).

RESULTS

Before flight, hydrostatic activation of the vasoconstrictor reflex reduced the subcutaneous blood flow by 37 ± 9\% \((P = 0.016; \text{Table 1})\). Following landing, the same procedure reduced the blood flow by 64 ± 8\% \((P < 0.001; \text{Table 1})\). There was no statistical significant difference between these two reductions \((P = 0.062). Mean arterial pressures (90 ± 1 and 93 ± 2 mmHg) and heart rate (61 ± 3 and 63 ± 2 beats/min) in the supine astronauts were similar before and after flight. Therefore, local vasoconstriction elicited by the vasoconstrictor reflex was not attenuated by prolonged weightlessness.

DISCUSSION

It is interesting from a phylogenetic point of view that the efficiency of a gravity-activated vascular reflex does not depend on the everyday stimulus of gravity. This implies that, in the mature organism, the vasoconstrictor reflex is predominantly affected by biological factors and less by the environment.

That the subcutaneous vasoconstrictor reflex in the lower legs is fully operable following spaceflight is in compliance with earlier results from our laboratory that subcutaneous vascular constriction in the forearm during lower body negative pres-

<table>
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<tr>
<th>Subject No.</th>
<th>Duration of Stay in Space, days</th>
<th>Time of Measurement After Landing, h</th>
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</table>

Relative (% change (Δ) in subcutaneous blood flow of lower legs during vasoconstrictor reflex activation by passive bending of the knee joint in 8 supine astronauts 23–65 days before (preflight) spaceflight for 4–6.5 mo on the International Space Station and 3–6 h on landing (postflight). Blood flow was measured by the \(^{133}\)Xe wash-out technique, and the decrease was calculated relative to the average of the wash-out rates before and after bending of the knee joint. *Significant decrease in blood flow during knee joint bending \((P < 0.02)\).
systemic vascular resistance in space. This is also supported by some of our observations from parabolic airplane maneuvers, where cardiac output promptly increases by as much as 29% during 20 s of acute weightlessness without an increase in mean arterial pressure (12), leading to a decrease in systemic vascular resistance of some 24%. Such a prompt arterial dilatation within 0–20 s can probably only be accomplished by short-circuit nervous connections such as in the vasoconstrictor reflexes. Therefore, the vasoconstrictor reflexes in the legs during very acute and more long-term weightlessness might participate in dilating the arterial resistance vessels from the very beginning and to the end of spaceflight.

It is known that intravascular volume decreases during spaceflight. Alfrey et al. (1) have shown that plasma volume can decrease as much as 17% within 22 h of flight. The question is whether such a decrease in plasma volume could have affected our results. A decrease in plasma volume induces some degree of peripheral vascular constriction through inhibition of the baroreflexes. If this was the case in our subjects during the postflight investigations, we would have expected the vasoconstrictor reflex to be attenuated during lowering of the lower leg, because further constriction of the arterioles would be less if they were more constricted from the outset. Because we did not observe an attenuated vasoconstrictor response, we do not think that intravascular fluid volume reduction had much of an effect. Whether a decrease in intravascular volume can induce a decrease in venous volume of the lower legs and thus affect the hydrostatic stimulus to the vasoconstrictor reflex during leg lowering is not clear at present.

It has previously been hypothesized that leg venous compliance is increased during spaceflight (15), and if this was the case in our subjects during the postflight investigations, it could theoretically have affected our results, because an increased distensibility of the veins in the lower leg could have led to a stronger stimulus to the vasoconstritory reflex. Watenpaugh et al. (16), however, showed that leg venous compliance is unchanged within 2 wk of spaceflight, whereas in earlier Skylab spaceflights for up to almost 3-mo duration, leg venous compliance was demonstrated to be increased (15). Therefore, it is a possibility that leg venous compliance was increased during our postflight investigations and that it accounted for maintenance of the strength of the vasoconstrictor reflex.

Our previous and present results indicate that the autonomic nervous responsiveness to orthostatic stimuli are not compromised by spaceflight in humans (7). This is in contrast to several studies in rats, where simulation of the effects of weightlessness by tail suspension and hindlimb unloading decreases the autonomic nervous responsiveness of the arteries in the hindlimb to hydrostatic pressure stimuli (18). The reason for this discrepancy is not at present clear, but the most likely explanation probably resides in species differences.

It cannot be excluded that what we examined was not solely the effects of weightlessness on the vasoconstrictor reflex but also the effects on the myogenic response (14). If this is so, our results indicate that the myogenic response is also intact after long-term lack of hydrostatic pressure stimulation in the lower limb. We do, however, think that the major component of vasoconstriction during isolated limb dependency is of vasoconstritory origin, because Henriksen (8) and Okazaki et al. (14) have observed that vasoconstriction by limb dependency can be blocked by a local anesthetic.

In conclusion, the subcutaneous vasoconstrictor reflex in the lower legs is not attenuated by prolonged weightlessness in space for up to 195 days. Thus the vasoconstrictor reflex does not need to be regularly exercised to maintain efficiency. Therefore, edema formation and capillary damage are unlikely to be obstacles in astronauts on landing even after very long missions.

Possible limitations. The astronauts were investigated between 3 and 6 h after landing. Therefore, it could be argued that in this period, where they were more or less upright depending on their orthostatic condition, the vasoconstrictor reflex was promptly adapted to gravity after having been attenuated in space. This cannot be totally excluded. We think, however, that it is unlikely, because the reduction in subcutaneous blood flow during activation of the vasoconstrictor reflex was the same in astronauts, whether they were investigated 3 or 6 h after landing (Table 1).

The 133Xe wash-out technique can introduce errors in estimation of blood flows. If the injected 133Xe moves away from the detector, it can change the measured radioactivity, which would indicate an erroneous change in flow. It is unlikely, however, that had this occurred; it would be systematically different comparing measurements before flight with those of after, because we used exactly the same procedures and same sites of injection in each subject during all of the interventions.

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REFERENCES


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