Effects of spaceflight on human calf hemodynamics

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Effects of spaceflight on human calf hemodynamics. J Appl Physiol 90: 1552–1558, 2001.—Chronic microgravity may modify adaptations of the leg circulation to gravitational pressures. We measured resting calf compliance and blood flow with venous occlusion plethysmography, and arterial blood pressure with sphygmomanometry, in seven subjects before, during, and after spaceflight. Calf vascular resistance equaled mean arterial pressure divided by calf flow. Compliance equaled the slope of the calf volume change and venous occlusion pressure relationship for thigh cuff pressures of 20, 40, 60, and 80 mmHg held for 1, 2, 3, and 4 min, respectively, with 1-min breaks between occlusions. Calf blood flow decreased 41% in microgravity (to 1.15 ± 0.16 ml·100 ml⁻¹·min⁻¹ relative to 1-G supine conditions (1.94 ± 0.19 ml·100 ml⁻¹·min⁻¹, P = 0.01), and arterial pressure tended to increase (P = 0.05), such that calf vascular resistance doubled in microgravity (preflight: 43 ± 4 units; in-flight: 83 ± 13 units; P < 0.001) yet returned to preflight levels after flight. Calf compliance remained unchanged in microgravity but tended to increase during the first postflight week (P > 0.2). Calf vasoconstriction in microgravity qualitatively agrees with the “upright set-point” hypothesis: the circulation seeks conditions approximating upright posture on Earth. No calf hemodynamic result exhibited obvious mechanistic implications for postflight orthostatic intolerance.

weightlessness; gravity; leg; vascular resistance; blood flow; venous compliance

Gravitational force creates pressure gradients in the circulation. For example, resting mean arterial pressure (MAP) at ankle level equals ~200 mmHg in a standing adult human. Therefore, lower body vascular structures bear loads imposed by gravity. In terrestrial animals, circulatory gravitational pressures required evolution of structural and regulatory mechanisms to maintain cerebral perfusion and prevent lower extremity fluid accumulation while in upright postures. In humans, these mechanisms include leg vasoconstriction in upright posture relative to supine conditions via baroreflexes, local venoarterial reflexes, and myogenic vasoconstriction (29–25, 43), relatively low venous compliance in the legs (45), and capillary basement membrane thickening in the lower body (49).

Existence in microgravity elicits hypothetically sustained reduction of lower body vascular transmural pressures relative to upright 1-G conditions. For example, ankle MAP decreases from ~200 mmHg while standing in 1 G to 100 mmHg in 0 G. This is similar to what occurs when one assumes recumbent posture on Earth (46). In 0 G, however, postural pressure changes in the leg vasculature no longer occur, and locomotion-induced leg blood pressure oscillations (31, 32) are probably also absent or greatly attenuated, such that lower body mean pressures remain relatively low and constant. Chronic reduction of leg vascular transmural pressures and pressure oscillations may well alter and perhaps compromise leg macro- and microvascular structure and function (11, 14, 46, 50).

Gauer and Thron (21) proposed that the normal operating set point for human cardiovascular function is the upright posture in 1 G. The corollary that cardiovascular and fluid regulatory systems seek this “upright set point” in microgravity constitutes a central hypothesis of studies of acclimation to microgravity. After a few days in microgravity, blood volume and thus cardiac stroke volume decrease ~10% relative to 1-G supine conditions, as occurs after the assumption of the upright posture on Earth (46). However, heart rate remains unchanged or even decreases (19), such that cardiac output tends to decrease in microgravity relative to supine 1-G conditions. Therefore, to maintain arterial blood pressure given reduced cardiac output, one might expect elevation of vascular resistance in space. Elevation of leg vascular resistance may provide one mechanism for arterial pressure maintenance in microgravity. Indeed, although small sample sizes and discrepancies among studies preclude firm conclusions (and justify the present work), most results suggest that leg vasoconstriction occurs at rest in microgravity relative to 1-G supine conditions, especially during the first 10 or so days in-flight (12, 46).

Maximal calf conductance (flow per unit arterial pressure after ischemic exercise) represents the maximal ability of the leg to vasodilate. Levine et al. (28)...

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associated elevated maximal calf conductance with low orthostatic tolerance. Buckey and co-workers (7) observed that astronauts with postflight orthostatic intolerance exhibit a relative inability to vasoconstrict while standing. Therefore, we expected that this relative inability to vasoconstrict might be expressed as an elevated postflight maximal calf vasodilatory capacity.

Most studies suggest that leg compliance increases during and after existence in 0 G. This observation is expected because leg dehydra\tion (26, 41), vascular and skeletal muscle disuse, and loss of skeletal muscle mass (15) in 0 G should all increase leg compliance during and after spaceflight. The deep leg veins contribute importantly to leg compliance, and their compliance characteristics depend on the mass and stiffness of surrounding skeletal muscle (8, 13). In general, leg hemodynamic results from bed rest agree with those from spaceflight (12, 18).

Therefore, based on the literature and the above ideas, we hypothesized that 1) resting calf blood flow decreases in microgravity (calf vascular resistance increases) relative to supine 1-G conditions, as occurs in upright posture on Earth; 2) maximal calf conductance is elevated after spaceflight; and 3) existence in microgravity increases calf compliance. In addition, we sought to determine whether any feature of calf circulatory acclimation to spaceflight could be associated with postflight orthostatic responses and tolerance, as reported previously by Buckey and co-workers (7) in these same subjects.

METHODS

Subjects. Seven subjects (2 women, 5 men) participated in this study after providing written, informed consent. Comprehensive physical examinations established their health. They ranged from 35 to 50 yr of age, they averaged 174 ± 8 (SD) cm in height, and they weighed 72.8 ± 8.9 kg. Institutional review boards at the University of Texas Southwestern Medical Center and at the National Aeronautics and Space Administration (NASA) Johnson Space Center approved this study, which constituted part of the SpaceLab Life Sciences-1 and -2 missions flown aboard the space shuttle Columbia.

Instrumentation. Venous occlusion plethysmography quantified calf compliance and blood flow (48). We employed a custom-built electromechanical plethysmograph to measure calf volume elevation during venous occlusion. Our laboratory has previously described in detail the features, operation, and performance of this system for venous occlusion plethysmography (SVOP) and has validated it against operation, and performance of this system for venous occlusion plethysmography (SVOP), to ensure that any observed differences between ground-based and in-flight results were not due to variability in experimental technique.

Experimental conditions and protocol. Between four and six baseline data collection sessions took place before flight. At least 3 wk separated these sessions from one another. Space-borne measurements were made between 4 and 12 days in-flight. Recovery (postflight) measurements occurred at 1–2 (referred to as R ± 1/2), 6–7, and 45–49 (referred to as R ± 3) days postflight. All data collection occurred at least 2 h after the subjects ate and at least 12 h after they consumed caffeine or ethanol. Subjects performed experimental (29, 35) and other exercise before, during, and after flight, although never before calf hemodynamic data collection on a given day. Although nonexperimental exercise was not quantified, we have no reason to believe that it systematically influenced our results. All data collection occurred at room temperature (22–26°C).

For pre- and postflight measurements, subjects were supine with the left leg elevated ~15° and with the knee slightly bent. This positioning was employed because it is a standard method for calf blood flow measurement (48), it simulates the relatively emptied leg venous conditions seen in microgravity (26, 39, 41), it approximates the posture astronauts naturally assume at rest in microgravity (40), and it is comfortable. Subjects were supine for 20–30 min before data collection. Subjects did not sleep during data collection.

After instrumentation of the subject, calf blood flow was measured in triplicate. We employed 60-mmHg (subdiastolic) thigh cuff pressure for all venous occlusion flow measurements. Inflation of an ankle cuff to 300 mmHg prevented interference of foot blood flow with calf blood flow measurements. Duplicate calf compliance measurements followed the flow measurements. Compliance equaled the slope of the calf volume elevation and venous occlusion pressure relationship for thigh cuff pressures of 20, 40, 60, and 80 mmHg held for 1, 2, 3, and 4 min, respectively, with 1-min breaks between occlusions. We designed our protocol with relatively short venous occlusions to emphasize assessment of the venous contribution to calf compliance, yet we appreciate that nonvenous factors such as capillary filtration influence limb plethysmography measurements (47); thus we simply refer to calf compliance, and not calf venous compliance, in this paper.

Maximal calf blood flow was measured before and after spaceflight. To elicit maximal calf blood flow, subjects performed dynamic lower leg exercise under ischemic conditions until exhaustion of the leg, as described previously (28, 36). After completion of all resting measurements, the thigh cuff was inflated to suprasystolic pressure (250–300 mmHg) and left open to the pressure regulator to ensure maintenance of this high cuff pressure and thus arterial occlusion during exercise. The subject then stood up and began a full range of motion of plantar flexion and dorsiflexion exercise of the leg until volitional exhaustion. Subjects performed the exercise at 0.5 Hz to a metronome (1 s for plantar flexion, 1 s for...
Subjects reported previously by Buckey and colleagues (e.g., also attempted correlations between the calf hemodynamic (e.g., calf compliance vs. calf vascular resistance, etc.). We therefore, repeated-measures analyses excluded his data, seven subjects did not participate at all data collection times; specific time points differed from one another. One of the hoc least significant difference tests further delineated which whether dependent variables changed over time, and post hoc multiple comparisons made all pairwise comparisons. No postflight calf blood flow mean differed significantly from preflight levels.

**Resting calf vascular resistance increased in microgravity.** Resting MAP increased in microgravity relative to preflight supine levels \( (P < 0.01) \); Table 1). Relative to in-flight levels, postflight supine MAP decreased by 8 mmHg (9%) at \( R = 1/2 \) and at \( R + 45 \) \( (P < 0.01) \). As stated above, resting calf blood flow decreased 41% in microgravity relative to preflight supine levels. Therefore, calf vascular resistance (MAP/flow) essentially doubled in microgravity (preflight supine: 43 ± 4 units; in-flight: 83 ± 13 units; \( P < 0.001 \)), Fig. 2). As with calf blood flow, calf vascular resistance returned to and remained at control levels by 1–2 days postflight. Resting heart rate tended to decrease in microgravity relative to preflight supine levels (4 beats/min; \( P = 0.12 \)), and all supine resting postflight heart rate means significantly exceeded the in-flight average (9–16%; Table 1; \( P < 0.03 \)).

**Maximal calf blood flow and conductance did not change after spaceflight.** Neither maximal calf blood flow nor maximal calf conductance changed significantly after existence in microgravity relative to preflight supine values (Table 2). However, a minor trend emerged for maximal calf flow and conductance to increase at 6–7 days postflight \( (P > 0.1) \).

**Calf compliance may have increased after, but not during, spaceflight.** Existence in microgravity did not change resting calf compliance relative to preflight supine levels: mean in-flight calf compliance equaled the preflight mean (Fig. 3). During the first week after flight, supine calf compliance tended to increase relative to preflight levels \( (P = 0.2–0.3) \). Over the weeks after spaceflight, calf compliance decreased: compliance at \( R + 1/2 \) significantly exceeded calf compliance at \( R + 45 \) \( (P = 0.04) \).

**RESULTS**

Resting calf blood flow decreased in microgravity. Resting calf blood flow decreased 41% in microgravity from supine preflight levels of \( 1.94 \pm 0.19 \) to \( 1.15 \pm 0.16 \) ml·100 ml\(^{-1}\)·min\(^{-1} \) \( (P = 0.01) \). Calf blood flow in space was also reduced significantly relative to all postflight measurements, including those made at 1–2 days postflight. No postflight calf blood flow mean differed significantly from preflight levels.

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**Table 1. Heart rate and mean arterial pressure before, during, and after spaceflight**

<table>
<thead>
<tr>
<th></th>
<th>Preflight</th>
<th>In-flight</th>
<th>R + 1/2</th>
<th>R + 6/7</th>
<th>R + 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>60 ± 2</td>
<td>56 ± 2</td>
<td>65 ± 2*</td>
<td>64 ± 3*</td>
<td>61 ± 3*</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>80 ± 2</td>
<td>85 ± 3</td>
<td>77 ± 2†</td>
<td>80 ± 2</td>
<td>77 ± 3†</td>
</tr>
</tbody>
</table>

Values are means ± SE; \( n = 6 \) subjects. \( R + 1/2 \), \( R + 6/7 \), and \( R + 45 \): recovery plus 1–2, 6–7, and 45–49 days postflight, respectively.

*Greater than in-flight levels, \( P < 0.05 \). †Less than in-flight levels, \( P < 0.05 \).
Other results. The seventh subject, who did not complete the full postflight data collection sequence and was, therefore, excluded from repeated-measures statistical analyses, exhibited responses similar to average responses of the six other subjects. At 71 units, his in-flight calf vascular resistance was about threefold greater than his preflight supine value of 22 units, yet his resistance equaled 34 units by the day after his return from microgravity. His calf compliance decreased 43% in-flight relative to preflight supine levels. At R + 1/2, his calf compliance increased 8% relative to preflight levels. He did not undergo calf maximal conductance assessment.

No variable pairs in the present data set correlated significantly, nor did any variables reported here correlate significantly with relevant variables in the pre- and postflight stand test (orthostatic tolerance) results reported previously by Buckey and co-workers (7) for the same subjects (all P > 0.1).

DISCUSSION

The above results indicate that 1) calf vascular resistance doubled in chronic microgravity relative to supine ground-based levels; 2) maximal calf conductance did not change significantly after spaceflight; and 3) existence in microgravity does not strongly affect calf compliance. Furthermore, all attempts to relate microgravity-induced changes in calf hemodynamics to postflight standing hemodynamic pathophysiology failed, implying that calf hemodynamic changes do not contribute strongly to postflight orthostatic intolerance. These results constitute the first study of leg hemodynamics in microgravity under relatively uniform and documented experimental conditions in a statistically meaningful number of subjects.

Calf blood flow and vascular resistance during and after spaceflight. As detailed in the Introduction, blood volume and cardiac stroke volume decrease in chronic microgravity relative to 1-G supine conditions, yet heart rate remains unchanged, such that resting cardiac output tends to decrease in microgravity relative to supine 1-G conditions (19, 46). Therefore, increased leg vascular resistance in microgravity is adaptive, in that it provides a mechanism for maintenance of arterial pressure in response to relatively reduced cardiac output.

The present findings support some literature results that indicate that leg vasoconstriction occurs during spaceflight (33, 42, 44). Other data, all from longer duration flight (>2 wk), indicate increased leg blood flow (or reduced leg vascular resistance) in chronic microgravity (2, 39). We measured calf hemodynamics between 4 and 12 days in-flight. Therefore, our findings of vasoconstriction agrees with prior observations within the first 2 wk of a flight, yet microgravity-induced leg vasodilation relative to 1-G supine conditions may prevail on longer duration flights.

How do the present results from spaceflight relate to leg hemodynamic assessments during and after simulated 0 G? One study found no change in resting leg blood flow during 20 days of bed rest relative to supine control conditions (5), yet three other studies found increases in resting leg vascular resistance during chronic bed rest relative to supine control conditions.
Takenaka and colleagues (37) found a doubling of leg vascular resistance at 20 days of bed rest (similar to what we observed during spaceflight); Louisy and colleagues (30) noted similar results at 41 days of bed rest; and Blamick and co-workers (4) noted a more modest increase at 10 days of bed rest. The latter group also found that 30 mmHg lower body negative pressure (LBNP)-induced leg vasoconstriction after bed rest (~21%) equaled that seen before bed rest.

Therefore, the majority of data suggest that leg vasoconstriction occurs at rest in actual and simulated microgravity relative to 1-G supine conditions. Because leg blood flow decreases by 50–70% in upright posture relative to recumbence (6, 23, 34), similar leg blood flow reduction in 0 G supports the upright setpoint hypothesis. However, leg blood flow reduction in upright posture occurs in the face of 150- to 200-mmHg local MAP, which requires a three- to fourfold increase in local vascular resistance relative to recumbent conditions. In 0 G, resting leg MAP hypothetically remains at ~100 mmHg, so that a 50% reduction in leg blood flow requires only a twofold increase in vascular resistance relative to recumbent 1-G conditions. The additional vascular resistance seen in 1-G upright conditions may result from local venoarteriolar and myogenic reflexes, which rely on local gravitational fluid pressure ("tone") and tissue mass (15, 27), in addition to shear stress in turn elicits release of nitric oxide (3), which is an established vasodilator. Therefore, removal of gravity may reduce net shear stress, which would then reduce nitric oxide release and lead to vasoconstriction.

In our study, arterial blood pressure increased in microgravity relative to postflight supine levels, and a similar trend appeared relative to preflight levels. In another recent study, Fritsch-Yelle and co-workers (19) found that arterial pressure in 0 G decreased relative to preflight levels. Differences in baseline conditions probably explain the disagreement between their study and ours: they compared routine, active in-flight blood pressure data with ambulatory ground-based measurements, whereas we compared quiet, resting in-flight data with supine resting blood pressure on Earth. Supine resting blood pressure is usually less than that measured during upright activity.

Maximal conductance equals maximum blood flow per unit arterial pressure. This variable represents the maximum vasodilatory capacity of a tissue. Snell et al. (36) found greater maximal calf conductance in endurance-trained athletes relative to untrained individuals, and Levine et al. (28) associated elevated maximal calf conductance with low LBNP tolerance. After a recent 16-day bed rest simulation of spaceflight, Engelke and Convertino (16) found a 37% reduction in maximal vascular conductance. In the present study, however, no systematic pre- to postflight changes in maximal calf conductance occurred, and we found no association between this variable and postflight orthostatic intolerance (7).

Calf compliance during and after spaceflight. We found no significant in-flight or postflight increase in calf compliance relative to preflight supine levels, nor did individual changes in calf compliance correlate with any feature of postflight orthostatic intolerance (7). The absence of significant 0-G-induced elevation in calf compliance surprised us. Multiple factors hypothetically favor increased leg compliance in 0 G. These factors include reduced leg skeletal muscle interstitial fluid pressure ("tone") and tissue mass (15, 27), increased capillary permeability, and reduced venous smooth muscle tone and mass. Also, most prior data suggest leg compliance increases in 0 G (reviewed in Refs. 12 and 46), and results from bed-rest simulation of spaceflight (reviewed in Ref. 18) mirror flight results.

No calf muscle mass data exist for this study, but this compliance-related factor (13, 27) may not decrease substantially in 4–12 days of spaceflight. As discussed above, the present data set and most other results indicate that leg vasoconstriction occurs in 0 G, and microgravity-induced sympathoexcitation could in part mediate such vasoconstriction. This raises the possibility that sympathetically mediated leg vasoconstriction also occurs in-flight (22). Any such neurally mediated vasoconstriction would oppose the multiple factors that hypothetically favor increased leg compliance during and after existence in 0 G. In addition, reduced leg blood flow by itself would tend to reduce leg vasoconstriction.
compliance assessed with venous occlusion, as in our study.

Calf volume elevation during orthostatic stress provides a less direct, more qualitative, yet also more functionally relevant, means of assessing calf compliance. Previous studies employing calf plethysmography during LBNP and head-up tilt yielded conflicting and inconclusive results concerning the effects of spaceflight on leg compliance (46). Leg muscle activation during standing should reduce leg compliance by stiffening the skeletal muscle around the deep leg veins (8, 13). Comparison of supine-to-standing leg volume elevation before and after flight provides a crude but functionally appropriate assessment of pre-vs. postflight leg compliance. Our laboratory previously reported essentially identical increases in leg volume from supine levels after 5 min of standing postflight (3.6%) relative to preflight (3.7%; n = 13) (7). A “normal” (preflight) degree of pooling in the legs observed postflight combined with postflight hypovolemia may compromise postflight cardiac filling pressure. However, subjects who did not tolerate 10 min of standing tended to exhibit less leg volume elevation on standing postflight relative to preflight, whereas those who tolerated 10 min of standing exhibited slightly greater leg volume elevation postflight. Finally, no correlations emerged between postflight postural leg volume elevation and stroke volume decrease or incidence of orthostatic intolerance. It appears that leg muscle activation while standing may prevent or reduce expression of any increased leg compliance sometimes seen in relaxed legs of supine astronauts postflight.

Limitations. Investigators collected all ground-based data, yet noninvestigator astronauts collected most in-flight data. This obviously introduces opportunity for inconsistent technique and error. Most spaceflight research must cope with this potential problem. To ensure consistent technique, we thoroughly trained all crew members assigned to make in-flight measurements to perform those measurements properly. This training included substantial crew member experience as subjects with investigators preflight. Also, we were fortunate to have a coinvestigator crew member on one of the two flights.

Ambient temperature affects limb blood flow, and temperature was not tightly regulated during our study. However, in-flight temperatures were not greater or less than those on the ground. Another limitation involves the technique itself: venous occlusion plethysmography does not differentiate clearly among vascular, transcapillary, and extravascular components of leg compliance. In a way, this feature improves physiological relevance, because gravity acts on all components of leg compliance during orthostasis, yet mechanistically, distinguishing among components adds information (47). Nevertheless, we customized the protocol with venous occlusion periods ≤4 min to emphasize the venous contribution to leg compliance.

Chronic aerobic exercise training appears to increase maximal calf conductance (28, 36). We did not rigorously control or quantify the total exercise subjects performed during the period of study; therefore, we do not know whether any training or detraining effects influenced our findings. However, we have no reason to believe that such effects occurred or systematically influenced our results.

Conclusions. The present results indicate that human calf blood flow decreases in chronic microgravity relative to supine 1-G conditions because of calf arterial vasoconstriction. This vasoconstriction approaches, but is probably less than, that which occurs on Earth on standing from the recumbent posture. Nevertheless, leg vasoconstriction in microgravity may help maintain blood pressure there, given that cardiac output tends to decrease in space relative to supine 1-G conditions. Despite expectations, we observed no increase in calf compliance in microgravity, and no in-flight or postflight feature of calf hemodynamics exhibited an obvious relationship to postflight orthostatic intolerance.

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