Vascular adaptation to microgravity: what have we learned?

LI-FAN ZHANG
Department of Aerospace Physiology, The Fourth Military Medical University, Xi'an 710032, China

Zhang, Li-Fan. Vascular adaptation to microgravity: what have we learned? J Appl Physiol 91: 2415–2430, 2001.—Findings from recent bed rest and spaceflight human studies have indicated that the inability to adequately elevate the peripheral resistance and the altered autoregulation of cerebral vasculature are important factors in postflight orthostatic intolerance. Animal studies with rat model have revealed that simulated microgravity may induce upward and downward regulations in the structure, function, and innervation of the cerebral and hindquarter vessels. These findings substantiate in general the hypothesis that microgravity-induced redistribution of transmural pressures and flows across and within the arterial vasculature may well initiate differential adaptations of vessels in different anatomic regions. Understanding of the mechanisms involved in vascular adaptation to microgravity is also important for the development of multisystem countermeasures. However, future studies will be required to further ascertain the peripheral effector mechanism of postflight cardiovascular dysfunction.

cardiovascular deconditioning; postflight orthostatic intolerance; arteries; arterioles; remodeling; vasoreactivity; perivascular nerves; countermeasures

THE PURPOSE OF THIS REVIEW is to summarize our understanding of vascular adaptation to microgravity and its implications in the development of effective countermeasures and to give a perspective on opportunities for future study to gain a clear understanding of postflight cardiovascular dysfunction and the scientific basis for future multisystem countermeasures.

For many years, the prevailing concept in space cardiovascular research has been that microgravity-induced hypovolemia, increased leg compliance, attenuated carotid baroreceptor-heart rate (HR) responsiveness, and altered cardiovascular control are important mechanisms responsible for postflight orthostatic intolerance (5, 19, 40, 60, 108, 128). However, new information is emerging to suggest that the mechanism of postflight cardiovascular dysfunction is more complex (3, 4, 12, 25, 39, 59, 128). Now it is well recognized that hypovolemia is likely the primary cause and necessary condition in microgravity-induced cardiovascular deconditioning, but it is not the unique cause and sometimes not a necessary one (3, 5, 13, 16, 108). For example, in head-down bed rest studies, restoration of plasma volume alone did not restore orthostatic tolerance (13, 40, 108) or maximal aerobic power (118). Although attenuated baroreflex sensitivity and increased leg compliance have been acknowledged as independent factors that appear to exaggerate the effects of hypovolemia (3, 19, 35, 108, 128), their relative contribution to the occurrence of postflight cardiovascular dysfunction still needs further assessment. The critical question is that whether baroreflex assessments based solely on changes in HR or R-R interval can reflect the overall physiological outcome of arterial baroreflexes (71, 108, 128). However, evidence from recent bed rest and postflight human studies indicates that inadequate vasoconstrictor responsiveness is an important factor in postflight orthostatic intolerance, which should be the new focal point in further studies (3, 8). Another important factor is the excessive dramatic reduction in stroke volume (16, 18, 72, 120, 128, 132). Blomqvist and colleagues (3, 4) have proposed that a degradation of the neurohumoral vasoconstrictor mechanisms may occur at one or more levels, i.e., afferent input, central integration, efferent.

Address for reprint requests and other correspondence: L.-F. Zhang, Dept. of Aerospace Physiology, The Fourth Military Medical Univ., Xi'an 710032, P. R. China (E-mail: zhanglf@fmmu.edu.cn).
output, and/or end-organ responsiveness. Although presently available information provides no conclusive answers, Blomqvist and co-workers and some other groups have emphasized the possibility that altered central integration of cardiovascular control mechanisms or functional changes at vascular receptors are contributory factors (3, 4, 12, 19, 40). In addition, the importance of altered cardiovascular sensory inputs that may trigger neural plasticity has also been suggested (50, 60). Contrary to speculations that emphasize the central integration mechanism and the aspect of functional adaptation, in the late 1980s, Hargens and co-workers made the important prediction of the possible structural adaptation of vessels to microgravity (53, 54, 55, 128), which were later confirmed by work from different laboratories (26–29, 47, 104, 112, 137, 139, 140, 142). During the past 10 yr, interest in studies on vascular deconditioning has grown with inspiring findings. The primary goal of this paper is to evaluate what we have learned and to provide a perspective on what should we try to learn in this new century. No attempt will be made to provide a complete review of this topic. The reader is referred to a number of reviews in which the reduction in muscle capillaryization (18, 30) and transcapillary fluid balance (55, 128) have been discussed.

VASCULAR ADAPTATION OBSERVED IN GROUND-BASED AND SPACEFLIGHT HUMAN STUDIES

Quite contrary to the simple logic that venoconstriction would minimize pooling in orthostasis, it has taken much longer to recognize that, in a one-gravitational-unit (1-G) environment, one major adjustment to upright posture appears to be vasoconstriction rather than venoconstriction. Arteriolar pressure is the major determinant of distending pressure and, indirectly, of venous volume. Therefore, passive changes in venous volume caused by splanchnic and peripheral vasoconstriction are probably significant during orthostasis (5, 108). Scientists ran into the same problem in microgravity studies during the past several decades. Increased venous compliance has been suggested as one of the important factors responsible for postflight orthostatic intolerance. It has been suggested that reduced leg interstitial fluid volume and pressure and leg muscle atrophy might be responsible for the elevated leg compliance in subjects exposed to microgravity (5, 19, 108, 128). Furthermore, data derived from a bed rest study suggests that reduced muscle size is the primary cause of increased leg compliance, which in turn affects orthostatic tolerance (5, 19, 22, 128).

However, the preponderance of recent evidence indicates that microgravity-induced orthostatic hypotension results from the body’s inability to adequately elevate peripheral vascular resistance. For example, Mulvagh et al. (96) analyzed echocardiographic data and found that the elevation of total peripheral resistance (TPR) normally seen on standing did not occur on landing day after spaceflights. Whitson et al. (130) reported that the elevated plasma catecholamines during standing postflight relative to preflight levels were not associated with an increased postural vasoconstriction relative to the preflight response, suggesting an inadequate function of resistance vessels (3, 129). Buckey et al. (8) found that the subjects who did not finish the postflight 10-min stand test (“nonfinishers”) exhibited less of an increase in TPR than the subjects who finished the test (3). However, no systematic and dramatic increase in postflight standing leg compliance was observed in this group of astronauts (8, 129).

Convertino (20) has offered another probable explanation that a less vasoconstrictive reserve might be a primary mechanism responsible for the impaired vasoconstrictor response in the nonfinishers. It seems that there is a finite maximal vasoconstrictive reserve that is not altered by adaptation to microgravity, but the reduction in central blood volume due to microgravity exposure may cause a greater vasoconstriction and reduce the reserve for further increase in vascular resistance. Findings from several human experiments investigating the relationship between central venous pressure and forearm vascular resistance (FVR) and the FVR response to graded lower body negative pressure (LBNP) before and after bed rest (21, 35, 119) supported this hypothesis. Furthermore, Gabrielsen et al. (44) reported enhanced forearm subcutaneous vascular resistance response during postflight LBNP testing. However, the vasoconstriction response to progressive LBNP is clearly nonuniform among various vascular beds, e.g., forearm blood flow (FBF) and conductance decrease significantly before splanchnic flow is affected (5, 108). The latter is the most important region and will exert the greatest effects on blood pressure regulation. Thus to what extent the FVR response can reflect the TPR response needs further clarification. Nevertheless, Shoemaker et al. (116) observed attenuated reactive hyperemic FBF and diminished ability of the cold pressor test to lower FBF after bed rest, suggesting alterations in vasodilatory function and the interaction between dilatory and constrictor influences in humans during adaptation to microgravity.

After exposure to microgravity, elevations in plasma catecholamines to upright posture and exercise are generally excessive (19, 35, 130). However, a comparison of responses in presyncopal and nonsyncopal astronauts during their 10-min standing tests on landing day clearly identified a subnormal increase in plasma norepinephrine in the presyncopal group as the critical difference. Furthermore, presyncopal astronauts also showed a preflight individual predisposition to being more susceptible to postflight orthostatic intolerance characterized by hypoadrenergic response during standing (41).

It has been postulated that adrenoreceptor hypersensitivity in the face of excessively high sympathetic activation may contribute to postflight attenuated vasoconstrictor responses (19, 24). The adaptation to a reduced plasma norepinephrine level in microgravity would presumably lead to a significant increase in the number and agonist affinity of $\beta_1$- and $\beta_2$-adrenocope-
tors. If the $\beta_2$ hypersensitivity were greater than the $\alpha_2$ hypersensitivity, as we observed in the Bradbury-Eggleston syndrome of severe autonomic failure, a normal vasoconstrictor response to upright posture might be transformed into a reduced vasopressor response (19). This hypothesis is supported by studies that have reported an enhanced vascular $\beta$-adrenergic receptor responsiveness after bed rest (24) and that the $\beta$-receptor antagonist propranolol has limited benefit as a countermeasure to cardiovascular deconditioning after bed rest (109). However, the cardiovascular responses to graded intravenous infusions of either $\alpha$- or $\beta$-adrenergic agonists were unchanged postflight in both Spacelab Life Sciences-1 and -2 mission (SLS-1 and SLS-2) crewmembers (3, 4). But negative results are inconclusive because the adrenergic agonist tests were conducted 24–28 h after return to 1 G (3).

Recently, attention has also been paid to the cerebral circulatory adjustments to chronically elevated arterial and intracranial pressures in microgravity. Furthermore, evidence is accumulating that adaptational changes in cerebral arterial vasculature in microgravity might also contribute to postflight orthostatic intolerance: cerebrovascular syncope-initiating mechanism (12, 128, 129). For example, one SLS-1 crewmember who experienced postflight orthostatic intolerance did not exhibit bradycardia or reduced mean arterial pressure (128). Bondar et al. (7) noted postflight reduction of arterial pressure and transcranial Doppler cerebral blood flow velocity in standing astronauts. Evidence supporting this idea is also from postflight data of a long Salyut-6 mission reported by Gazenko et al. (46). Using impedance rheography, they found significant reduction in the cerebral blood flow pulsatility (“pulse blood filling”) during head-down tilt (HDT; 6 min at $-15^\circ$ followed by 6 min at $-30^\circ$) relative to preflight values. These changes suggest an enhanced cerebral vasoconstriction, perhaps resulting from adaptation to chronic elevation of cerebral vascular pressure during microgravity. Furthermore, the effect was substantially more apparent and prolonged after longer flights (12, 46, 128). After a long Salyut-6 mission, the flight-related changes in cerebral vascular function did not resolve for $-5$ wk. It has also been postulated that such a mechanism could be exacerbated by hypersecretion of vasopressin, which can constrict human cerebral arteries (128). Rheoencephalography has also been used to reveal altered reactivity in cerebral circulation to exercise or LBNP during Salyut-6 flights. Cerebral perfusion decreased more at given levels of LBNP and increased more at cessation of exercise. Postflight rheoencephalogram responses were similar to those observed during flight and seem to persist for several weeks after prolonged flight (12).

Two studies have further demonstrated the microgravity-induced vascular adjustments and their association with reduced orthostatic tolerance. One is a 2-wk bed rest study by Zhang et al. (147), who found that the increase in vasoconstrictor outflow to muscle was attenuated and the cerebral autoregulation was impaired as evidenced by an earlier and greater fall in cerebral blood flow velocity during LBNP after bed rest. These results suggest that the failure of peripheral resistance to elevate and the less effective autoregulation of cerebral circulation may contribute to the reduced orthostatic tolerance after adaptation to microgravity. In another study, Arbeille and co-workers (1, 59) measured the blood flow velocity and estimated the vascular resistance from the Doppler velocity spectrum in different vessels of cosmonauts during several short-term and three 6-mo Mir spaceflights. Measurements were made at rest with vs. without thigh cuffs or during LBNP compared with preflight data as the control. At rest, the renal and femoral vascular resistances decreased, whereas the cerebral vascular resistance did not show significant changes and the cerebral blood flow was stable and close to the preflight levels. During LBNP challenge, increases in both the femoral vascular resistance and the ratio between cerebral and femoral blood flow were markedly attenuated. The thigh cuffs induced moderate but significant increases of cerebral, renal, and femoral arterial vascular resistances in all six cosmonauts. However, despite the daily use of cuffs during the 6-mo flight, it did not prevent the development of postflight cardiovascular deconditioning. The cross-sectional area (CSA) of jugular and femoral veins remained enlarged throughout the flight. Finally, more than 1 wk after return to the 1-G condition, the lower limb arterial resistance and the ratio between cerebral and femoral blood flow remained abnormal and were associated with orthostatic intolerance during postflight stand tests in all of the cosmonauts (59). More recently, calf blood flow decrease and vascular resistance increase were reported for subjects during spaceflight (127). A bed rest study has suggested that an imbalance between sympathetic vasoconstrictor traffic and nitric oxide (NO) release might contribute to elevated leg vascular resistance (64).

Clearly, there are also difficulties and limitations of human studies to clarify the vascular adaptation to microgravity from its various aspects and to delineate its mechanism at different levels. Methodological difficulties are associated with using noninvasive techniques to make the necessary and critical measurements. In most cases, hemodynamic measurements have been limited to volume changes of whole limbs and estimates of blood flow, vascular resistance, or pressure in large vessels obtained with ultrasound, impedance, or pulsographic methods (12). The concept that the arterial system is “not greatly influenced by direct hydrostatic effects” and is “very sensitive to reflex stimuli arising from changes in blood distribution” (12) has usually influenced the relevant work to be confined to functional studies at certain levels.

**VASCULAR ADAPTATION TO ALTERED LOCAL STRESS CAUSED BY LOSS OF HYDROSTATIC PRESSURE GRADIENTS**

It has been found that all tissues adapt their design when exposed to sustained alterations in local activity...
and/or stress (38, 42, 53). The most obvious example is the musculoskeletal system, the structure and function of which might be severely affected during microgravity exposure (37, 121). Whether the blood vessels are no exception to this universal characteristic of tissues and similar adaptational changes might occur in arterial vasculature during microgravity received relatively little attention in space cardiovascular research. This ignorance might be related to a traditional concept viewing the mature vascular system being a stable structure and not sensitive to hydrostatic effects. In fact, the vascular system is capable of remodeling its structure over a surprisingly short time frame (38, 63, 68, 97). In dealing with the problem of structural response of arteries to sustained hemodynamic changes, two important components of stresses acting on the surface of the vessel should be considered, i.e., the normal stress that blood pressure applies to the vessel wall and the shear stress due to blood flow applied parallel to the endothelial surface. It has been established that any sustained change in arterial pressure or flow may lead to a stimulus-specific remodeling process, resulting in a change primarily in wall thickness or vessel diameter, respectively. The structural autoregulation serves to keep the average circumferential stress (vessel wall tension per unit of wall thickness) to a constant level or shear stress to near-normal levels (38, 63, 68, 97, 103). Furthermore, some vasoactive substances and endothelium-derived relaxing and contracting factors, such as NO, prostacyclin, and endothelium-derived hyperpolarizing factors, as well as contracting factors, seem to be growth inhibitors and/or promoters for smooth muscle cells (SMCs) (113). The expression of genes encoding numerous factors (immediate early response genes and some growth factors) has been shown to be regulated by shear stress or cyclic stretch. The identity of the molecules responsive to mechanical forces suggests also that hemodynamics can influence vascular cell growth (48). Furthermore, perivascular adrenergic and peptidergic nerve fibers may also contribute to the local vascular adaptations, because endothelial cells, SMCs, and perivascular nerves are integrated as a functional entity to accomplish the complex and unified autoregulation of vessels (10, 62, 105, 113). In addition, location, maturity, humoral factors, and response characteristics of vessels are also factors affecting the structural adaptation. Thus the vascular remodeling process appears to be a rather complicated structural change with various types (97, 98). Finally, model studies have shown that the relationship between responses of individual vessels and those of the complete network is complex. The results showed that vascular growth in response to shear stress alone would result in an unstable adaptation under most circumstances. For example, if two parallel vessels are under the same driving pressure, the vessel with lower flow resistance will receive a higher flow fraction and experience a higher level of shear stress. Then the increase of shear stress will trigger an increase of vessel diameter, the flow resistance in this vessel would decrease further, whereas that of the high-resistance vessel would increase. This process would continue until one vessel is completely eliminated and the network turns into a single arteriovenous channel (51). If a response to transmural pressure on vascular structure is considered in addition (“pressure-shear” hypothesis), such unstable adaptive behavior is still not eliminated. It has been demonstrated that adaptation of vascular diameters can yield stable and realistic network structures only if it entails responses to a combination of at least four stimuli, i.e., shear stress, transmural pressure, local metabolic conditions, and a conducted stimulus (102, 103). For these reasons, caution should be exercised when extrapolating data from individual small arteries or arterioles to vascular beds.

In space cardiovascular research, the concept that the smooth muscle of the blood vessel wall may lose tone, strength, and mass in the weightless state was first suggested in 1972 by Bullard (9). This is pure speculation based simply on an extrapolation from the changes of the skeletal muscle. In the late 1980s, on the basis of their studies on circulatory adaptation to gravity in the giraffe and the progress in biomechanics of vessels (42, 43, 53–55, 128), Hargens et al. proposed an important concept to predict the structural adaptation of vessels to microgravity. Terrestrial animals and humans have adapted to a constant force of 1 G over millions of years. Exposed to microgravity, undoubtedly all gravitational blood pressure gradients from head to feet that are associated with upright posture on Earth disappear, and a redistribution of transmural pressures and blood flows across and within the arterial vasculature is induced by the removal of hydrostatic pressure gradients. Therefore, blood vessels in dependent body regions are chronically exposed to lower than normal upright 1-G blood pressure, whereas vessels in upper body regions are exposed to higher than normal 1-G blood pressure. Hargens et al. predicted that the thick-walled arteries in the feet and thin-walled arteries of the head would undergo smooth muscle atrophy and hypertrophy during extended exposure to microgravity. Such adjustments can start within hours after initiation of the stress (42, 43). They further predicted that the vascular adaptation may be more important than early adjustments to microgravity during and after prolonged existence in microgravity (55, 128).

However, experimental animal studies to address the vascular adaptation to microgravity have been rare, and mostly were confined to ground-based functional studies. Before the prediction by Hargens, Dickey et al. (31) had reported a reduced pressor response to norepinephrine and phenylephrine in horizontally casted primates. Later, reduced sympathomimetic-induced pressor response associated with attenuated increase in mesenteric vascular resistance in both head-down and horizontally suspended rats was reported by Overton and Tipton (101). The attenuated pressor responses in both suspension groups can be attributed, in part, to physical restraint associated with the whole body suspension (101). Furthermore,
Simulated microgravity also resulted in a less precise matching of blood flow to muscle oxidative capacity (92, 132). In addition to the work with intact animals, Delp et al. (27, 29) have demonstrated that hindlimb unweighting may also induce reductions in the maximal contractile force of the abdominal and thoracic aortic smooth muscle in rats.

### Vascular Adaptation Observed in Ground-Based Animal Studies with a Rat Model

In the past 5 yr, there has been an increased interest in studies on vascular adaptations using the tail-suspended hindlimb-unloaded rat model. Some studies were designed to clarify whether differential adaptations would occur in vessels from different anatomic regions as a result of prevailing regional hemodynamic conditions (139, 140).

**Structural changes in conduit arteries.** Mao et al. (85) reported morphological changes in large and medium-sized arteries of 4-wk tail-suspended and 1-wk recovered rats. They showed that in the hindquarter arteries, like the femoral and anterior tibial arteries, both the lumen diameter and media CSA of the vessel wall were significantly decreased, whereas in the forebody arteries like the common carotid and basilar arteries, both lumen diameter and media CSA were significantly increased (see Fig. 1). The thickness of media parameter did not show significant changes for the four kinds of vessels among different groups. The results are basically consistent with two relevant papers but with certain discrepancies. Chew and Segal (14) showed that after prolonged (10–14 wk) tail suspension, the internal diameter of femoral arteries was significantly decreased, but no differences were observed for carotid, axillary, and iliac arteries between tail-suspended and control groups. They further reported that the wall thickness for all four kinds of arteries after tail suspension was increased. Wilkerson et al. (131) demonstrated that the media CSA and media wall thickness were increased in the basilar artery and showed no significant changes in mesenteric and splenic arteries after 2-wk tail suspension. These discrepancies may be related to the methods for vessel preparation and proper morphometric protocols. According to Lee et al. (69, 70), to preserve the in vivo morphology and to compare accurately vessel wall dimensions, vessels should be perfusion fixed at a low flow rate and perfusion pressure in a maximally relaxed state and the media CSA parameter instead of wall thickness alone should be used. In the work of Mao et al. (85), the suggestions raised by Lee et al. were adopted. Ultrastructure of vessels also showed differential structural changes (88). For the hindquarter arteries, like the femoral and anterior tibial arteries, a reduction in the number of layers of SMCs, fewer myofilaments in SMCs, and an increased amount of intercellular substance were observed after 4-wk tail suspension compared with that of controls. After 1 wk of recovery, the internal elastic lamina thickened, the amount of myofilaments in SMCs increased, and some neoformative SMCs emerged under the endothelium. With respect to arteries in the neck region and brain, like the common carotid and basilar arteries, an increase in the number of layers of SMCs, hyperplasia, and conversion of SMCs of contractile phenotype into that of synthetic phenotype and migration toward the subendothelial layer were observed. After 1 wk of recovery, the alterations were partially restored, and some synthetic-type SMCs were still present in the subendothelial layer. The adaptational changes in both lumen diameter and media CSA seemed to level off after 4 wk of simulated microgravity. Within the time frame of our experiments, these changes were reversible (see Fig. 1).

**Functional changes in conduit arteries.** Delp et al. (27, 29) demonstrated that maximal isometric contractile tension evoked by both receptor-mediated and non-receptor-mediated vasoconstrictors was lower in abdominal aortic rings from 2-wk tail-suspended rats. Ma et al. (77, 78) and Zhang et al. (145, 146) extended the observation to other conduit arteries from different anatomic regions and showed differential adaptational changes in vasoreactivity after simulated microgravity. For the hindquarter arteries, like abdominal aorta and mesenteric and femoral arteries, the vasoconstrictor responses of the arterial rings to both receptor-mediated and non-receptor-mediated agonists, as well as Ca\(^{2+}\) ionophore A23187, significantly decreased at the end of week 2, further decreased after week 4, and then leveled off at the end of the eighth week of simulated microgravity. The impairment in vasoreactivity was more striking in distal arteries with relatively larger medial area. After release from simulated microgravity, these changes were reversible, with the time for recovery being more prolonged for the more distal vessels. On the contrary, the vasoconstrictor responses of the basilar arterial rings to both receptor-mediated and non-receptor-mediated agonist were significantly enhanced (see Fig. 2). However, Purdy et al. (104) reported that simulated microgravity caused a nearly universal reduction of contractility in arteries. They examined the changes in responsiveness of arterial rings of abdominal aorta, common carotid, and femoral arteries of Sprague-Dawley (SD) and Wistar rats after 20 days of hindlimb unloading (HU). Their results showed that HU treatment decreased the contraction to both 68 mM KCl and norepinephrine in aorta, carotid, and femoral arterial rings from Wistar rats and in aorta and carotid arteries from SD rats; but HU treatment had no significant effect on femoral arterial rings from SD rats. Opposing views may result from the fact that the cerebral arteries were not examined after HU and the carotid arterial rings manifested decreased contractility in their experiment. Contrarily, Ma et al. (77, 78) demonstrated that the vasoconstrictor responses of carotid arterial rings from SD rats did not show any significant change. The reason for this discrepancy is unclear and needs further clarification. In addition to the factor of rat strains, the necessity of determining proper length-tension relationship for each individual vessel ring should be considered be-
cause one cannot assume that the optimal tension of one vessel ring will be the same as in another vessel ring, especially in situations in which the biomechanical properties of the remodeled vessel may be changed due to HU treatment (122; V. Miller, personal communication). However, in the work of Purdy et al. (104) the optimal resting force for each vessel type instead of each individual ring was used.

Because the removal of the endothelial lining did not influence the depression of contractility of hindquarter arteries induced by tail suspension (29, 110), it seems that the depressed vascular responsiveness is mainly due to the decrement in the ability of smooth muscle contractile apparatus to generate force. This may be due to reductions in myofibrillar protein content, calmodulin expression, myosin light-chain kinase activity, and so forth (29, 139, 140). Nevertheless, the contribution of endothelial mechanisms to the simulated microgravity-induced vascular hyporesponsiveness should be further examined with more sophisticated methods to detect subtle changes that may occur. Upregulation of inducible NO synthase (iNOS) expression...
in the thoracic aorta, heart, and kidney and neuronal NOS (nNOS) in the brain and kidney, but no discernible change in endothelial NOS (eNOS) expression in rats after 20-day tail suspension has been demonstrated by Vaziri et al. (123). Furthermore, this up-regulation was associated with a depressed pressor response to epinephrine and an enhanced pressor response to the nNOS-selective inhibitor aminoguanidine. With respect to cerebral vessels, Zhang et al. (146) provided evidence indicating that after simulated microgravity the enhanced contractile responsiveness of basilar arterial rings to 5-hydroxytryptamine is due to the inability of the endothelium to release an endothelium-derived hyperpolarizing factor-like substance. It is intriguing that similar impairment in endothelial function has been observed in basilar arteries of spontaneously hypertensive rats (135).

Reported changes in vasodilatory responsiveness after simulated microgravity are inconsistent and not as evident as those in response to vasoconstrictors. With respect to hindquarter arteries, Delp et al. (27) reported that hindlimb unweighting and aging both resulted in a decreased dilatory responsiveness to ACh in abdominal aorta. They further suggested that this compromised responsiveness may reflect alterations in the cGMP-mediated dilatory mechanism within SMCs (27). Vasodilatory responsiveness to isoproterenol in the presence of phentolamine was decreased in femoral but not in common carotid, abdominal aortic and mesenteric arterial rings after 8-wk tail suspension (79). With respect to cerebral arteries, Zhang et al. (146) did not find any significant change in dilatory responsiveness of basilar arterial rings to vasodilators, like ACh, thrombin, adenosine, and sodium nitroprusside. Taken together, changes in vasodilatory responsiveness induced by simulated microgravity need further clarification.

Structural and functional changes in small arteries and arterioles. The adaptational changes in conduit arteries do not necessarily reflect those in resistance vessels. It is evident that differential adaptations also occur in resistance vessels. For example, Geary et al. (47) showed that simulated microgravity resulted in an increase in myogenic tone and a greater vasomotion of rat middle cerebral arteries. They also found that the enhanced myogenic tone was due to a downregulation of NO-dependent vasodilatory mechanism and changes in regulatory mechanisms intrinsic to the vascular smooth muscle. In contrast, Looft-Wilson and Gisolfi (76) showed that myogenic tone in small mesenteric arteries was attenuated after simulated microgravity in rats.

Likewise, other investigators have examined functional and structural changes of isolated feed arteries and arterioles dissected from hindlimb muscles of simulated microgravity rats. Delp (26) demonstrated that HU does not uniformly affect the resistance vessels in different skeletal muscles. HU diminished the myogenic autoregulatory and contractile responsiveness of arterioles from muscle composed predominantly of fast-twitch type IIB fibers (white gastrocnemius). In contrast, HU did not affect vasoconstrictor or myogenic responsiveness of arterioles from muscle composed of slow-twitch type I fibers (soleus), but it did induce remodeling changes, as indicated by a decrease in the maximal diameter of arterioles. However, there were no significant changes in internal diameter of small mesenteric arteries after 28-day tail suspension (76).

Recent studies have also provided information regarding the adaptational changes in vasodilatory responsiveness of resistance vessels in hindlimb muscles after simulated microgravity. Jasperse et al. (61) showed that HU attenuated flow-induced vasodilation and decreased maximal dilation to ACh in rat soleus feed arteries. Furthermore, this was associated with a reduced expression of eNOS mRNA and eNOS protein, suggesting an attenuated endothelium-dependent vasodilation. They further showed that the impaired ACh-induced vasodilatory responsiveness associated with a downregulation of eNOS expression also occurred in rat soleus 1A arterioles after simulated microgravity (112). In addition, the relative contribution of NO (NOS) and PGI2 (cyclooxygenase dilator pathway) in ACh dilation may also be altered by HU (112).

McCurdy et al. (91) provided evidence supporting the concept that dilatory responsiveness of arterioles varies in muscles composed of different fiber types. They reported that HU had no effect on vasodilatory responses induced by isoproterenol but diminished the maximal dilatory responses elicited by adenosine and sodium nitroprusside in 1A arterioles from both muscles. However, maximal dilation induced by isoproterenol and adenosine was greater in arterioles from white gastrocnemius than from soleus muscles. Collectively, these results suggest that the inability to adequately elevate peripheral vascular resistance might be due to the lowered vasoconstrictor responsiveness and myogenic activity but not the result of an enhanced vasodilatory responsiveness of the skeletal muscle resistance vasculature. However, microgravity-induced reductions in aerobic capacity may be related to the diminished vasodilatory responsiveness and capacity of skeletal muscle arterioles (92, 132) and the decreased maximal conductance in exercising muscle (18, 34).

Two relevant studies demonstrate that structural adaptation of resistance vessels occurs in skeletal muscle of the simulated microgravity rat, apparently as a result of changes in local hemodynamic conditions. Delp et al. (28) showed that the media CSA of feed arteries and 1A arterioles from both the gastrocnemius and soleus muscles was diminished after 2-wk HU, whereas the media CSA of the feed artery from the forelimb triceps brachii muscle was unaltered. They further suggested that these alterations are apparently remodeling changes due to reductions in transmural pressure and shear stress in the resistance vessels in hindlimb skeletal muscles. Mao et al. (84, 86) reported that, after 4-wk tail suspension, the lumen diameters of the feeding arteries, arcade arterioles, and the transverse arterioles of order V and II in the arteriolar network of rat soleus muscle decreased (the
Differential plasticity of perivascular innervation.
Recent discoveries on interactions that occur between classes of perivascular nerves and the trophic influence of perivascular nerves on vessel wall highlight the possible important role of them in vascular adaptation to microgravity (10, 105, 113). Mao et al. (82, 87) have shown that simulated microgravity-induced changes in the density and morphology of adrenergic (norepinephrine-containing) and peptidergic (neuropeptide Y- and calcitonin gene-related peptide-containing) nerve fibers around small arteries and arterioles from different anatomic regions are quite different (see Fig. 4). In the hindlimb muscles, the three kinds of nerve fibers around the small arteries and arterioles were in a state of hypoinnervation during simulated microgravity followed by a state of hyperinnervation during recovery. These fibers were thinner and pale in staining and the fiber densities significantly declined in 4-wk suspended rats, whereas they were thick and dark with their swellings clearly discernible and their densities significantly increased after 1-wk recovery (82). In contrast, hyperinnervation of the adrenergic and neuropeptide Y-, calcitonin gene-related peptide-, and substance P-containing nerve fibers around the main cerebral arteries during simulated microgravity followed by hypoinnervation during recovery were observed. In 4-wk simulated microgravity rats, all these nerve fibers were clear, thick, and deeply stained and their fiber densities significantly increased, whereas in 1-wk recovered rats, they became dim and discontinuous in appearance (87). These data indicate that both the perivascular adrenergic and peptidergic innervation are quite sensitive to local hemodynamic changes during simulated microgravity as well as during recovery, and the adaptive plastic changes may occur rapidly. Furthermore, significant increase in adventitial nerve density of saphenous artery and vein in chronic +45° head-up tilted rats (94) and increased quantity of innervation in small arteries in spontaneously hypertensive rats (97) also suggest that increased local transmural pressure is associated with hyperinnervation of vessels. It is suggested that in addition to their role in regulating vascular tone and responsiveness, for example via the venoarteriolar axon reflex (58), perivascular nerves may also have a trophic influence in modulating the local vascular remodeling process during both microgravity and readaptation to normal gravity. However, a ground-based human study showed that the local venoarteriolar vasoconstrictor response in the foot skin was still preserved after 20 days of bed rest (45).

Other aspects of differential adaptation. Using radio-labeled microspheres, Colleran et al. (15) demonstrated that simulated microgravity differentially alters the perfusion to the fore and aft skeleton and that such alterations correspond to local changes in bone mass. HU rapidly diminished blood flow to femoral and tibial metaphysis and diaphysis and the femoral marrow. Prolonged unloading further decreased the perfusion due to increases in vascular resistance. In contrast, HU acutely elevated blood flow to the humerus, clavicle, mandible, and skull. The decline and increase in blood flow may provide a stimulus for altering the balance between bone resorption and bone formation during simulated microgravity. These results are in accordance with earlier findings from rats flown on COSMOS 1887 (32), which showed smaller media CSA...
of vessel wall and signs of endothelial degeneration in blood vessels on the periosteal surface of the tibial diaphysis.

It is important to elucidate whether simulated microgravity differentially alters the expression of heat shock proteins (HSPs) in arteries of the fore and hind body regions because vascular SMCs produce a high level of HSPs to protect the host from damage during hemodynamic stress (134) and HSPs might influence the process of vascular remodeling via their effects on vascular SMC apoptosis and proliferation in response to hemodynamic stress (133). Liu et al. (74) reported that after 4 wk of simulated microgravity both the level of HSP72 mRNA and the amount of HSP70 induced by a heat stress significantly increased in the rat basilar arteries, whereas in the femoral arteries, expressions for both HSP72 mRNA and HSP70 showed only trends for decrease.

The shape and alignment of the endothelial cells may reflect the direction of blood flow and the shear stress imparted by the flowing blood on the endothelial surface (100). Using the en face preparation, Mao et al. (83) showed differential changes of such parameters in arteries from fore and hind body regions after simulated microgravity. In the femoral arteries, the length and width of the endothelial cells decreased and increased, respectively, in rats exposed to 4-wk simulated microgravity and returned to their control level after 1-wk recovery. Contrarily, in the common carotid arteries, the length and width of the endothelial cells increased and decreased, respectively, during simulated microgravity and were restored after 1-wk recovery (see Fig. 5).

Evidence from studies with perfused vascular beds and intact animals. In addition to the aforementioned integrative studies with intact animals (31, 92, 101), recent studies have provided further evidence suggesting the prime importance of the altered intrinsic characteristics of resistance vessels in the mechanism responsible for the postflight orthostatic hypotension. This inability to adequately increase peripheral vascular resistance could be due to depressed sympathetic stimulation and/or decreased vascular responsiveness. There is evidence of decreased baroreflex-mediated lumbar and renal sympathetic nerve activity in rats after simulated microgravity (93). Rodionov et al. (106) reported that vasoconstrictor responsiveness of perfused hindlimb to direct electric stimulation of sympathetic chain was attenuated in rats after 3 wk of simulated microgravity. Furthermore, the pressor responses of isolated perfused hindlimb and mesenteric vascular beds to various agonists decreased in rats.
and flows within the arterial vasculature may well initiate differential adaptations of vessels in different anatomic regions. However, direct measurements to characterize the prevailing hemodynamic and local stress conditions are rare. Experimental data have indicated a decreased blood flow in the hindquarter arteries of suspended rats (92, 107). It is estimated that HU decreased flow through the rat abdominal aorta by \( \sim 23\% \) (29, 92). Data concerning the changes in blood flow of cerebral arteries in rats during simulated microgravity, on the other hand, are scarcer. Changes in geometry of endothelial cells in en face preparations of the common carotid arteries have suggested an increased blood flow to the head region during simulated microgravity (83). Whether this is due to an increase in the extracranial blood flow with cerebral blood flow unchanged remains to be clarified. Data obtained by direct measurement for cerebral blood pressures during simulated microgravity in rats are lacking. However, it is estimated that the mean blood pressure in the basilar artery would be increased by \( \sim 17 \) mmHg during tail suspension compared with standing (131).

Existing data concerning hemodynamic changes in human cerebral circulation during both bed rest and real microgravity are fewer and inconclusive (12, 55, 128). Hypothetically, because microgravity elevates cerebral arterial pressure relative to upright 1-G conditions, autoregulation should increase vascular resistance to hold blood flow relatively constant (55, 128). A study showed that blood flow velocity in the middle cerebral artery increased for at least 6 h after the onset of \(-6^\circ\) HDT in humans (66). Results for long-term effect of microgravity on cerebral blood flow vary (128). Whether brain edema does occur during simulated microgravity (65, 114) remains to be elucidated.

Changes in transmural pressures during simulated microgravity are complex, because the cerebral vessels are surrounded by cerebrospinal fluid (CSF), exerting a hydrostatic force outside of the cerebral vessels (108). Hypothetically, during microgravity, removal of hydrostatic pressure gradients would induce changes of similar magnitudes in both vascular and CSF pressures. Thus the change in transmural pressure across cerebral arterial vessels would be greatly minimized. Elevation of intracranial pressure during simulated microgravity has been shown experimentally in rats (90), rabbits (114), monkeys (67), and humans (99). However, the nature of the adaptational changes in cerebral vessels during simulated microgravity (46, 47, 85, 88, 131, 139, 146) strongly suggests a sustained elevation of transmural pressures in the cerebral arterial vasculature. This discrepancy may be related to factors, like a somewhat elastic nonrigid nature of the CSF container (108), reduced CSF production (89), and so on. Lack of counterpressure exerted by the fluid in the extravascular spaces surrounding the vessels in the lower/hind body part may be due to extravascular fluid that does not form a continuous column (108). In brief, initiating factors leading to differential adaptations of vessels to microgravity should be further de-

![Image](http://jap.physiology.org/)

**Fig. 5.** Photomicrographs of en face preparations showing differential changes in the geometry of endothelial cells in rat common carotid and femoral arteries after 4-wk simulated microgravity. Arrow indicates the direction of blood flow. Scale bar, 40 \( \mu \)m. For common carotid arteries, average length and width of the endothelial cells increased and decreased by 10 and 24\%, respectively, in Sus-4 compared with that in Con rats. Contrarily, for femoral arteries, length and width decreased and increased by 10 and 45\%, respectively, in Sus-4 compared with Con. These changes were basically restored after 1-wk recovery (Rec-1) [cited from Ref. 83 with permission].

After 2 wk of simulated microgravity (80, 144). Under resting conditions in conscious, freely moving rats, half the mesenteric vascular resistance resides outside the intramural circulation, primarily in the arcade small arteries (36). However, data concerning effects of simulated microgravity on these small vessels are still lacking. In addition, the relative importance of changes in splanchnic venoconstriction mechanism should be further clarified. The splanchnic venous bed is the largest vascular region in terms of capacitance, and animal studies have shown that splanchnic veins are very responsive to baroreceptor-mediated sympathetic stimulation (57). Relevant studies have shown that simulated microgravity in rats results in an attenuated contractile response of the vena cava (111) and mesenteric small veins (33).

**Local hemodynamic changes that may initiate differential adaptation of vessels.** The findings thus reviewed substantiate in general the hypothesis that the microgravity-induced redistribution of transmural pressures

---

**INVITED REVIEW**

**J Appl Physiol • VOL 91 • DECEMBER 2001 • www.jap.org**

---

2024 INVITED REVIEW
fined by experimental studies and modeling with computer simulations (49).

Collectively, although most of the results are fairly clear-cut in indicating differential adaptation of arterial vasculature to local prevailing hemodynamic conditions during simulated microgravity, caution should still be exercised in interpreting these data. Discrepancies should be further clarified by appropriate experimental design and by using adequate methods under precisely controlled conditions. For example, the reliability of studies on structure and function of vessels depends on the methods of vessel preparation and the morphometric protocols used (69, 70), and the proper determination of the apex of the length-developed tension relationship ($L_{\text{max}}$) for each individual vessel ring (122; V. Miller, personal communication). The modes of remodeling changes, detailed cellular basis, and stress-remodeling relationship and its association with the molecular events during the process of differential adaptation need further studies (48, 75, 97, 98). The pivotal mechanisms underlying the differential adaptive changes in vasoreactivity remain unclear (26, 29).

To understand the overall adaptation of resistance vasculature, detailed knowledge of changes in the geometric and topological parameters of the arteriolar networks, the local autoregulatory function of the vascular beds, and the integrated response of the resistance vasculature is needed (6, 51, 102, 103). Finally, the question of whether prolonged microgravity exposure may lead to similar structural and functional adaptations in arterial vessels in the human body needs attention. In vascular biomedicine, many important conclusions are drawn from experimental studies with rodents. Folkow (38) postulated that locally induced vascular structural adaptation in rats can be largely completed within 2 wk and in humans within a few months, presumably reflecting the five- to sixfold lower metabolic rate. Furthermore, the difference in gravitationally dependent distribution of blood volume between the human (biped) and the rat (quadruped) (108) does not influence the applicability of the HU rat model to simulate the redistribution of transmural pressures across the arterial vessels in the human body during microgravity. Nevertheless, this review is just to emphasize the significant gaps between findings on vascular adaptations from experiments with the HU rat model and that observed from ground-based and spaceflight human studies with an attempt to stimulate new concepts on what can be done to narrow or fill some of them.

PERIPHERAL EFFECTOR MECHANISM HYPOTHESIS AND GRAVITY-BASED COUNTERMEASURES

On the basis of the findings from relevant ground-based and spaceflight studies reported recently, it has been speculated that, in addition to hypovolemia, the microgravity-induced adaptational changes in the structure and function of the two main effectors of the cardiovascular system, i.e., the arterial smooth muscle and the cardiac muscle, might be among the most important mechanisms responsible for postflight cardiovascular dysfunction and orthostatic intolerance. The term “peripheral effector mechanism” is used to imply that the vascular SMCs, endothelium, and perivascular nerves are integrated as a functional entity to accomplish the complex and unified structural and functional autoregulation (62, 105, 113, 137, 139, 140, 142; with respect to adaptational changes in the heart muscle, the reader is referred to Refs. 72, 136, 141, and 142). Hypothetically, when astronauts return to 1-G environment, the microgravity-induced down- and upregulation in resistance vasculature of the lower body and brain may act synergistically in the development of postflight orthostatic hypotension with compromised cerebral perfusion. Microgravity-induced adaptational changes in cardiac muscle and heart might be responsible for the excessive reduction in stroke volume during orthostasis (4, 16, 18, 72, 136, 141), and significant reductions in cardiac output, maximal oxygen uptake, and endurance during upright exercise postflight (3, 4, 120, 128, 132). A preliminary computer simulation study has thus been attempted to integrate the experimental results and to reveal discrepancies between experimental results and theoretical predictions (52). The understanding of the physiological mechanisms involved in the adaptation of vessels to microgravity is also important for the development of multisystem countermeasures.

The search in the last four decades for effective countermeasures to prevent or alleviate the adverse effects of microgravity has met with limited success (16–18). The reason for the limited success of exercise-based countermeasures in preventing or alleviating cardiovascular deconditioning might be that the initiating factors leading to the structural and functional adaptational changes in the vascular smooth muscle are the sustained alterations in the vascular local stress conditions caused by altered distribution of pressures and flows within the vasculature during microgravity that cannot be restored to their 1-G level by exercise alone. Moderate effectiveness of present exercise-based protocols has led to a number of additional proposals to apply missing gravitational stimuli during exercise (17). For example, Hargens and co-workers (55, 56, 128) proposed the use of treadmill exercise within an LBNP chamber to provide muscle-skeletal stresses similar to gravity as well as Earthlike transmural pressures across blood vessels of the lower body during long-duration spaceflight. However, LBNP treadmill exercise does not provide Earthlike distribution of transmural pressures across the cerebral vessels. Whether this may affect the effectiveness of this countermeasure remains unknown. The reason why repeated use of thigh cuffs over the 6-mo Mir spaceflight did not prevent the development of orthostatic intolerance (59) might be that the thigh cuffs can only create a more Earthlike fluid distribution (73), but not the normal distribution of transmural pressures across the arterial vasculature. Recently, integrating LBNP with respiration at negative pressure has been proposed as countermeasure to restore the normal gradi-
ments of blood pressure along the body axis during microgravity (2). In addition, the effects of a single bout of intense exercise in counteracting the cardiovascular dysfunction after HDT reported by Convertino and his colleagues (16, 17, 23, 35) should also be mentioned. Orthostatic tolerance was maintained at pre-HDT levels when subjects performed acute intense exercise 24 h before returning to the upright posture after 16 days of –6° HDT (23, 35). Interestingly, this maintenance was associated with restoration of plasma volume and peak vascular conductance, increased plasma levels of norepinephrine, greater FVR, and enhanced carotid baroreceptor-HR reflex responsiveness (23, 34, 35). Understanding the mechanism of this exercise countermeasure is of special interest because of its relevance to the peripheral effector mechanism of the cardiovascular system (142). The possibility that maximal aerobic exercise may provide an overall hemodynamic condition and tissue stress distribution for the vessels and cardiac muscle needed to stimulate the restoration of blood pressure regulation merits further consideration. Although this exercise countermeasure has demonstrated some protective effect in spaceflight (95), its effectiveness in preventing or alleviating adverse effects for a multitude of physiological systems after long-term spaceflight remains to be elucidated. Many investigators agree that artificial gravity may ultimately be required during long-duration manned space missions (11, 115, 117, 138). Recent studies have shown that continuous exposure to gravity does not appear necessary to prevent the adverse effects of microgravity (124–126). Vil-Viliams et al. (126) reported the effectiveness of using short-arm centrifuge runs at +Gz (positive, footward G) acceleration as a countermeasure against the deconditioning of subjects induced by bed rest or dry immersion. Vernikos et al. (124, 125) reported that 1-G intermittent exposures with and without walking exercise were effective in preventing physiological deconditioning with 4-day –6° head-down bed rest and that 2 h/day standing might be sufficient to prevent orthostatic intolerance. The tail-suspension rat model has also been used to assess the effectiveness of intermittent gravitation of various protocols in counteracting the simulated microgravity-induced adverse effects on muscles and bones (37). It is surprising that the vasoreactivity of both the basilar and femoral arterial segments was also responsive to the daily intermittent gravitation (137, 143). An exposure as short as 1 h/day of –Gz, (back to chest G) by standing was sufficient to prevent their up- and down-regulations in contractile function during simulated microgravity. On the other hand, 4 h/day of standing or 6 h/day head-up tilt was required to prevent the mass reduction of soleus muscle. The indexes of the bone mass and mechanics were more resistant to these treatments, with 4-h/day of standing or head-up tilt being partially effective in preventing the adverse bone changes. Furthermore, the treatments with daily intermittent gravitation were also effective in preventing vascular remodeling changes (L. N. Zhang et al., unpublished results). Nevertheless, further studies are needed to define the minimum gravitation and exposure time requirements for a multitude of organ systems for practical purposes and to clarify the “memory mechanisms” (124) that can be triggered by a surprisingly short intermittent daily gravitation exposure to maintain the 1-G homeostasis of the vessels.

SUMMARY AND FUTURE DIRECTIONS

Over the past 5 yr, ground-based animal studies have demonstrated differential adaptations in the structure and function of the cerebral and hindquarter arterial vessels of rats after simulated microgravity. Furthermore, these findings have also been on the whole consistent with the data obtained from space animal research and ground-based and spaceflight human studies. Evidence is mounting that, in addition to hypovolemia, the peripheral effector mechanism might be among the most important mechanisms responsible for postflight cardiovascular dysfunction and orthostatic intolerance. However, multidisciplinary studies focusing in greater depth are needed to better define the changes in the prevailing local hemodynamic conditions and physical stresses that may initiate the differential adaptations in the fore and aft vessels in the microgravity environment, to elucidate the adaptational process in vessels at cellular and molecular levels, to better characterize the structural and functional adaptation of microvascular networks, and to understand the physiological implications and ultimate possible pathological consequences of the adaptational changes in the vessels over long-duration microgravity exposure. It is also important to extend the observation with primates and humans using innovative noninvasive techniques in future ground-based and International Space Station researches to fill the gaps in our knowledge. Finally, these studies may lead to a universal theory to explain microgravity-induced cardiovascular deconditioning, muscle atrophy, and bone loss as tissue response to altered local stress, providing the physiological basis for the development of multisystem countermeasures and the ultimate use of artificial gravity, such that the exploration of Mars can become a reality.

I thank my co-workers, Drs. Yu Zhi-Bin, Ma Jin, Mao Qin-Wen, and Zhang Le-Ning, and my present graduate students, who have, by argument and experiment, aided me in learning about vascular adaptation to microgravity. I am particularly grateful to Dr. A. R. Hargens for helpful comments during the preparation of the review. My thanks are also due to Dr. Wang Shou-Yan and to Feng Han-Zhong and Sun Biao who helped me to prepare this manuscript. This work was supported by the National Natural Science Foundation of China (Grant nos. 39380021, 39670800, and 39800157) and the Defense Medical Fund (Grant no. 98Z083).

REFERENCES

2. Baranov VM, Tikhonov MA, Kotov AN, and Kolesnikov VL. Some mechanisms of modeling the hydrostatic component of


