The following is the abstract of the article discussed in the subsequent letter:

Zhang, LF. Invited Review: 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.

Vascular Adaptation to Microgravity: Extending the Hypothesis

To the Editor: The review by Dr. Zhang (10) on vascular adaptation to microgravity brings clarity to what has been a confusing field. Dr. Zhang has pointed out that vasoconstriction plays a critical role in the maintenance of blood pressure in the standing position. Moreover, it is generally accepted that the global effect of microgravity on the vasculature is a reduction in vasoconstrictor capacity. This was shown in astronauts by Buckey and co-workers (1), who found that a decreased vasoconstrictor response was the singular hemodynamic characteristic that distinguished those who could not complete a postflight stand test.

The confusion in the field arises from the observation of disparate effects of microgravity on individual blood vessels. For example, studies of vessels from rats subjected to simulated microgravity (hindlimb suspension) have revealed both increases and decreases in 1) vasoconstrictor capacity, 2) myogenic tone, 3) medial cross-sectional area, and 4) lumen diameter, depending on the vessel studied (see Ref. 10).

Dr. Zhang (10) proposed what may become a unifying hypothesis to explain the disparate effects of microgravity in the vasculature. He points out that microgravity produces a nonuniform redistribution of transmural pressures and flows throughout the arterial vasculature and that this may well initiate differential adaptations among blood vessels. For example, in the hindlimb-suspended rat, blood pressure and/or flow may be decreased in the hindquarters and increased in the forequarters. Dr. Zhang and his colleagues (8) found that lumen diameters and medial cross-sectional areas were decreased and increased in hindquarter and forequarter arteries, respectively. In addition, in a hindquarter vessel (the femoral artery), Dr. Zhang’s laboratory (7) and our laboratory (9) found that hindlimb suspension impaired vasoconstrictor response.

Dr. Zhang refined his hypothesis further by suggesting that local vascular changes are stimulus specific; i.e., vessels experiencing a change in distending pressure or shear stress will respond with a change in wall thickness or vessel diameter, respectively. Both stimulus-response relationships were confirmed by Delp and colleagues (3), who studied the gastrocnemius vs. the soleus feed arteries in hindlimb-suspended rats, respectively.

Dr. Zhang’s hypothesis raises the possibility that the microgravity-induced structural changes in arteries could underlie, in part, the impaired vasoconstrictor responses. We believe his hypothesis can be extended to cover impaired functional responses occurring in the absence of structural change. Hindlimb suspension impairs vasoconstriction in the rat abdominal aorta but has no effect on vessel diameter, wall thickness, and wet or dry weight (2, 9). Our laboratory has found that certain second-messenger signaling pathways mediating vasoconstriction are impaired in aortas from hindlimb-suspended rats. In particular, the contribution of Src (5) and p38 mitogen-activated protein kinase (p38 MAPK; Ref. 6) to vasoconstriction is abolished after hindlimb suspension. Moreover, hindlimb suspension reduces Src protein expression in aorta by 50%. Src and p38 MAPK are, respectively, early and late signaling molecules linking both G protein-regulated and integrin receptors to the phosphorylation of heat shock protein 27 (HSP27). In turn, phosphorylation of HSP27 removes the HSP27-mediated inhibition of actin assembly, contributing to vascular contraction (4). We propose that the reduced pressure in abdominal aorta seen with hindlimb suspension (see Ref. 10) causes a sustained reduction in vascular smooth muscle integrin receptor stimulation. In turn, we hypothesize that this could lead to the decreased function of Src and p38 MAPK and the decreased expression of Src. This means that these signaling molecules would also be unavailable to mediate G protein receptor stimulation in vessels from hindlimb-suspended rats. We offer this extension of Dr. Zhang’s hypothesis as a fruitful area for future research.
REFERENCES


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REPLY

To the Editor: Thank you for the opportunity to respond to the letter by Drs. Purdy and Kahwaji in reference to my review article (4).

Differential adaptational changes in structure and function of conduit and resistance arteries from different anatomic regions of simulated weightless rats, first reported by our group (5), are not only in accord with the prediction made by Hargens et al. (3) but are also confirmed by findings from other laboratories (1, 2). Furthermore, these findings have also been on the whole consistent with the observations in ground-based and spaceflight human studies (3, 4). It is speculated that microgravity-induced downregulation and upregulation in resistance vessels of the hindquarter (including the splanchnic region) and brain, respectively, may act synergistically in the development of postflight orthostatic hypotension with compromised cerebral blood flow. Therefore, in my review paper (4), extending the observation with primates and humans using innovative noninvasive techniques was suggested.

Nevertheless, to elucidate the cellular and molecular mechanisms accounting for the differential adaptation of vessels is certainly of importance. In this respect, studies aimed at elucidating the changes in Src and p38 MAPK expression in the abdominal aortic tissue due to simulated microgravity will certainly enhance our understanding of the mechanism underlying the depressed vasoreactivity. I sincerely hope that this study could also be extended to cerebral vessels. Finally, I would like to point out that the functional and structural adaptations are interrelated and integrated as a whole. Minute changes involved in vascular structural adaptations perhaps cannot be detected from changes in gross morphological parameters of the vessels. Experiments to elucidate the adaptational process in vessels at cellular and molecular levels are also ongoing (6). Let us each do our part to enhance our understanding of vascular adaptation to microgravity.

REFERENCES


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