CARDIOVASCULAR ADJUSTMENTS to real or simulated microgravity appear to be appropriate adaptations as long as the microgravity environment is maintained. It is when the subject returns to 1 G that problems with these adjustments arise.

Rat models simulating microgravity use head-down tilt (HDT), where the rat ambulates on its forelimbs while suspended from its tail (see Fig. 1). This model provides two fundamental changes that occur in human spaceflight, namely a cephalic fluid shift and muscle atrophy of the locomotor muscles in the hindlimbs (3, 16, 17, 19). When these rats resume four-legged posture, they exhibit some similarities to, as well as some differences from, humans returning from spaceflight or experiencing bed rest. Rats and humans both experience reduced exercise capacity (12, 19), and rats and some humans demonstrate an inability to maintain blood pressure (BP) during an orthostatic challenge (orthostatic intolerance; OI) (2, 7, 9, 18). Do these two earthly shortcomings share a common vascular mechanism?

After HDT, exercise cardiac output is reduced, and it is abnormally redistributed (10, 19). Specifically, skeletal muscle blood flow is reduced and the splanchnic bed is overperfused. Excess splanchnic blood flow can be explained by a reduced adrenergic vasoconstriction of mesenteric arteries (1, 11). Many arteries, both conduit and resistance, exhibit blunted vasoconstrictor responsiveness following HDT (3, 4, 13). A notable exception are cerebral arteries, which we will visit again later.

What about the role of the venous circulation in HDT cardiovascular dysfunction? Reduced venoconstriction should again later.

What has been lacking in this field is direct evidence for poor venoconstriction, along with a viable, testable mechanism that evokes weak venoconstriction and might contribute to poor cardiac filling.

In their study in the Journal of Applied Physiology, Delp’s group (1) provides with food for thought, not only with regard to new studies of veins, but also a better integrative picture of the physiological stimuli during HDT that evoke vascular dysfunction.

Using classic microcirculation techniques in isolated vessels, Behnke et al. (1) study both vaso- and venoconstrictor properties in Sprague-Dawley rats following 14 days of HDT. Several key findings are of note. First, mesenteric (~250 μm) arteries clearly show blunted vasoconstriction to NE following HDT. Second, mesenteric veins (~240–250 μm) from HDT rats exhibit impaired constriction to increased luminal pressures, even in a scenario with “maximal” (10⁻⁴ M) NE stimulation as background. Third, impaired vaso- and venoconstriction occurs without structural changes observed in many other vascular beds (smooth muscle atrophy, altered diameter). A fourth, Behnke and colleagues (1) report increased levels of atrial natriuretic and brain natriuretic peptides (ANP and BNP, respectively). Most importantly, they use ANP and BNP acutely to mimic the chronic effects of HDT on mesenteric vascular dysfunction and provide a novel mechanism for microgravity-induced vascular changes.

The impaired vasoconstriction of mesenteric arteries seems to fit well with reports of diminished adrenergic vasoconstriction in arteries including aorta, femoral, carotid, and some skeletal muscle arterioles (3, 4, 13). The exceptions to this rule are cerebral arteries, which show enhanced constriction after HDT (6, 18, 20). Classically, the explanations for these divergent findings are pressure and flow differences in relation to the hydrostatic indifference point. Interestingly, arteries “above the heart,” like cerebral arteries, encounter large fluid and BP stimuli during HDT and exhibit vascular wall hypertrophy and...
enhanced vasoconstrictor properties (6, 17, 18, 20). Conversely, many hindlimb muscles experience low blood flow (shear) (10) and low BP during HDT, and arteries exhibit reductions in diameter and smooth muscle content (and impaired constriction) (4, 13) (see Fig. 1). With no evidence of structural remodeling in mesenteric arteries or veins (1, 8), it is unlikely smooth muscle atrophy is the culprit for lack of constriction. Moreover, splanchnic blood flow is not altered during HDT (10). These observations raise the question, what are the stimuli for blunted mesenteric vas- and vеноconstriction?

The novel findings of decreased venoconstriction and increased ANP and BNP in plasma of HDT rats are thought provoking. The study of Behnke et al. (1) is the first report of how HDT might alter BNP levels and tilts the literature slightly in favor of ANP influencing vascular function (2 studies show increased, 1 shows decreased, and 1 shows no change in ANP with HDT or bed rest). While these peptides are known to reduce smooth muscle contractile function by interfering with protein kinase C and inositol 1,4,5-trisphosphate, the increased peptides alone are a weak explanation for the present findings. However, Behnke et al. (1) take the next step and use acute exposure of ANP or BNP of mesenteric arteries and veins in vitro. As hypothesized, both small vessels exhibit markedly reduced constriction to NE after only a 20-min incubation with ANP or BNP. Taken together, the authors used a systemic change in two peptides to mimic the anemic constrictor responses in mesenteric arteries and veins, providing convincing support for a novel systemic HDT stimulus (1). This is the first study that does not rely on local, tissue-specific changes in blood flow or BP during HDT to evoke vascular dysfunction on return to a 1-G environment. Of course, ANP and BNP are excluded from the cerebral circulation by the blood-brain barrier. Is this further evidence why nearly all peripheral arteries exhibit impaired adrenergic constriction, while the cerebral arteries are spared (or even enhanced from increased BP stimulus)? It appears this newly discovered systemic factor is not quite systemic after all.

What questions remain? First, why do vessels from HDT rats, which presumably were exposed to the peptides for up to 14 days, show impaired constriction without ANP or BNP in the bathing solution, but the peptides can impart dysfunction after only 20 min in control rat vessels? Future studies are needed to determine the acute vs. chronic effects of these peptides, as well as the signaling cascades involved. Second, do astronauts who exhibit OI show increased ANP or BNP levels, and if so, what is the time course? Third, what other hormones may be changing in microgravity that might impart vascular consequences? Can any of these systemic circulating “factors” cross the blood-brain barrier and influence the cerebral circulation, possibly exacerbating OI? Fourth, are any pharmacological interventions available to counteract the smooth muscle effects of ANP and BNP?

The functional consequences of blunted vеноconstriction and thus functionally increased venous capacitance are potentially large, given the related observations of OI and exercise intolerance, both of which appear to be associated with lack of splanchnic vеноconstriction and poor maintenance of stroke volume during stress (14, 15). Delp’s laboratory is acknowledged for a rich tradition in physiological studies of vascular function from “head to tail” in the HDT rat model. Their studies are innovative and have consistently showed the complexity of changes in cerebral, skeletal muscle, and mesenteric circulations, traditionally attributed to the fact that shifts in pressure and/or flow are driving the changes in a tissue-specific manner. Behnke et al. (1) should be commended for exploring new ideas regarding mechanisms that work in HDT in a systemic manner. These new data on ANP- and BNP-mediated vascular dysfunction offer inspiration for research design in future studies examining novel ideas for the physiological stimuli during real or simulated microgravity.

REFERENCES