

Does altered blood flow to bone in microgravity impact on mechanotransduction?

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Dramatic fluid shifts occur within minutes of arriving in microgravity and have a major impact on astronaut cardiovascular function and general comfort. Whether nutrient blood flow to bone exhibits similar shifts during spaceflight in humans is largely unknown. Quantifying blood flow precisely requires invasive methods, restricting these inquiries to appropriate animal models.

The tail suspension (or hindlimb unloading [HU]) model in rodents is well accepted as the best small animal model for simulating microgravity effects on cardiovascular outcomes as well as musculoskeletal changes in the unweighted hindlimbs¹. The elevated hindlimbs are free to move but cannot bear any weight. Importantly, the head-down posture of the tail-suspended rat also induces the headward fluid shifts observed in bipedal humans during spaceflight. HU is unique among rodent "immobilization" models in this respect. Using radiolabelled microsphere injections to quantify blood flow, studies from the laboratory of Michael Delp have produced invaluable data on blood flow to unweighted as well as normally weight-bearing bones in adult male rats exposed to 10 minutes, 7 days or 28 days of HU². By simultaneously measuring aortic and caudal arterial pressures, one can determine whether changes in blood flow are due to changes in resistance in a vascular bed or to reduced perfusion pressure or, possibly, to both.

Within 10 minutes of assuming the head-down posture of tail suspension, blood flow is significantly reduced to all but the distal ends of the femur and tibia (Figure 1). These reductions are not transient but maintained after 7 days and, in the case of femoral shaft and marrow, even greater after 28 days of HU. Reductions in blood flow to the distal femur

reach statistical significance by 7 and 28 days HU, but there are no significant changes in flow to the distal tibia. Because caudal arterial pressure does not change with 10 minutes or 7 days of HU, the reduced blood flow at these time points is due to increased vascular resistance (vessel constriction). Interestingly, vascular resistance increases further after 28 days in the femoral shaft but not in marrow; hence the greater reduction in blood flow to marrow at 28 days is due entirely to reduced perfusion pressures. Numerous previous studies have confirmed decreases in bone formation rates in cortical and cancellous compartments in mature rats with similar durations of HU as used in this study^{3,4}. By 28 days of HU, reductions in volumetric bone mineral density can be detected in cancellous bone in the tibial metaphysis but not in midshaft cortical bone⁵.

Examining alterations in blood flow to muscle in the hindlimb is instructive, as it graphically illustrates the fine regulation of blood flow to match metabolic activity of the tissue (Figure 2). The *increase* in white gastrocnemius muscle blood flow after 7 days HU implies greater metabolic activity in fast-twitch motor units with HU; however, metabolic activity and blood flow at rest in the control standing animals are 6 to 10 times lower in this muscle as compared to red gastrocnemius and the soleus muscle. The decreased blood flow after 10 min and 7 days of HU to soleus and red gastrocnemius muscle is due to increased vascular resistance, whereas decreased perfusion pressure after 28 days also contributes to the chronic reduction in flows.

As one might expect, aortic arterial pressure increases with the assumption of the head-down posture, but increased vascular resistance in the bones of the head and in the humerus by day 7 of HU corresponds with normalized aortic pressures, and blood flow returns to near control values. Interestingly, increases in bone mineral content or density have been observed in the skulls of HU rats⁶ and in humans after bed rest⁷. This suggests that transient elevations in either blood flow and/or interstitial pressures for some hours or days with the assumption of head-down postures (and low-earth orbit) stimulate increased osteoblast

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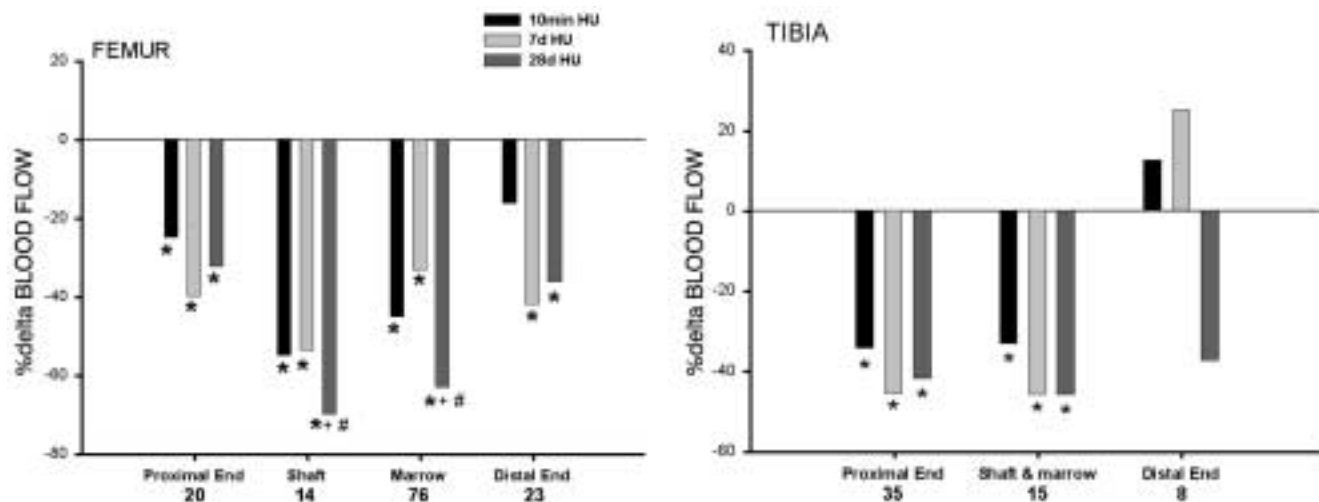


Figure 1. Changes in blood flow (expressed as % change vs. control weight-bearing rats) in the hindlimb bones of 6-month-old male Sprague-Dawley rats exposed to 10 min, 7 days or 28 days HU. * $p < 0.05$ vs. control; + $p < 0.05$ vs. 10 min HU; # $p < 0.05$ vs. 7 days HU [statistics as computed on absolute values of blood flow]. Absolute values for blood flow (in ml/min/100 g tissue) in control standing rats are indicated under each bone/tissue segment on x-axis. Adapted from data in Collier PN et al.².

activity and a net increase in bone formation. More chronic alterations in blood flow to bone, as with normal aging, have been demonstrated to coincide with reductions in bone material properties in a rodent model⁸.

Elegant work in the laboratory of Yi-Xian Qin has demonstrated significant increases in bone formation rate with oscillations in intramedullary pressures independent of any bone deformation in the functionally isolated turkey ulna model⁹. The change in bone formation is tightly correlated with the transcortical fluid pressure gradient at any one bone site, underlining the critical importance of interstitial fluid pressures to the adaptive response to mechanical loading. Reductions in either perfusion pressure and/or blood flow to bone with hindlimb unloading or actual exposure to microgravity would reduce the minimal pressures observed due to blood flow to the intramedullary compartment, and, this author proposes, proportionately reduce the magnitude of intramedullary and intracortical pressure oscillations with mechanical loading.

Then the question becomes: can any exercise regimen engaged in during low-earth orbit (or hindlimb unloading in rodents) generate large enough oscillations in interstitial fluid flow, given the reduced blood flow to bone and reduced perfusion pressures demonstrated by these ground-based experiments simulating microgravity conditions? The continued loss of bone mineral density in the femoral neck in astronauts aboard the International Space Station¹⁰, where resistance and aerobic training is mandated daily, suggests that strategies to boost interstitial fluid pressures in the lower limbs, even if only during exercise bouts, should be tested. Lower body negative pressure (LBNP) is one means of achieving this and has been extensively tested in combina-

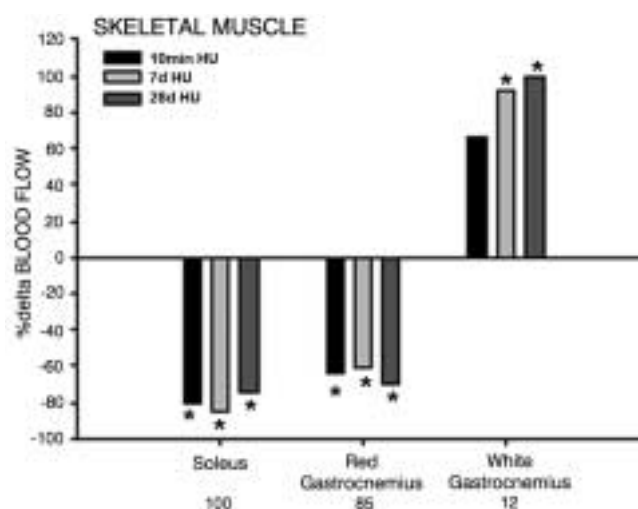


Figure 2. Changes in blood flow (expressed as % change vs. control weightbearing rats) in the hindlimb skeletal muscles of 6-month-old male Sprague-Dawley rats exposed to 10 min, 7 days or 28 days HU. * $p < 0.05$ vs. con [statistics as computed on absolute values of blood flow]. Absolute values for blood flow (in ml/min/100 g tissue) in control standing rats are indicated under each muscle on x-axis. Adapted from data in Collier PN et al.².

tion with treadmill running. LBNP effectively increases transmural pressures across capillary walls¹¹, and in a non-compliant tissue like mineralized bone, may effectively increase interstitial fluid pressures. It may be impossible to confirm in a human model whether these increased transcapillary pressures result in increased intramedullary and/or

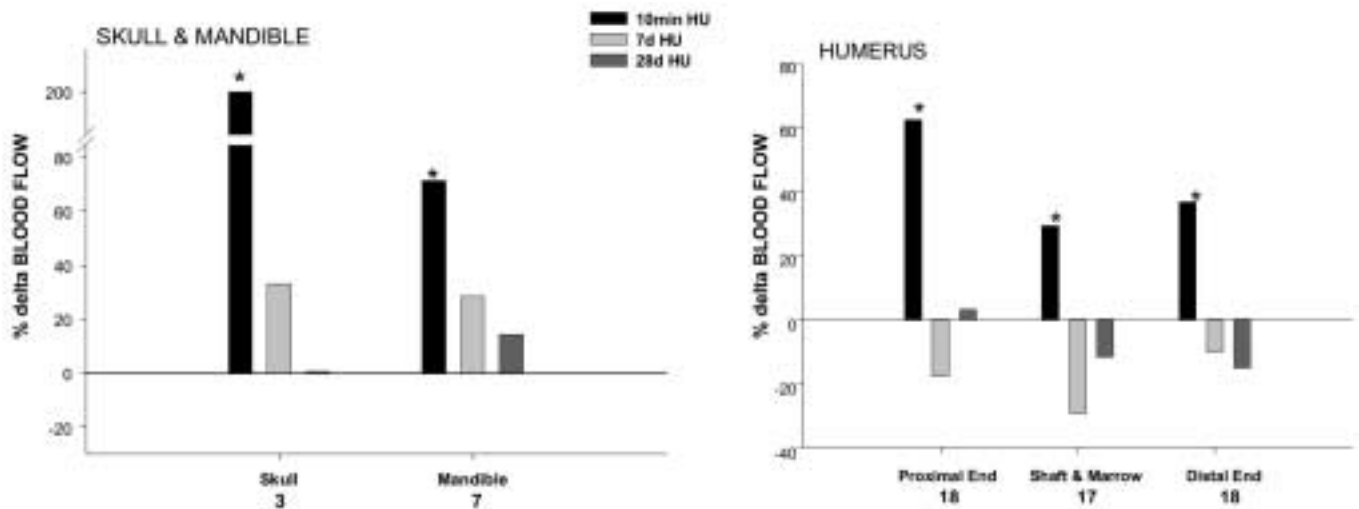


Figure 3. Changes in blood flow (expressed as % change vs. control weight-bearing rats) in the head and forelimb of 6-month-old male Sprague-Dawley rats exposed to 10 min, 7 days or 28 days HU. * $p < 0.05$ vs. control [statistics as computed on absolute values of blood flow]. Absolute values for blood flow (in ml/min/100 g tissue) in control standing rats are indicated under each bone site on x-axis. Adapted from data in Collieran PN et al.².

intracortical fluid pressures, but data describing mitigation of bone resorption in human bed rest subjects performing supine LBNP treadmill exercise are encouraging¹².

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