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VIEWPOINT

Jumping at a chance to control cerebral blood flow in astronauts

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KEYWORDS
astronaut, cerebral blood flow, exercise, gravity, space, spaceflight-associated neuro-ocular syndrome (SANS)

In this issue of *Experimental Physiology*, Ogoh et al. (2021) explore how gravity (or rather, the lack of!) and exercise impact the delicate balance underlying the regulation of cerebral blood flow (CBF) and outflow. This topic is especially relevant because gravitational acceleration has been a constant force throughout the ~4 billion years of Earth's history, having helped to shape evolution of the human brain, given the pressure for bipedal locomotion when life transitioned from water to land. Much thanks to its phenomenal processing power, our brain has since developed into a 'gas-guzzling energy-hog', demanding a disproportionate chunk of our basal oxygen budget (~25%) despite weighing <1/50th of our total body mass. Given that the brain is so expensive to run, we are equipped with extensive and sophisticated vasoregulatory mechanisms that preserve cerebral perfusion and substrate delivery, allowing our brains to 'stand up' to the seemingly innocuous challenge of 'standing up' against the vertical hydrostatic pressure gradient in normogravity (1 G_Z) (Bailey, 2019).

These familiar hydrostatic pressure gradients are, of course, lost in the weightlessness of space, posing unique challenges for the brain. Indeed, the red, round faces and skinny legs of astronauts floating aboard the International Space Station (ISS) belie an almost 2 litre cephalic shift of blood and cerebrospinal fluid (Moore & Thornton, 1987); a phenomenon coined the 'Charlie Brown' or 'puffy-head bird-legs' syndrome. These fluid shifts pose a major risk to mission operational success by contributing to headaches, malaise, cognitive impairment and a constellation of adverse changes in visual acuity known collectively as the spaceflight-associated neuro-ocular syndrome (SANS) (Mader et al., 2011). Although its underlying aetiology remains widely contested, especially regarding the role of intracranial hypertension, SANS is among the highest priority human health risks for long-duration spaceflight, including a return trip to the moon and the more ambitious multi-year crewed mission to Mars. Although the long(er)-term implications of SANS for the brain remain completely unknown, they are likely to extend well beyond the eye, sparking intense research efforts to recreate SANS in terrestrial cohorts and develop practical countermeasures to mitigate risks.

To that end, Ogoh et al. (2021) sought to determine the extent to which one such potential countermeasure [jump exercise training (JET)] impacts the regulation of CBF in response to the microgravity recreated by 60 day of (−6°) head-down-tilt bed rest (HDTBR). Although HDTBR is not the perfect 'space simulator', because it fails to

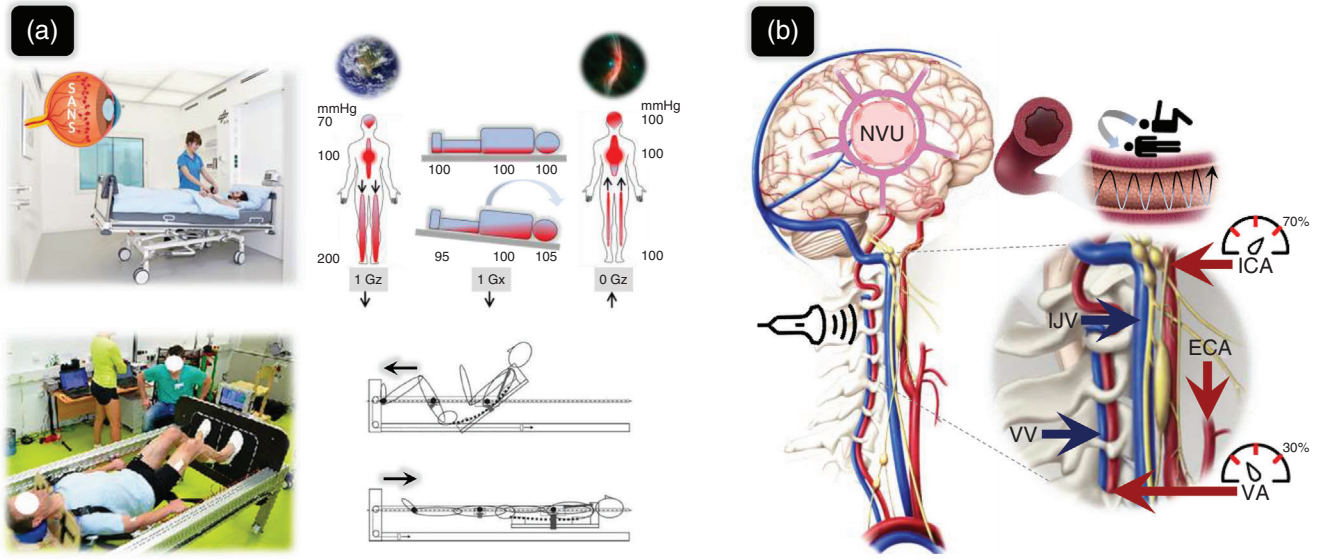

FIGURE 1 (a) The long-duration 6° head-down-tilt bed rest (HDTBR, top left; ©DLR) model is considered arguably to be the most reliable ground-based spaceflight analogue that can simulate arterial pressure changes, gravitational unloading (excluding the G_x or chest-to-back vector) and cephalad fluid shifts (top middle, adapted from Hargens & Vico, 2016) similar to those observed in microgravity that predispose to the spaceflight-associated neuro-ocular syndrome (SANS). It is an ideal model for countermeasure testing, including supine jump exercise training (JET) using the sledge jump system (SJS, bottom left; ©DLR) that incorporates pistons and ropes to pull the participant onto force plates (bottom middle, adapted from Kramer et al., 2017). (b) Anatomical location of the major arteries and veins insonated by Ogoh et al. (2021) and predicted sinusoidal flow/shear across the cerebrovascular endothelium during JET (see main text). Abbreviations: ECA, external carotid artery; ICA, internal carotid artery (delivers 70% of total blood flow); IJV, internal jugular vein; NVU, neurovascular unit; VA, vertebral artery (delivers 30% of total blood flow); VV, vertebral vein

remove the G_x (chest-to-back) loading vector, it is widely considered the most effective terrestrial analogue for recreating the pronounced cephalic fluid shifts and upward (superior–posterior) shift of the brain that potentially predispose to SANS subsequent to head-to-foot gravitational unloading (Figure 1a).

Ogoh et al. (2021) used duplex ultrasound mapping of regional changes in the extracranial distribution of conduit arterial and venous blood flow to extend their earlier research demonstrating that over the course of a 60 day campaign, 30 days of HDTBR was sufficient to reduce blood flow to the anterior circulation, whereas posterior perfusion remained preserved (Figure 1b). What caused the selective hypoperfusion is unclear, although potentially related to dynamic cerebral autoregulation-mediated myogenic vasoconstriction to 'buffer' initial surges in cerebral perfusion pressure that could destabilize the fragile cellular architecture of the neurovascular unit. Indeed, the observed diversion of flow from the internal to external carotid artery provides indirect support for neuroprotective 'crosstalk', although it could equally represent passive redistribution. Another explanation might be an active downregulation of cerebrospinal fluid production through ultrafiltration to counter raised intracranial pressure during HDTBR by means of lowering internal carotid artery pressure levels, because the predominant mass of choroid plexus, which is located in the lateral ventricles, has its arterial input via the anterior choroidal artery from the internal carotid artery (Damkier et al., 2013). Additionally, hypoperfusion might simply reflect reduced cerebral metabolism because, after all, the brain rested mostly idle, with motor/cognitive stimulation supressed. Regardless, these findings certainly justified a countermeasure, given that the microgravity-induced reduction in anterior perfusion could potentially be linked to the 'space fog' or cognitive impairment that plagues astronauts and has been linked to poorer landing accuracy in Space Shuttle pilots (Roy-O'Reilly et al., 2021). Indeed, you need look no further than patients who have undergone carotid endarterectomy (an elective surgical procedure that shells out stenotic atherosclerotic plaque at the origin of the carotid artery to prevent a major stroke) to appreciate fully the cognitive gains afforded through revascularization when the anterior circulation is 'refuelled'.

Importantly, in the present publication (Ogoh et al., 2021), JET failed to restore the regional deficits in anterior perfusion, arguing against its suitability as a potential neuroprotective countermeasure. This is frustrating, given the recently documented cardiopulmonary and musculoskeletal benefits conferred by JET and 'potential' for sinusoidal hyperaemia incurred during the 'squat–stand' nature of exercise previously suggested to compound cerebrovascular endothelial adaptation by optimizing the pressure–strain–shear stress phenotype (Figure 1b) (Calverley et al., 2020).

However, before we reject the 'JET-propelled brain' completely, there are a few points worth raising. First, we must consider whether the training stimulus was of sufficient magnitude (intensity/frequency/duration) to kick-start cerebrovascular adaptation. Second, the training group was comparatively more hypocapnic (end-tidal P_{CO_2} was ~2.5 mmHg lower on day 57 of HDTBR), which probably

masked any elevations in CBF by ~8% and probably contributed to the observed reduction in arterial shear rates owing to cerebral vasoconstriction (assuming 1 mmHg reduction in end-tidal P_{CO_2} translates into ~3% reduction in flow). Third, the inherent biological variability associated with the regional mapping of CBF illustrated in figure 2 of their original publication is an equally important take-home message that serves as a sober reminder for future researchers to ensure that their study is adequately powered.

The new information presented by Ogoh et al. (2021) makes an important contribution to a complex and clinically relevant topic, while encouraging the need for further research. This quest is especially relevant, given the European Space Agency's recent revamp of the Science in Space Environment research programme, with an eye on deep space exploration to Mars and intensifying efforts to find suitable countermeasures to bolster the brain.

COMPETING INTERESTS

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