Translational perspective (Journal of Physiology) – *(maximum 900 words)*

The aetiology of Spaceflight-Associated Neuro-ocular Syndrome (SANS) might be explained by a neural mechanism regulating intraocular pressure

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The recent study by Ficarrotta and Passaglia (2020), particularly their theory of an, as yet undetermined, neural feedback loop regulating intraocular pressure (IOP), provides an exciting new perspective in explaining the aetiology of Spaceflight Associated Neuro-ocular Syndrome (SANS).

Fundamental to the evolution of the human species, in particular the ability to maintain appropriate perfusion of vital organs during rest and activity in the upright position, is the evolution of the structure and function of the cardiovascular system. The remarkable feature of cardiovascular regulation is that in the upright posture, 70 to 75% of the blood volume is below the heart (i.e. pump) in the upright posture. As remarked by Loring B. Rowell in his 1993 book on Human Cardiovascular Control:

"If an engineering analysis of the aeronautical features of the bumblebee could lead to the conclusion that these insects cannot fly, then a hemodynamic analysis of the human circulation could also lead to the conclusion that human beings cannot stand up."

The maintenance of an upright posture is possible due to the regulation of blood pressure, which ensures adequate perfusion of all tissues, including the eye.

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Withdrawal of the head-to-foot gravitation vector, either by changing body position, or exposure to microgravity, will induce changes in the perfusion of several tissues, particularly if an acute exposure is concomitant with increased physical exertion. Chronic exposure to microgravity has been shown to cause impairment in visual function, which was initially attributed to the increase in intracranial pressure (ICP), but recently perfusion-induced modifications of the retinal circulation have also been implicated. The majority of astronauts participating in long-term missions on the International Space Station (ISS) experience visual impairment, manifesting as blurred vision for near and distance, as well as significant morphological changes in the eye and optic nerve, including optic disc oedema, choroidal folds, and retinal haemorrhages (Mader et al. 2011). The unresolved aetiology and high incidence of these visual impairment among astronauts jeopardizes all future long-term deep space missions planned to the Moon and Mars.

Ficarrotta and Passaglia (2020) demonstrate quite elegantly that ICP is the afferent arm of a central neural feedback mechanism, which provides an efferent signal modulating the outflow facility (aqueous humor), thus regulating IOP. As they point out, IOP has a much greater influence on the biomechanics of the optic nerve head than ICP, and that the principal aim of IOP regulation is the maintenance of the translaminal pressure (TLP) across the lamina cribrosa.

Their experiments were performed on a (prone) rat model, and the fluid dynamics are different to that of an upright human. Nevertheless, their theory would suggest that factors other than ICP might elevate IOP, and may also pose a threat to retinal cellular structure and function. Using self-tonometry, Draeger et al. (1993) were the first to report a transient elevation of IOP in microgravity, whereas Chung et a. (2011) reported a persistent elevation of IOP measured by the first Korean astronaut during her sojourn on the ISS. In female subjects confined to bed rest for 10 days, we observed that choroidal thickness is influenced by hydrostatic pressure (i.e. comparison of measurements taken in the seated and supine positions), whilst hypoxia and hypercapnia control the the neural fibre layer (Jaki Mekjavic et al. 2016). The increased blood flow in the retinal circulation will not affect ICP, and will thus presumably not initiate the feedback mechanism postulated by Ficarrotta and Passaglia (2020). It may, however, affect IOP. Based on our results (Mekjavic et al. 2020) and those of Anderson et al. (2016) we hypothesise that the supine 6° head down tilt (6°HDT) model may not be an appropriate simulation of the microgravity-induced effects on the choroidal circulation. In contrast to the supine position, the prone 6°HDT position, is most likely a better model, as it elevates IOP substantially above the glaucoma threshold. The prone 6°HDT position in humans elevates the episcleral venous pressure, due to a previously reported hydrostatic effect (Anderson et al. 2016; Jaki Mekjavic et al. 2016). This may result in an IOP increase through a different mechanism to that described in the prone rat model used by Ficarrotta and Passaglia (2020). Such contributions of reduced outflow in microgravity models require evaluation. Furthermore, the daily static exercise performed by astronauts on the ISS to mitigate microgravity-induced sarcopenia, may cause IOP elevations. Interestingly, the substantial static exercise-induced elevations in IOP observed in older (astronaut-aged) individuals are not observed in younger adults (Mlinar et al. unpublished; Mekjavic et al. 2020), perhaps due to the known age-related modifications in the biomechanical properties of the lamina cribrosa.

The focus of research to explain the aetiology of SANS, thus far, has been on the effects of microgravity on ICP. However, it would appear that increased IOP, particularly by factors influencing ocular fluid dynamics, may be the prime cause for the impaired vision observed in astronauts.

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