Noninvasive Measurement of Cerebral Blood Flow (CBF) Autoregulation (AR) and Intracranial Pressure (ICP) with Rheoencephalography (REG)

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Abstract

It has been documented that space flight increases ICP, causes space flight-associated neuro-ocular syndrome, damages CBF AR, causing orthostatic intolerance, headache, and impaired neurocognitive performance of astronauts. Research attention was focused on ICP and not on CBF. The cerebrovascular function was mentioned for the first time only in the 2019 solicitation. REG is a noninvasive method to study CBF and its AR. A recent clinical study demonstrated that REG pulse wave morphology shows identical alteration as ICP by reflecting ICP elevation. Miniaturized REG device is available today.

Introduction

It has been documented that long-duration space flight increases ICP, causes space flight-associated neuro-ocular syndrome (SANS), impairs dynamic cerebrovascular AR, and reduces cerebrovascular CO_2 reactivity, causing orthostatic intolerance, headache, accelerated vascular aging, blood-brain barrier (BBB) integrity, and impaired neurocognitive performance of astronauts (1-20). The reasons for the development of eye changes in space have not been clarified. NASA research attention was focused on ICP and not on CBF and its AR. In animal studies, it was demonstrated that prolonged microgravity remodels the walls of blood vessels (8). The cerebrovascular function was mentioned for the first time only in the 2019 solicitation (Solicitation Number 80JSC020L0003). SANS is a secondary risk and relevant gap (Solicitation Number: 80JSC019L0001; 2019) and 2021 (2). A recent publication details impacts of spaceflight on CBF AR (12). NB: 1) SANS is a unique condition with no perfect terrestrial analog. 2) The recent list of SANS gaps (n=14) doesn't mention CBF or its AR (2). Also, it was out of focus that the ophthalmic artery is a branch of the internal carotid artery, i.e., showing CBF AR. A lecture on intravascular pressures in space did not mention CBF or its AR (21).

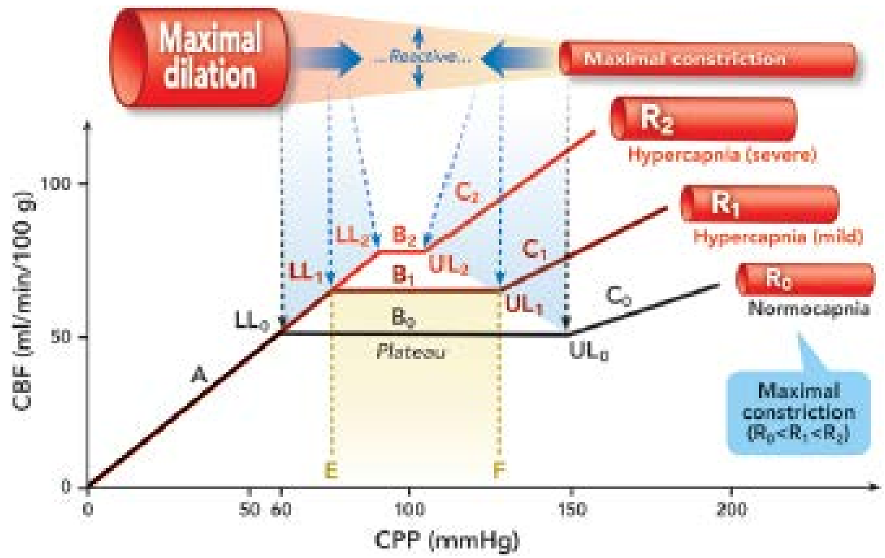
Although NASA has sought the development of a real-time noninvasive monitoring method of ICP for use on the International Space Station (ISS) until recently no noninvasive, continuous brain monitoring device has been available to measure CBF AR on ISS. Because ICP measurement is invasive, it is not ideal in real-time on astronauts, while on the ISS. CBF was measured typically with Transcranial Doppler (TCD) only after they return from the space mission. Additionally, TCD is used to determine CBF in the middle cerebral artery, but CBF AR, a function of arterioles, is not measured. Early studies by the US Army Walter Reed Army Institute of Research (WRAIR) proved that REG reflects both CBF and ICP (39). This fact was confirmed additional studies and based on these results, the US Department of Defense supported the development of a non-invasive, continuous brain monitor, using REG technology. Unit dimensions are: 85 x 58 x 16 mm; mass: 102.06 g (24, 25). This operator-independent device can use regular ECG electrodes or reusable conductive fabric, placed on the forehead and lower arm. NB: Russians used REG in the 1970-is on Salyut 4 but did not measure CBF AR nor change of REG pulse wave morphology (26, 27).

REG

The Food and Drug Administration definition has been stated that "A rheoencephalograph is a device used to estimate a patient's cerebral circulation by electrical impedance methods with direct electrical connections to the scalp or neck area" (28). REG name was suggested by Jenkner (29). REG is based on monitoring pulse synchronous variations in cranial electrical impedance over time. The significant physiological information derived from the REG signal relates to vasoconstriction and vasodilation in the brain. This is manifested by decreasing and increasing REG pulse amplitudes, respectively. Additionally, REG reflects the elasticity of the vessel wall (compression chamber function) and shows identical morphological distortion to the ICP waveform during ICP elevation (32). The units of REG amplitude are measured in Ohms, however, there are no normative values associated with the REG pulse amplitude value. REG pulse wave formation is influenced by many factors (41). REG pulse wave amplitude is due to the conductivity differences between brain tissue, and cerebrospinal fluid and blood, with blood and cerebrospinal fluid being better conductors than the brain and other 'dry' tissue. The lower limit of CBF AR by REG was closely correlated to invasive ICP in WRAIR and Johns Hopkins University study by measuring ICM+ program (33, 34). REGx, a CBF AR index, is calculated from REG and arm bioimpedance pulse waves that can replicate PRx without the need for invasive methods. REGx calculation is identical to PRx calculation, which is calculated from invasive ICP and arterial pressure by ICM+ program. Several WRAIR animal and human validation studies were performed demonstrating that REG reflects cerebrovascular reactivity, correlates with ICP, carotid flow, laser Doppler flow, TCD flow, quantitative CBF, tissue O_2 (35-39). Recent clinical work suggests that REG can be used to detect the status of CBF AR as well as elevated ICP since REG pulse wave has identical morphology change to those described on ICP (42). Influencing factors of REG pulse waves were detailed elsewhere 41). Early REG studies not measured CBF AR (41-46). NASA translated REG-related Russian publications from the mid-1960-ies (47).

CBF AR and CO_2

Cerebral blood flow autoregulation (48, 49) describes a mechanism that maintains CBF stable despite fluctuating perfusion pressure. Hypercapnia increases CBF by cerebral vasodilation (50). Hypercapnia causes the plateau to progressively ascend, a rightward shift of the lower limit, and a leftward shift of the upper limit (51). In other words, CBF AR capacity is decreased during hypercapnia.



Effect of hypercapnia on cerebral autoregulation. Autoregulation curves are in black at normocapnia and red at hypercapnia. Cerebral resistance vessels are illustrated in red/pink. The bold solid blue arrows indicate the dynamic shift of the maximally dilated and constricted cerebral resistance vessels at hypercapnia. The dashed black and blue lines/arrows indicate the lower and upper limits at normocapnia and hypercapnia, respectively. A = the curve below the lower limit; B = the plateau at normocapnia (B0), mild hypercapnia (B1), and severe hypercapnia (B2); C = the curve above the upper limit at normocapnia (C0), mild hypercapnia (C1), and severe hypercapnia (C2); CBF = cerebral blood flow; CPP = cerebral perfusion pressure; LL = the lower limit at normocapnia (LL0), mild hypercapnia (LL1), and severe hypercapnia (LL2); R = calibers of cerebral resistance vessels at normocapnia (R0), mild hypercapnia (R1), and severe hypercapnia (R2); UL = the upper limit at normocapnia (UL0), mild hypercapnia (UL1), and severe hypercapnia (UL2) (51).

Suggestions/Impact

Use of REG 1) helps measure the cerebrovascular aspect of SANS and ICP 2) fits in NASA RFI Solicitation (Number: 80JSC020L0003 HRP) d. Cerebrovascular function; 3) can help to create and testing an adequate countermeasure for long-duration/deep space exploration; 4) has terrestrial applications such as neuromonitoring in ICU, and 5) military-medical use for transportation of wounded service members with traumatic brain/blast injury, hemorrhage, and hypotensive resuscitation.

Recommendations and or Priorities

What are the priorities and/or recommendations that you are suggesting that NASA implement to address these questions?
1) standardization of a CBF AR test (breath-holding) for increased CO_2 concentration on ISS; 2) Software and hardware modification of miniaturized REG device for use on ISS; 3) Establishment of a correlation between REG and 1) TCD; 2) fMRI BOLD demonstrating that REG

reflects local vascular response; 4) Measure REG immediately before or after fundoscopy and optical coherence tomography scan on ISS.

This is a cross-disciplinary topic

1) Such a device can also be modified as a life sign monitor to record EEG, ECG, and respiration as well
as to support dead-or-alive decision making both in space and on Earth
2) Other areas of research: Countermeasures

The above proposal covers two suggested priorities:

1. Science that can or must be done in space, with anticipated value to human exploration 2. The science that can be done in space, with anticipated value to humans on Earth (52).

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