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Physiological Challenges of Space Travel and Ground-Based Simulation Possibilities for Monitoring Brain Circulatory Changes: A Rheoencephalography Study

The functional integrity of brain perfusion and oxygen transport profoundly determines mental performance during military flight missions and spaceflight. Presently, at the selection phase of pilot candidates, there are no screening methods to evaluate cerebral circulation and its autonomous regulation (AR), meanwhile the pilot information processing capacity could be insufficient in dangerous flight situations with high mental workload or during high "head-to-foot" G loads. On-board ISS (International Space Station) and during deep-space missions circulatory changes can be evolved in the opposite direction due to the microgravity: blood shift toward the head-neck region can increase ICP (Intracranial Pressure) and tenfold increase of carbon-dioxide concentration can provoke complaints and disturbances in eye and brain blood circulation (Space Associated Neuro-Ocular Syndrome – SANS). The alteration of brain perfusion dynamics and oxygen utilisation was investigated on the head-down tilting table (HDT) test and in the hypobaric (low-pressure) chamber. We registered the brain regional pulse wave changes by the bioimpedance (Rheoencephalography – REG) on 19 volunteers in rest and after the breath-holding manoeuvre. We found that during the head-down tilt (HDT) position, the amplitude of the second peak of the REG pulse wave increased, like the ICP pulse wave, being an unfavourable sign for intracranial pressure increase in clinical cases. Manual readings resulted in significant differences during HDT between the female ($P = 0.0007$) and male ($P < 0.0001$) groups. With automated analysis, the increase in REG P2 wave was significant, and the ratio was 4/5 (80%) for women and 10/14 (71%) for men. The newly written automatic program script was able to detect this in 92% of the cases. The calculated values detected the state of cerebral circulatory autoregulation and the identity between the male and female groups. Based on this result and previous REG correlation studies, it can be concluded that REG could be used to monitor fighter pilots, astronauts, and neurocritical care patients in real-time as emergency alert in the transitory cessation of brain perfusion.

Keywords: *intracranial pressure, noninvasive, rheoencephalography, simulation in Trendelenburg position, hypobaric hypoxia*

1. Introduction

Military aviation and space flight are the same as "pushing the limit" beyond the overall physical and mental capability of well-trained pilots and astronauts require special psychological and somatic stress tolerance. The functional integrity of brain perfusion and oxygen transport is essential to maintain proper mental performance. It could be crucial to forecast the possible individual decrement of that in an emergency situation, during dogfight in military mission or during spaceflight in microgravity, easily leading to a narrowed conscious state even to sudden incapacitation.

1.1. Military aviation

Hypoxia has long been recognised as a significant physiological threat at altitude. Aircrew has traditionally been trained to recognise the symptoms of hypoxia using hypobaric chamber training at simulated altitudes of 25,000 feet or more. Hypoxia in flight remains a serious threat to aviators and can result in fatalities seriously considered a major risk in the physiological capability domain in all presently adopted human error models [1], [2], [3]. Ever-present risks of hypobaric hypoxia and decompression sickness accompany military aviation. Neuroprotection against those hazards is conferred through fractional-inspired oxygen concentrations of 60-100% (hyperoxia). Hyperoxia reduces global cerebral perfusion, increases reactive oxygen species within the brain, and leads to cell death within the hippocampus. However, an understanding of hyperoxia's effect on cortical activity and concomitant levels of cognitive performance is lacking. This limits our understanding of whether hyperoxia could lower the brain's tolerance threshold to physiological stressors inherent to extreme aviation, such as high gravitational forces [4].

On board of military fighter aircrafts, the possibility for human performance measurement including mental and physical parameters is very limited, from the physiological (circulatory) aspect, we have no information about actual fighting capability (compared to the detailed information of technical data in "black box" as flight recorder). From the flight safety aspect, it would be essential to understand and forecast just in time the pathophysiology of UPE (Unexplained Physiological Events/Incidents), which might lead to sudden incapacitation during flight even "on-mask" position. Since 2002, US NAVY lost four F-18s, and the US Air Force one F-22 aircraft, because the pilot was unaware of the sudden progression to an unconscious state while flying at high altitude, being unable to switch on emergency oxygen and prevent a fatal outcome [3].

Cerebral circulatory problems have already been detected in the Stuka (Junkers Ju-87) and US dive-bombers. In pilots of modern 5.-6. Generation fighter jets' high rate of manoeuvrability can disrupt brain circulation (G-induced loss of consciousness) and the loss of cockpit cabin pressurisation and the threat of hypoxia in emergency accompanied by carbon-dioxide washout from blood can cause loss of consciousness. Without the protection effect of the Aircrew Equipment Assembly, this situation could surely lead to fight-and-flight incapability.

During high G-s (accelerations and overloads due to the increased agility and manoeuvrability of combat aircraft), the inertial shift of blood to lower body parts can provoke blood pressure drop and pulse undulation leading to the transient cessation of brain perfusion and G-induced loss of consciousness (G-LOC). After military sorties, longer deterioration of mental performance can commence due to A-LOC (almost LOC with repetitive changing brain perfusion during acceleration episodes) or hypoxia hangover (disturbed oxygen utilisation for hours at the brain cell level) [5].

Continuous monitoring of biomedical data would be beneficial to prevent these scenarios, providing automatic feedback about circulatory parameters and tissue oxygen level (esp. in the brain). From this aspect, the monitoring of the alteration of Cerebral (brain) Blood Flow (CBF and Near Infrared Spectroscopy [NIRS] measurement for regional Oxygen saturation level) would be a valuable method, using dry electrodes inserted into the helmet, and possible warning signs are indicated on the pilot displays. From the technical aspect (during a real flight), the experience is still minimal. Still, it might be useful in the evaluation of protective efficiency regarding personal altitude and anti-G Suit (aircrew equipment assembly) and recovery procedures (breathing protocol during subsequent critical tasks) [6]. Simulated flight (in barochamber performing VR [virtual reality] based flight sorties) would be another approach to characterise in hypoxia the possible decrement in flight multitasking capabilities and loss of situational awareness [7], [8].

1.2. Space flight

The normal hydrostatic gradient at 1 G from head to toe linearly increases, but in microgravity, a dramatic redistribution of fluids from the legs to the upper body (torso and head) can commence within only a few moments of weightlessness, which is completed within days. Due to the cephalad shift fluid volume in the legs decreased by 10%, accompanied by a 17% reduction in plasma volume due to the initially increased filtration through the kidneys. This fluid redistribution phenomenon is called "puffy head and birdy legs" and refers to significant facial swelling and significantly (by 10–30%) decreased leg circumference. Astronauts subjectively often complain of buzzing headache, nasal congestion, anosmia (loss of smell), diminished taste (and appetite), and eye and visual abnormalities (blurred vision, diminished visual acuity) after extended stays in space, which are likely symptoms of increased intracranial pressure in spaceflight associated neuro-ocular syndrome (SANS) [9], [10], [11], [12].

The follow-up for CBF changes would be essential to understand better the SANS, where intracranial pressure (ICP) increase driven by cephalad fluid shift (toward the upper torso and head) could easily threaten the success of deep space missions [13], [14], [15]. Elevated CO_2 concentration on ISS cause additional increases in brain blood volume. Overall CO_2 elevation is caused by less effective chemical absorption and possible accumulation of exhaled CO_2 around head of spacecrew due to the lack of equalising convections (airflow) in microgravity [16]. Studies described that living on ISS caused accelerated cerebrovascular aging and decreased cerebrovascular reactivity [16], [17], [18], [19].

Tilting table test in head down position – HDT (Trendelenburg position) – is a widely used method in ground-based situations to simulate microgravity with headward blood shift and demonstrate cardiovascular reflex changes [20], [21]. Not only would the peripheral parameters (systemic blood pressure and heart rate) be informative, but brain circulatory effects can be monitored as well.

1.3. Prehospital and clinical neuromonitoring

The goal of neuromonitoring is to prevent secondary brain injury during clinical treatment (and possibly provide triage information about battlefield injuries to evaluate the severity and priority of the wounded casualties). Brain imaging methods (X-ray, computer tomography, magnetic resonance imaging, etc.) are used to diagnose morphological changes such as haemorrhage, tumour, vasospasm, etc. These methods are good in spatial resolution but bad in time resolution. Neuromonitoring methods involve invasive and noninvasive ones. Invasives are ICP, tissue O_2, temperature, quantitative CBF, laser Doppler flowmetry, spreading depolarisation, and microdialysis [22]. Noninvasive methods are electrophysiological (EEG, bispectral index, evoked potential) and vascular (TCD, NIRS, REG) [23, p. 53]. The computerised invasive method is the real-time calculation of the CBF AR index, called the pressure reactivity index (PRx). The calculation uses invasive arterial pressure and ICP waveforms and the program name is ICM+ [24]. PRx is Pearson's correlation coefficient, calculated as the continuous correlation between 30 consecutive time-averaged (10 s) ABP and ICP values. A positive index (positive correlation) implies impaired CBF AR, while a negative index (inverse correlation) implies intact AR [25]. Several publications described the morphological change of ICP pulse wave as a function of ICP elevation [26], [27, [28], [29], [30], [31], [32].

2. Method for brain circulation monitoring – rheoencephalography

The alteration of brain perfusion dynamics and oxygen utilisation in microgravity was investigated in the ground-based simulation of microgravity on the head-down tilting table (HDT) test and in the hypobaric (low-pressure) chamber. We registered the peripheral and brain regional pulse wave changes by the bioimpedance-based rheoencephalography (REG) on 19 volunteers at rest and after a breath-holding manoeuvre.

2.1. Subjects

The study was conducted in the Aeromedical, Military Screening, and Healthcare Institute, Medical Centre of the Hungarian Defence Forces in Kecskemét, Hungary. The test procedure was by the Declaration of Helsinki, and was approved by the Medical Research Ethics Review Board of the Ministry of Defence, Budapest, Hungary on 16 September 2020. After the information about the purpose and details of the tests, the subjects signed the consent form. Abdominal circumference was measured at the navel level in a standing position.

We measured 19 healthy volunteers (6 females and 13 males). They were in a supine position on the tilting table. The length of the files were 45.47 ±5.45 (mean ± SD) minutes in the tilting table and the sitting position in the LPC chamber was 77.87 ±8.41 minutes. The mean age (n = 19) was 22.68 ±1.49 years; height was 177.63 ±6.18 cm, and body mass index was 22.94 ±2.43. There was no significant difference between the male and female groups. There was a significant group difference in weight (male 76.62 ±7.16 kg and female 63.33 ±3.98 kg; p = 0.0001). Abdominal circumference was significantly different (p = 0.03) for the male (84.31 ±5.41 cm) and female (75.17 ±7.81 cm) groups.

2.2. Methods

2.2.1. REG/REGx

According to the USA FDA, "A rheoencephalograph is a device used to estimate a patient's cerebral circulation (blood flow in the brain) by electrical impedance methods with direct electrical connections to the scalp or neck area" [33]. Studies noted that REG reflects decreased vessel wall elasticity [34], [35], CBF AR [36], [37], ICP [38], intracranial volume change [39] showing a correlation with LDF [40]. An animal study using the ICM+ program demonstrated that the lower limit of CBF AR is well correlated to ICP and REG [41]. A human study presented the coincidence of CBF AR active/passive status and REG peak 2 (P2) morphological change [42]. A computer program was developed for monitoring, storing, and data processing analogue physiological signals (DataLyser – DL) [43] involved a menu to calculate PRx/REGx and Hjorth analysis [44].

2.2.2. Trendelenburg position

Head-down tilting (HDT) is a test used for military pilots/astronaut candidates as well to simulate microgravity [21]. The cause of elevated ICP in the HDT position is that venous outflow from the brain is damped. The morphological alteration of the ICP pulse wave increase was published in several articles [26], [27, [28], [29], [30], [31], [32].

2.2.3. Breath-holding

There is a correlation between blood CO_2 concentration and CBF. This relationship is used in clinical EEG practice as a test to provoke pathological EEG waveforms during hyperventilation: The decreased CO_2 concentration decreasing CBF. To test the status of CBF AR, 5–10% CO_2 inhalation is used. Another clinical test is the acetazolamide injection. CO_2 increase can be triggered physiologically by breath-holding. Such a test applies to the ISS.

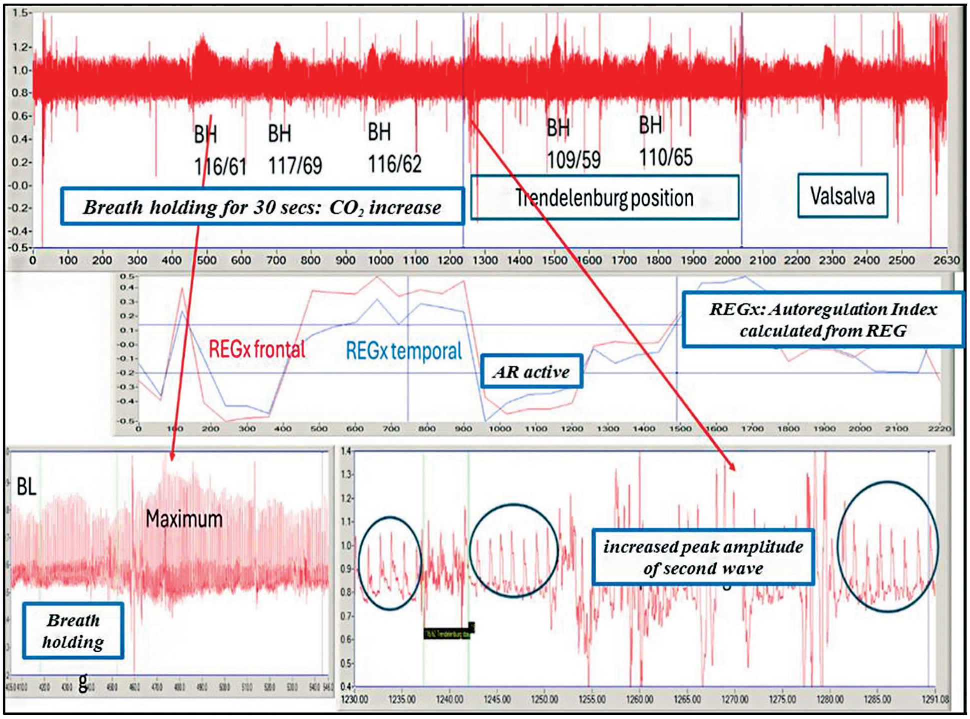

Figure 1.
Trace of bifrontal REG (upper trace) on a tilting table (edited by Michael Bodó in Datalyser program) [64]

(Note: HDT is labelled as Trendelenburg position. BH indicates the breath holdings. Under its label are the blood pressure [systolic/diastolic] numbers. The middle traces are the REGx traces. The lower trace shows fragments of REG during breath-holding [left side] and transition from horizontal to HDT position [right side]. Arrows indicate the location of magnified portions. The Y-axis is in Volt. The X-axis is in seconds. The window size is 2630 seconds, 43.83 min. The file name is April 26. 1.)

2.3. Equipment and materials

1) *A bedside monitor* (BeneVision N15, Mindray North America, Mahwah, NJ) was used to record CO_2, O_2, peripheral (SpO_2), and brain O_2 saturation by near-infrared spectroscopy (NIRS) with 1/sec sampling rate. The type of file is CSV. Arterial blood pressure (ABP) was measured by the arm cuff on the left arm on the tilting table. Also here, the ABP was measured 6 times: 3 times during the control period and 3 times during the Trendelenburg position, in both cases before 30-second breath-holding.

2) *A bipolar bioimpedance amplifier* (ReoRON-61, Medicor, Esztergom, Hungary; measuring frequency 167 kHz) was used with an additional amplifier (BK-094-1; Elsoft BT, Budapest, Hungary) to amplify, filter, and switch symmetrical-to-asymmetrical signals. REG and lower arm bioimpedance signals were recorded together. The analogue signal of the air pressure of the LPC chamber (Chemical Machinery Factory, Kiskunfélegyháza, Hungary) was recorded, too.

3) *The sampling rate* of the analogue signals was 200 Hz with DataLyser software and an analogue-digital converter (USB 6211, National Instruments, Austin, TX). Data collection was performed with a laptop (Alienware, Dell, Round Rock, TX). Home-made electronics (John von Neumann University, Kecskemét, Hungary) created a pressure-related analogue signal and another for event markers, which were stored together with bioimpedance signals. Text notes were entered during the recording as events with time stamps, which helped identifying the challenges' start, stop, and numbers of actual ABP during data processing. DataLyser creates unidentified files by automatically generating both the waveform (binary) and the note file (ASCII).

2.4. Preparation

Electrodes were placed while volunteers were in a sitting position. Before electrode placement, the skin was cleaned with benzine and EEG cleaning paste. The electrodes were regular electrocardiogram electrodes. Their location were bifrontal: Fp1-Fp2 and bitemporal: F7-F8 according to the EEG 10-20 International System of Electrode Placement [45]. Rheogram electrodes were placed on the lower arm at the elbow and wrist, on hairless areas. NIRS sensors were placed above the REG electrodes on frontal areas and a headband was placed to secure them together with REG cables. During both recordings, a face mask (Varifit, with AIR gel technology; Sleepnet Corporation, Hampton, New Hampshire) was used to measure exhaled CO_2 and inhaled O_2 concentrations.

2.5. Tests

In this descriptive study, our goals were to describe changes in REG and its derivatives during the following tests: 1. HDT; 2. 30-second breath-holding; 3. simulated altitudes and hypoxia/hyperoxia; 4. to compare bifrontal to bitemporal REG derivations; 5. compare automatic P2 detection to manually calculated results.

The challenges were as follows:

A. *Tilting table* (Figure 1) 1. control/rest (0°) on tilting the table in the supine position for 20 minutes; 2. 30-sec breath-holding 3 times; 3. HDT – Trendelenburg position (–15°) during about 20 min and 30-sec breath-holding 3 times.

B. *LPC chamber* (Figure 2) at simulated altitudes of 0, 2500, and 4000 meters: 15 minutes; at 5200 meters 10 minutes. At each level, 100% O_2 was administered during the last 5 minutes, except at 5200 m, when it was administered all the time. The last 10 minutes were also at a 0-meter level (Figure 3).

2.6. Data processing

1. REG amplitudes: REG pulse wave's peak amplitudes were measured by manual cursor operation before and during breath-holding by DL in which there is an automatic peak detection menu, and the values of 5-10 pulse waves – involving the maximum amplitude – were marked and copied into Excel (Microsoft, Redmond, WA) spreadsheet. 50 Hz interference contamination

was eliminated by smoothing with a running average of 0.04 sec. Eye blinking, talking, etc. artifacts containing waveforms were excluded from data processing. For the control period, REG was measured before breath-holding. The effect of CO_2 was measured when the REG pulse first peak (P1) was the maximum. To compare manual and automatic detection of P2, a 10 REG pulse wave sample was selected.

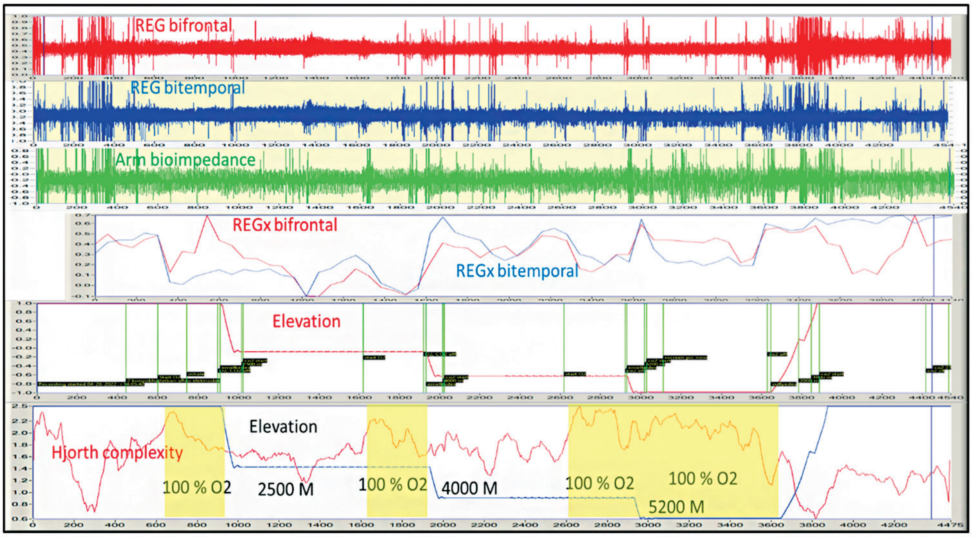

Figure 2.
Recording and data processing in the LPC chamber (edited by Michael Bodó in Datalyser program) [64]
Note: Traces are: bifrontal [upper trace], bitemporal REG, and arm bioimpedance pulses in the upper three are on upper three traces. REGx bifrontal and REGx bitemporal are on the middle panel. NB: The first REGx number is calculated at 300 sec/5 min. The two lower panels show the elevation levels [change of air pressure in the LPC chamber] as a function of time. The last but one block involves notes. At the bottom, there are traces of the levels in meters and the Hjorth complexity of frontal REG derivation. At each level, 100% O_2 was administered during the last 5 minutes, except at 5200 m, when it was administered all the time, indicated by the yellow colour. The window size is 4540 seconds [75.67 min.]. X-axis is in seconds. The file name is April 26 2.

2. PRx-REGx: The method of calculating secondary indices of CBF AR is based on the “moving correlation coefficient” [7], [9]. This method allows analysis of the degree of correlation between two factors within a time series where the number of paired observations is large. Time-averaged values from each factor (10 seconds) are plotted in an x–y scattergram in a moving correlation window of 5 minutes and renewed every interval from 10 seconds to 1 minute. The correlation coefficients are calculated as a simple Pearson correlation coefficient and range from maximal –1 (negative correlation) to +1 (positive correlation), and can be further analysed as a time-dependent variable [46].

3. Hjorth analysis: Hjorth developed an EEG analysis method [44]. One of these parameters is complexity, sometimes called the form factor. Complexity, giving a measure of excessive details concerning the “softest” possible curve shape, the sine wave, corresponds to unity. It is expressed as the number of standard slopes generated during the average time required to generate one standard amplitude as given by mobility. Due to the non-linear calculation of standard deviation, this parameter will quantify any deviation from the sine shape as an

increase from unity Hjorth complexity, giving a measure of excessive details concerning the “softest” possible curve shape, the sine wave, which corresponds to unity. It is expressed as the number of standard slopes generated during the average time required for generating one standard amplitude as given by the mobility.

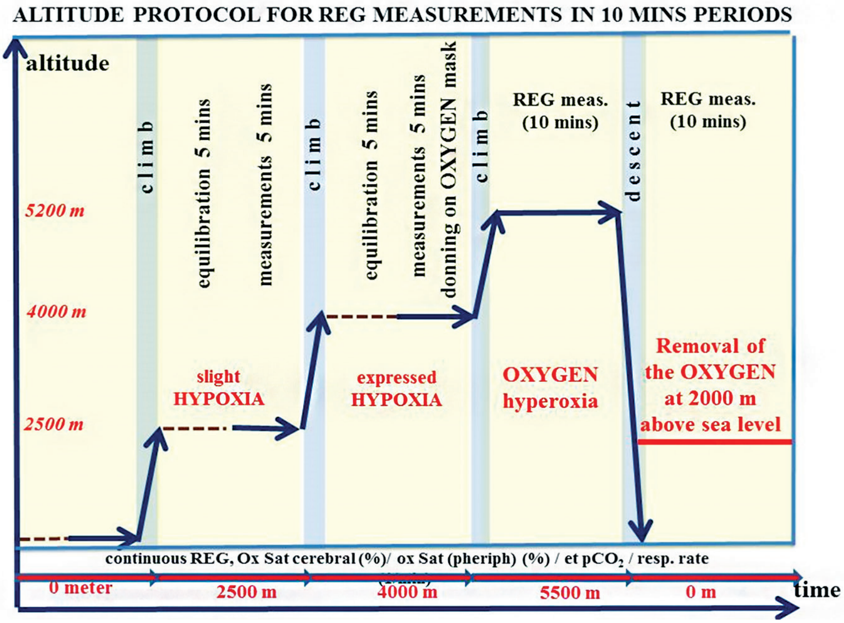

Figure 3.
REG altitude protocol with hypoxic and hyperoxic episodes in the LPC chamber [edited by Sándor Szabó]

Hjorth analysis was performed with a 5-second time window. From the REG signal Hjorth, variables were calculated and smothered with running averages of 60 seconds, and data was copied into an Excel spreadsheet and averaged by male and female, as well as bifrontal and bitemporal groups – see Figure 3. A chamber pressure trace was added, and the last five minutes and the previous minute’s mean were calculated. The initial 5 minutes were considered as control or baseline, and values during 100% O_2 inhalation were compared to this mean.

2.7. Statistical analyses

Two-way ANOVA was used to compare male and female REGx (Prism, GraphPad Software, Boston, MA). The t-test (in Excel) was also used to compare group means. Compared modalities were: 1. REG bifrontal and bitemporal derivations; 2. female-male groups. For automatic REG pulse wave analysis, an algorithm was developed and written in MATLAB (MATLAB R2023a), and the estimated P1s and P2s were also analysed with the MATLAB program (MATLAB R2023a, Statistics and Machine Learning Toolbox version 12.5) [47]. $P < 0.05$ was considered significant.

3. Results

3.1. Tilting table

3.1.1. REG amplitude

There was no significant difference in mean bifrontal REG 1st peak amplitudes during breath holding between 1. control (before Trendelenburg position) and Trendelenburg position (p = 0); neither 2. between male and female groups (male: 2.35 ±7.5% and female −0.27 ±3.6% (p = 0.33). Out of 19 subjects, only 10 (53%) showed REG 1st peak amplitude increase (0.02%; p = 0.46). The 2nd peak increased in 15 subjects (78%); the "shoulder" formation on the catacrotic (descending) side was in 11 subjects (58%). The mean percentage increase was 6.94% for females and 13.66% for males. The increase was significant in 5 cases (out of 6; 83%; P < 0.0001; 95% confidence interval −0.04123 to −0.02710) for females and 8 for males (out of 13; 62%; P < 0.0001; 95% confidence interval −0.05796 to −0.05178). However, the change of shape of the REG pulse waveform deformation was relevant (Figure 4).

3.1.2. REG amplitude–breath-holding

There were three 30-second breath-holding tests during the control period and the HDT position. REG pulse first peak increased, but it was not significant (p = 0.16) comparing control to HDT position for males (p = 0.16) nor for females (p = 0.53). The only significant differences were between male and female groups after the second (p = 0.02) and the third 30-second breath-holding (p = 0.01). There was no significant difference between male and female groups in REG pulse amplitude increases during the control period after 30-second breath-holding, nor between control and HDT position.

3.1.3. REG derivatives

There was a significant difference (p = 0.03) between male and female groups in bifrontal REGx, possibly because of the difference during the HDT position, starting about at the 15th minute. The correlation coefficient was 0.49, probably for the same reason. During HDT position (between 15–37 minutes) both groups' REGx values decreased, but the male values were more than the females (p = 0.0002).

3.1.4. Automatic P2 calculation

In the case of duration-matched data, the result was that the increase in P2 values during HDT was significant in 4 cases in the female group (4/5; 80%) and 11 cases in the male group (11/14; 79%). When using only the Wilcoxon test, the ratios were 4/5 (80%) and 10/14 (71%). Using the full length of the recording in each of the three phases, the results were slightly different (Figure 5).

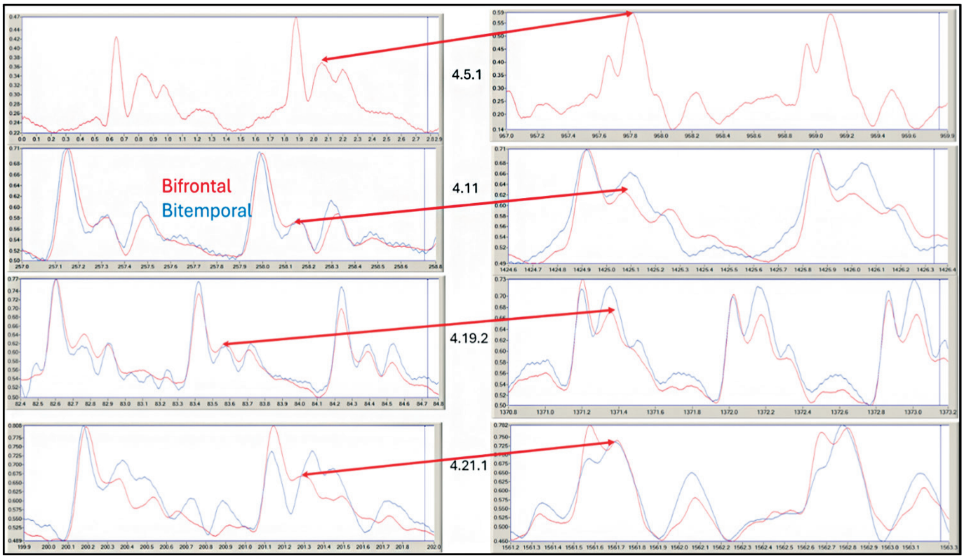

Figure 4.

Fragments of recording of bifrontal and bitemporal REG pulse waves during control/rest (before HDT position; 0°), on the left side) and during HDT positions (–15°) (on the right side) in four subjects chamber [edited by Michael Bodó in Datalyser program]

Note: The color indicates derivation. The Y-axis is in Volt. X-axis is in seconds. The window size is about 3 sec. Subjects are labelled by the recording date, for example, 4.5.1: the first recording that day.

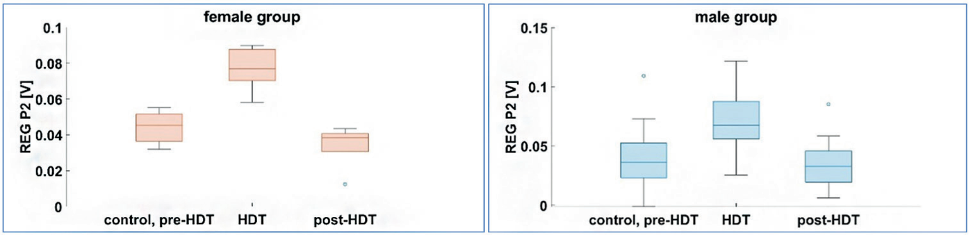

Figure 5.

Comparison of the group results of automated P2 calculations, the female group (left) and the male group (right) [edited by Michael Bodó, István Pintér, Mihály Bagány]

Note: REG P2 increase was significant for both females [p = 0.01] and for males [p = 0.02]. NB: the evaluation involved the full length of each phase. The mean file length was 45:47 ±5:45 min. HDT lasted about 15 minutes. There were 3 times 30-second breath-holding before and during HDT positions.

3.2. Low-pressure chamber (LPC)

3.2.1. REG amplitude

REG traces showed a minimal amplitude decrease during 100% O_2 inhalation. During 4000 m before 100% O_2 inhalation, the REG amplitude decreased: in bifrontal derivation –4.19 ±8.39%, P = 0.039. During 100% O_2 inhalation in the bifrontal derivation, REG amplitude decrease was –8.69 ± 9.66%, p = 0.0004. In bitemporal derivation, it was –7.19 ±34.08%, p = 0.0007. REG pulse amplitude decreased (percentage of control –3.92 ±8.14%) during 5200 m, but it was not significant (p = 0.09). Neither the difference between the female and male groups (p = 0.69).

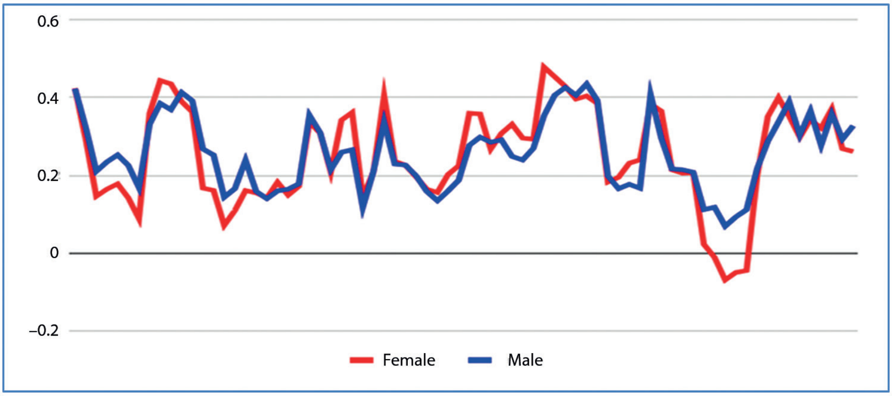

Figure 6.
Group average of bifrontal REGx in female and male groups in the LPC chamber
[edited by Michael Bodó, István Pintér, Mihály Bagány]

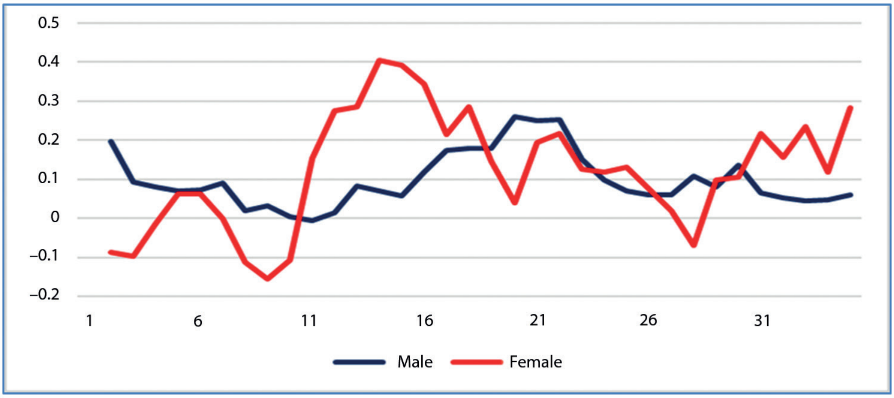

Figure 7.
Group average of bitemporal REGx in female and male groups in the LPC chamber
[edited by Michael Bodó, István Pintér, Mihály Bagány]

3.2.2. REG derivatives

Calculated REG variables (REGx and Hjorth parameters) showed similar oscillations, but there was no correlation to the simulated altitude. Hjorth complexity: The correlation coefficient between bifrontal and bitemporal REG derivations in the LPC chamber was 0.80 ±0.12. The male-female difference was not significant ($p = 0.36$). The correlation coefficient between bifrontal and bitemporal REGx was 0.77. The difference between males and females REGx was significant ($p = 0.0001$; R2: 0.51). The overall trend was similar. The difference was not significant ($p = 0.41$; correlation coefficient: 0.09) (Figures 6–9).

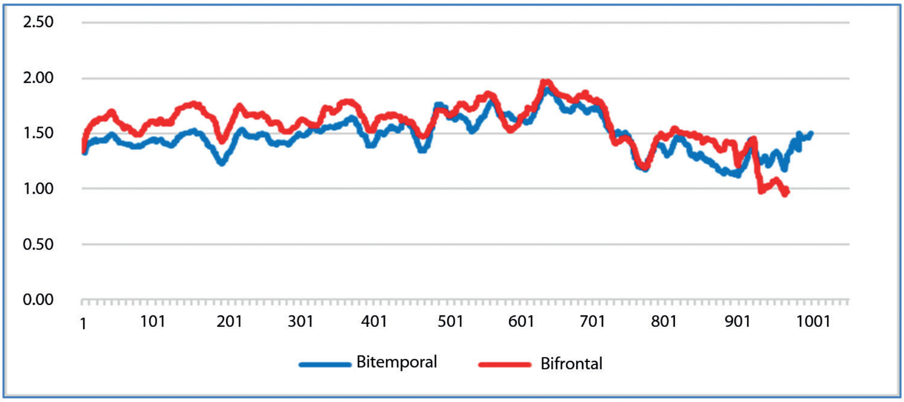

Figure 8.
Group average of bifrontal and bitemporal Hjorth complexity in female and male groups in the LPC chamber
[edited by Michael Bodó, István Pintér, Mihály Bagány]

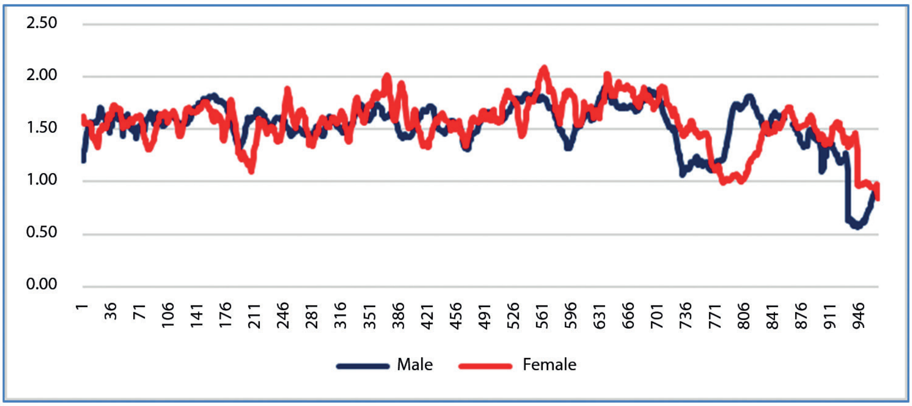

Figure 9.
Group average of bifrontal Hjorth complexity in female and male groups in the LPC chamber
[edited by Michael Bodó, István Pintér, Mihály Bagány]

4. Discussion

From the flight safety aspect, the proper working capability and mental performance of the pilot are emphasised in all human error models, assuming proper functional responsiveness in brain circulation and oxygen utilisation in any flight manoeuver related to acceleration (or microgravity) and hypoxia [1], [5]. In this descriptive study, we described that *during HDT position,* 1. REG pulse wave morphology changed like ICP pulse wave morphology during ICP elevation (P2 increase); 2. REGx indicated active CBF AR at the start of HDT; 3. bifrontal and bitemporal REGx group averages were similar in female and male groups; 4. bifrontal and bitemporal Hjorth complexity group averages were similar in female and male groups. The 30-second breath holding resulted in REG pulse amplitude increase with interindividual differences. The developed program was able to detect a P2 increase of 92%. During *simulated altitude,* REG pulse amplitude decreased during 100% O_2 inhalation. Bitemporal and bifrontal REGx correlated well, as well as the Hjorth complexity for female and male groups.

4.1. Military aviation

A counteraction of the G force of a dive-bomber pilot [48] was described by Kleiss [49], who said he rarely used 4G pullout in a high-threat area. He often used 7, 8, or even 9Gs, significantly reducing his pullout altitude. But during a pullout at 9G's, a 200-pound pilot would weigh about 1,800 pounds, and every part of his body – arms, legs, head – would weigh an equivalent to nine times its normal weight. His blood would rush toward his lower extremities. When the flow of the blood passed his eyes, he would begin to black out. A gray curtain would seem to descend over his eyes. He would still be conscious, but temporarily blind. To prevent this, Kleiss used a technique that today we call an "anti-G straining manoeuver," or AGSM, which is like a breathing method known as Valsalva [50]. He would take a big breath, hold it, and strain or grunt to help prevent the blood from continuing its downward flow. He would then quickly release the breath, draw another, and grunt again. Once the pullout was completed, he would discontinue this AGSM [49].

The good news is that the Canary™ system [6] is available today and measures blood perfusion, heart rate, and oxygen saturation; noninvasive; fully integrated into the Helmet Mounted Display (HMD) system, supporting JHMCS-II, Digital-JHMCS, and the Targo™ families; no external hardware or wiring modification required; provides pilots with early warning of developing hypoxia condition; provides feedback on the quality of pilots' Anti-G Straining Manoeuver (AGSM) and G-LOC hazard level; detects and helps prevent G-LOC, and enables autopilot recovery [6].

4.2. Space flight

Long duration spaceflight alters intracranial tissue and fluid position [51]. In the Apollo–Soyuz collaboration, bioimpedance measurement was introduced in space research. It was used to study systemic and regional hemodynamics [52] and brain circulation [53]. There are several Russian language REG-related publications translated to English in the NASA database (NASA

Technical Reports Server – NTRS). The 2024 NASA Human Research Program Investigators' Workshop (February 13–15) involves SANS sections as well. SANS develops in approximately 70% of crewmembers completing ~6-month long standard-duration missions to the International Space Station, and is thought to result from the weightlessness-induced headward fluid shift. Terrestrial analogue studies that have used a 30-day strict 6° head-down tilt (HDT) bedrest to mimic this chronic fluid shift have demonstrated similar ocular changes to SANS, including optic disc oedema and chorioretinal folds. Several presentations/posters have used HDT, since it was established as a spaceflight analogue to investigate SANS [54]. The ICP measurement is planned to be performed before and after space flight invasively, by lumbar puncture [55]. The primary signs of SANS include optic disc oedema (ODE), chorioretinal folds, posterior globe flattening, and hyperopic shifts in refractive error. Each of these signs presents a potential risk to a crewmember's vision and mission effectiveness, with ODE posing the highest risk overall [56]. Based on the above facts, the noninvasive REG is a potential tool to study the cerebrovascular aspect of SANS. While the aetiology of SANS is currently unknown, headward fluid shifts due to microgravity in space are hypothesised to be a major contributing factor. A countermeasure (CM) that can successfully redistribute body fluids like the upright position on Earth may thus be important for SANS prevention [57]. REG can be used to quantify the effect of CM.

4.3. Hjorth complexity

As a relevance for signal processing modality, a PubMed search was executed with the keywords "Hjorth complexity and brain blood volume"; "Hjorth complexity and ICP"; "Hjorth complexity and hypoxia"; "Hjorth complexity and CBF" which resulted in no hits. On the contrary, "Hjorth complexity and EEG" resulted in 41 hits (15 December 2023). Articles covered health subjects and patient studies. Many hits were found based on EEG and did not involve Hjorth complexity. A study found a significant decrease in Hjorth complexity following alcohol consumption [58]. Pathological disorder studies on schizophrenia, posttraumatic stress disorder, panic disorder, and epilepsy have reported lower Hjorth complexity in pathological states compared to healthy subjects [59]. A study claims that lower EEG complexity is attributed to abnormal neural integration in the above-mentioned mental disorders [60].

4.4. Actuality

The first Hungarian in Space event was in 1980: Bertalan Farkas, along with Soviet cosmonaut Valery Kubasov, was launched into space on Soyuz 36 from Baikonur Cosmodrome on 26 May 1980, at 18:20 (UTC). While in orbit, Farkas conducted experiments in material and medical sciences. After 7 days, 20 hours, and 45 minutes, and having completed 124 orbits, Farkas and Kubasov returned to Earth, landing 140 km southeast of Jezkazgan. He used a device, called Balaton (Medicor, Budapest, Hungary) to test psychophysiological status [61].

The Hungarian government decided to send a second Hungarian astronaut to ISS with Axiom Space Agency (www.axiomspace.com/) in 2024/25 for one month. This was the background that we started testing REG measurements with this goal: let's bring the Hungarian astronaut a REG device to the ISS, similarly as it was done in 1980.

We applied for the Hunor grant program to build a REG device that the Hungarian astronaut can bring to the ISS and make measurements at the same time when the OCT and fundoscopic measurements will be performed to establish a correlation to the SANS status.

5. Conclusions

- REG pulse wave morphology change (peak 2 increase) during HDT is identical to ICP pulse wave change during ICP elevation/decreased intracranial compliance;
- a MATLAB script was created and successfully identified REG peak 2 automatically;
- manual and automated measurement of REG Peak 2 showed a strong correlation (92%);
- REG offers additional data processing;
- REGx can be a suitable, noninvasive alternative to PRx for use in head-injured and hypotensive patients;
- REG can monitor the status of CBF AR on the battlefield, during transport, hypotensive resuscitation, and in PEEP-ventilated subjects;
- REG monitoring fits into the USU Surgical Critical Care Initiative (SC2i), which focuses on developing Clinical Decision Support Tools for Critical Care [62];
- a study was initiated to compare invasive and noninvasive neuromonitoring (ICP & REG);
- a US Army grant application was submitted to build a prototype REG monitor as a useful tool for prehospital care and triage;
- bioimpedance offers multimodal noninvasive monitoring;
- conductive fabrics can be used as reusable electrodes [63];
- REG electrodes and electronics can be placed into the helmet;
- the applications of REG monitoring can be used in neurocritical care, space research, military aviation and transporting wounded Service Members, civilian emergency medicine, and mass casualty evacuation.

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Disclosure information

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Az űrrepülés élettani kihívásai és földi szimulációs lehetőségek az agyi keringési változások nyomon követésére: reoenkefalográfiás eredmények

A katonai repülés és az űrrepülés különleges pszichés és szomatikus stressztűrő képességet kíván, amelyhez alapvető a szellemi teljesítményt meghatározó agyi vérkeringés és oxigénszállítás teljes funkcionális épsége. Jelenleg a jelöltek alkalmassági vizsgálatánál, szűrésénél azonban a mai napig nincs ilyen, az agyi keringést és annak önszabályozását (autoregulációját –AR) minősítő eljárás, miközben a pilóta mentális terhelése vagy „fej-láb irányú túlterhelése" alatt információfeldolgozó képessége kritikus helyzetben elégtelenné válhat. Az űrállomáson, a tervezett mélyűri missziók során viszont ellenkezőleg, a súlytalanság miatt feji-nyaki régióba irányuló véráthelyeződés koponyaűri nyomás- (ICP) fokozódást, és a földi körülményekhez képest akár tízszer magasabb szén-dioxid-szint a szemben és az agyban keringési problémákat és panaszokat okozhat (Space Associated Neuro-Ocular Syndrome – SANS). A keringési dinamika és agyi oxigénellátás változásait billenőasztalon és barokamrában vizsgáltuk, 19 főnél regisztráltuk a bioimpedancia elvén működő eljárással (reoenkefalogram – REG) a pulzushullámot a fejen és az alkaron, légzésvisszatartás után. Megállapítottuk, hogy a billenősztalon „fej-le" helyzetben a REG pulzushullám második csúcsának amplitudója megnő, hasonlóan az ICP-pulzushullámhoz, amely a klinikumban koponyaűri nyomásfokozódásként kedvezőtlen jel. A kézi leolvasás szignifikáns különbséget eredményezett a női (P = 0,0007) és a férfi (P < 0,0001) csoportban a nyugalmi és a „fej-le" helyzet között. Automatizált elemzéssel is a REG P2 növekedése szignifikáns volt, és az arány 4/5 (80%) volt a nőknél és 10/14 (71%) a férfiaknál, ezt a munkacsoport által megírt automatikus program 92%-ban képes volt kimutatni. A számított értékek detektálták az agyi keringési autoreguláció állapotát és a férfi és női csoport közötti azonosságot. Ezen eredmény és korábbi REG korrelációs vizsgálatok alapján megállapítható, hogy a REG mint agyi keringést és koponyaűri nyomásváltozást noninvazív módon jelző eljárás használható vadászpilóták, űrhajósok és idegsebészeti őrző osztályos betegek valós idejű monitorozására, vészhelyzeti riasztás céljából, az agyi keringés átmeneti megszűnésekor.

Kulcsszavak: *koponyaűri nyomás, noninvaziv, reoenkefalográfia, szimuláció, Trendelenburg pozíció, hypobárikus hypoxia*

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