REVIEW. SUSTAINABLE TECHNOLOGIES COLLECTION

A noninvasive, continuous brain monitoring method: rheoencephalography (REG)

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This paper deals with the sustainability under anoxic conditions of human beings, both when healthy, and diseased. As our attention is focused these days on the environment, sustainability, and green energy, a similar effort is being made in neuromonitoring to switch from invasive to noninvasive monitoring methods. Keys to these changes are computerization and shrinking size of electronic hardware. Computerization is going on in all areas of biomedical engineering, both in research and in clinical fields of medicine. In neurology, brain imaging is the most characteristic change in recent decades. These modalities of imaging (MRI, CT, PET scan, etc.) are predominantly utilized for localizing brain pathology. Brain imaging offers great spatial resolution, but poor time resolution. Therefore, for continuous monitoring, neurocritical care departments require an additional tool with good time resolution. There are invasive and noninvasive neuromonitoring methods. The standard method to monitor intracranial pressure (ICP) is an invasive method. Computerization allows for calculating the cerebral blood flow autoregulation (CBF AR) index (pressure reactivity index - PRx) from ICP and systemic arterial pressure (SAP) in real time, continuously, but invasively. The new development, discussed in this paper, is to calculate this index noninvasively by using rheoencephalography (REG), called REGx. We present the road to this invention and summarize multifold REG related results, such as using REG for primary stroke prevention screening, comparison incidence of arteriosclerotic risk factors, various studies by using CBF manipulations, and correlations with other neuromonitoring methods, and validation with in vitro and in vivo methods. REG by using different algorithms allow for real time calculation of autoregulated blood flow. This paper presents results of validation of CBF algorithms as an effective, noninvasive method. The author's intent is to supply sufficient physiological background information. This review covers the author's research efforts over several decades; it pertains multiple studies and has an updated addition to human sustainability by considering that Covid-19 is increasing stroke and cardiovascular disease (CVD) morbidity and mortality.

Keywords: Brain monitoring, REG, Rheoencephalography, Neuromonitoring, MRI, CT, PET

1. Introduction

The first published studies of bioimpedance measurements of brain circulation, in the 1950s, show a trajectory like early measurements of heart and brain electrical activity (electrocardiogram - ECG and electroencephalogram - EEG). Early bioimpedance research (Nyboer, 1954; Kubicek et al., 1975) began with thoracic (cardiac) measurements, which were soon followed by measurements of brain circulation (Nyboer, 1960, 1970; Lifshitz, 1963, Geddes et al., 1964, Yarullin, 1965, Polzer and Schuhfried, 1962). The original bioimpedance device was a four-electrode system (Kubicek et al., 1974; Patterson, 1995), later modified to two electrodes (Markovich et al., 1967, Seipel, 1967, Namon, et al., 1967). The electrical impedance method (measuring blood flow by alternating current) is known in clinical practice; however, it is used primarily in cardiology to determine cardiac output (ICM) and peripheral circulation (venous occlusion plethysmography). Electrical impedance plethysmography measured on the head is called cephalography or REG. The United States Food and Drug Administration (US FDA) definition states: 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. (Anonymous 1). PubMed search with keyword Rheoencephalography found 312 hits (Anonymous 2). Bioimpedance amplifiers use a two-stage Wheatstone bridge-differential amplifier circuit design (Anonymous 3). Frequency is measured is in the range from 15 kHz to 1 MHz (Moskalenko, 1980, Jenkner, 1986, Meghdadi et al., 2019). REG is based on monitoring pulse synchronous variations in cranial electrical impedance over time.

Two-electrode system can record pulsatile component only, which is a small portion of total impedance. The advantage of four-electrode system is that it can measure basic impedance; it is used for cardiac output (thoracic bioimpedance - ICG) and peripheral circulation measurements. Significant physiological information derived from the REG signal relates to fluid content, vasoconstriction, and vasodilation in the brain. This is manifested by decreasing and increasing REG pulse amplitudes, respectively. The units of these amplitude changes are measured in Ohms, however, there are no normative values associated with the REG amplitude values due to the many factors that can affect it, detailed by Moskalenko (1980). The electrical impedance/REG pulse curve

looks like an inverted arterial pressure pulse curve. REG pulse wave amplitude is due to the conductivity differences between brain tissue, cerebrospinal fluid, and blood. Blood and cerebrospinal fluid are better conductors than the brain and other 'dry' tissues. Various correlations have been established between REG and cerebral blood flow (CBF) (volume, flow, or pressure, detailed by Jenkner, 1986, Eniya, 1973, Naumenko and Skotnikov, 1975). Consensus from a review of published REG literature is that the REG signal represents volume change. It was demonstrated that REG signal reflects information of cerebrovascular reactivity, intracranial pressure, arteriosclerotic change of brain vessels (McHenry, 1965, Jenkner, 1970). REG pulse amplitude is quantified most frequently by using its derivative (Jacquy et al., 1974, Hadjiev, 1968) or integral. Both variables are sensitive to changes in CBF induced by perturbations such as CO₂ inhalation, Trendelenburg position, carotid occlusion, breath holding, Valsalva maneuver, and hemorrhage. Earlier studies (Moskalenko, 1980) made an initial effort to establish pathophysiological correlates to REG (McHenry, 1965, Jenkner, 1986), but did not establish a correlation between arteriolar/venular blood volume and CBF autoregulation (AR). The correlation of REG anacrotic (raising) portion (minimum – maximum time) and cerebral arteriosclerosis was established by Jenkner (1970). He published in 1970 that “anacrotic part of REG (in seconds) as averaged from 100 phases in 178 normal persons and 246 arteriosclerotic subjects, all of which had been submitted to carotid arteriography” (Fig. 68 in Ref. 25). A publication certified REG from intracranial component (Perez, 2014). Nevertheless, previously, opposite opinions had been voiced, as well (Waltz and Ray, 1965, 1967, Perez-Borja, Meyer, 1964).

Figure 1. REG pulse wave (purple) and its relationship to electrocardiogram (blue). Pulse wave was inverted.

The advantages of REG are its non-invasive nature, the ability to monitor continuously, and low cost. A disadvantage is that REG is sensitive

to movement artifact, much like EEG. There is an international organization for electrical bioimpedance (Anonymous 4) with regular conferences and journal (Anonymous 5). REG was listed as a noninvasive neuromonitoring method (Rubin et al., 2009).

REG data processing: Historically, REG analysis has calculated pulse amplitude changes in the waveform, recorded on paper in chart form, and analyzed visually. Contemporary REG analysis, accomplished by computerized data processing software, enables continuous CBF AR monitoring (REGx – Brady et al., 2010). Best illustration of how REG development is a multidisciplinary subject is the used data processing. In the 1970s REG filtering was realized by using analogue filter and integrator. Additional data processing modules were also built based on analogue circuitry and a digital calculator was used to calculate absolute CBF by H₂ clearance in animal studies. In addition, new REG devices were introduced (Peredi et al., 1981; Bodo et al., 1981; Peredi et al., 1987; Zoltai et al., 1987). From the late 1970s, software development has supported REG data processing (Jenkner, 1986; RheoSys: Montgomery, et al., 1989; Weinstein et al., 1978; Moskalenko, 1980; Sokolova et al., 1977; Sokolova and Yarullin, 1982; Jenkner, 1986). By this line 3 data acquisition systems were created and used to collect, display, and process REG and other physiological signals (Bodo et al., 1995, 1996; Heilig et al., 1998; Nagy et al., 2001; Baranyi et al., 2018). In addition to REG data processing, the Cerberus system (Bodo et al., 1995) provides a model for storing analog physiological signals in a computer-based medical record. Cerberus was prepared to be turned into an expert system, and was also tested (Kabakcioglu et al., 1994). Similarly, to EEG, REG data processing was also computerized (Traczewski et al., 2005; Meghdadi et al., 2019). Electrical impedance brain scanner was proposed in 1978 (Benabid et al.); Maltron International becoming a manufacturer of Bioelectrical Impedance Analysers (BIA) and Electrical Impedance Tomography (EIT) imaging technology. There are many bioimpedance device/BIA manufactures (Maltron, UFI, Medis, etc.), not only for REG but for lung function and body composition analysis. BIA analyzers are using a multifrequency measurement.

2. REG related results

REG - ICP – Cerebral blood volume correlation during CO₂ inhalation in humans

The REG pulse amplitude relationship to cerebral blood volume was documented in humans with radio-iodinated human serum albumin (RIHSA) method during CO₂ inhalation. This study revealed that REG transiently increased reflecting the intracranial blood volume increase and correlated with ICP increase, as well (Bodo et al., 1986; Bodo 1990).

2. Cerberus system

Stroke is unique among neurological diseases since it has a high incidence rate, severe burden of illness, high economic cost, and it may be preventable (Gorelick, 1994). Described here is a system for screening the cerebral- and vascular status of individuals to detect the initial stages of vascular disorders.

Cerberus, a computer based polygraphic system questions subjects about risk factors, stresses, neurologic symptoms of transient ischemic attack (TIA), and monitors impedance pulse waves of the head (REG) and extremities, EEG, and ECG. For technical details, see Bodo et al. (1995 and 1996).

Cerberus measurement 1; Healthy group 1.

In this study a Cerberus prototype was used, built in Budapest, Hungary, by Metracomp Ltd. The used program was GRAL (Nagy, et al., 2001).

Methods: A cross-sectional survey (546 subjects) was conducted in the early 1990s, by means of the Cerberus system, which includes: 1. a questionnaire addressing the risk factors for stroke/cardiovascular disease; 2. amplifiers to record the pulse waves of cerebral (REG) and peripheral arteries, EKG, and EEG. Additionally, subjects were measured for carotid stenosis by Doppler ultrasound and 12-lead ECG; they were also screened for blood cholesterol, glucose, and triglyceride levels. REG was considered arteriosclerotic if its anacrotic (rising) portion was above the 180 ms threshold, modified after Jenkner (1970). Additionally, anxiety, depression, dementia, neurosis was evaluated (Sipos et al., 2008).

Findings: Prevalence of the following stroke risk factors was identified: overweight, 63.25%; sclerotic brain arteries by REG, 54.29%; heart disease, 37.92%; pathologic carotid flow, 34.24%; smoking, 30.55%; high blood cholesterol, 28.70%; hypertension, 27.83%; high triglyceride, 24.35%; abnormality of electrocardiogram, 20%; high glucose level, 15.95%; symptoms of transient ischemic attack, 16.07%; alcohol abuse, 6.74%; and diabetes, 4.53% (Bodo et al., 1992, 1998, 2008).

Figure 2. Significant correlations among measured variables. Cerebrovascular alteration (REG-Doppler-TIA) was in a bridge position between measured somatic (left) and psychological (right) variables ($n=546$, $p<0.05$). SAP: systemic arterial pressure; cer. art. scler: cerebral arteriosclerosis; REG: rheoencephalogram; Doppler: carotid flow systolic velocity measured by Doppler ultrasound; veget. bal: vegetative balance by Kerdo-Sipos; blood cholest: blood level of total cholesterol; TIA: symptoms of transient ischemic attack entered Cerberus inquiry (Sipos et al, 2008). Conclusion: The study demonstrates a possible model for primary cardiovascular disease/stroke prevention. The simple, noninvasive test uses the bioimpedance method of measurement. This method offers a standardizable, cost-effective, practical technique for mass screenings by identifying the population at high risk for cardiovascular disturbances, especially cerebrovascular disease. In this model, REG can detect cerebrovascular arteriosclerosis in the susceptibility/pre-symptomatic phase, earlier than the Doppler ultrasound technique.

Cerberus measurement 2; Psychiatric population and healthy group 2

In our next study we used an upgraded Cerberus system, built in Budapest, Hungary, by Quintlab Ltd. The program was a newly developed software (Heilig et, et al., 1998 and Quintlab Ltd.).

Methods: Test subjects were 48 alcoholic patients in Hungary; the control group consisted of 12 drug-addicted and depressed patients in Hungary and 13 healthy male subjects in the United States. Additional subgroups were formed according to smoking habits and average daily alcohol dose. REG was measured by a computer-based system, Cerberus; REG anacrotic time above 180 ms was considered pathological (Szalay et al., 2006).

Findings: ANOVA showed that daily alcohol consumption and smoking were significantly greater for alcohol abusers than for drug-addicted

and depressed patients. Twelve alcoholics showed a pathological REG anacrotic time. Longer REG anacrotic time was correlated with higher daily alcohol consumption. In the alcoholic group, the steeper regression line of REG slope reflected the pathological impact of alcohol abuse. The healthy control sample showed a nearly identical slope for both REG and age. Correlation of increased REG anacrotic time and daily alcohol consumption supports the hypothesis that REG detects accelerated cerebrovascular aging (arteriosclerosis) in alcoholic subjects.

Conclusion: Obtained data support the hypothesis that a correlation exists between anxiety, excessive alcohol consumption and cerebrovascular disorders (Sipos and Bodo, 2019).

Figure 3. Sorted age and REG anacrotic time in alcoholic group. Sorted age and REG anacrotic time in alcoholic group. The steeper REG anacrotic time slope reflected the pathological impact of alcohol abuse. After being sorted independently for REG anacrotic time and for age, these variables showed the following regression values: age, $y=0.5697x+29.341$ $R^2=0.9398$ (linear); REG anacrotic time, $y=4.3882x+7.4492$ $R^2=0.8682$ (linear) and $y=36.685e^{0.0404x}$ $R^2=0.9279$ (exponential).

Figure 4. Sorted age and REG anacrotic time in healthy group. Sorted age and REG anacrotic time in healthy group. Physiological cerebrovascular aging. REG anacrotic time showed an identical slope with age. Age and REG regression values (calculated as one group, $n=13$) are as follow: Age: $y=3.4505x+11.769$, $R^2=0.9509$, and REG anacrotic time: $1.7912x+50.385$, $R^2=0.9527$ (both linear).

Cerberus measurement 3; Mobile phone testing

Cerberus system was used to measure brain effect of mobile phone use (Thuroczy, et al., 1999). A slight decrease in the REG amplitude during the exposure was observed.

Figure 5. Breath holding. Breath holding, REG (red) and NIRS (blue) signals during breath holding (see 350-380 seconds: breath holding is indicated by light blue vertical lines). REG and NIRS amplitude increases were simultaneous: 20.2 % of baseline (after test). Y-axis values are shown in AD conversion units; X-axis values are shown in seconds (Bodo et al, 2018).

Cerberus measurement 5; Demo and measurement*

Table 1: Events and Academic Institutions in Europe

Event	Location	Year
International Fair	Budapest, Hungary	1991, 1992
Salon International de L'invention de Paris (Concours Lepine)*	Paris, France	1993
International Technical Expo	Hannover, Germany	1994
Semmelweis Medical School, Geriatric Research Center	Budapest, Hungary	1994
University of Physical Education	Budapest, Hungary	1996
Frédéric Joliot-Curie National Research Institute for Radiobiology and Radio Hygiene	Budapest, Hungary	1997

*Cerberus was the only awardee by the French Minister of Scientific Research

Table 2: Events and Academic Institutions in USA

Event	Location	Year
International Expo of Invention	Pittsburgh, Pennsylvania	1993
University of Miami School of Medicine, Department of Neurology	Miami, Florida	1994
Massachusetts Institute of Technology, Clinical Research Center	Boston, Massachusetts	1995
Life Resuscitation Technologies, Inc.	Chicago, Illinois	1996
University of South Florida, Department of Neurology and Public Health	Tampa, Florida	1996
Health Department	Baltimore, Maryland	1998

*NB: The above list shows Cerberus system demos/use. After 2000, only the Cerberus amplifier was used in USA.

Cerberus measurement 4; Healthy group 3

The US FDA concluded that Cerberus is a “non-significant risk device”. An electromagnetic safety test has proven its applicability (MET Laboratories, Inc., Baltimore MD, 2009).

The cited study compares cerebrovascular reactivity monitored by REG, a noninvasive continuous monitoring modality, to cerebrovascular reactivity measured by currently used neuromonitoring: transcranial Doppler (TCD), near infrared spectroscopy (NIRS), and laser Doppler flowmetry (LDF). Fourteen healthy volunteer subjects were examined. Tests used for comparison of cerebrovascular reactivity were breath-holding, hyperventilation, CO₂ inhalation, the Valsalva maneuver, and the Trendelenburg and reverse Trendelenburg positions. Data for all modalities were recorded by computers and processed offline. All measured modalities reflected cerebrovascular reactivity with variabilities. Breath-holding, CO₂ inhalation, and the Valsalva maneuver caused CO₂ increase, resulting in brain vasodilatation; hyperventilation caused CO₂ decrease and brain vasoconstriction. The Trendelenburg and reverse Trendelenburg positions caused extracranial blood volume changes, which masked intracranial cerebrovascular reactivity. The hyperventilation test was ineffective for measuring cerebrovascular reactivity with REG due to respiratory artifacts. Some discrepancies among the various tested modalities were observed. Further validation studies are under preparation to test the

applicability of REG for noninvasive continuous brain monitoring, including enhanced computational methods, animal studies and clinical monitoring studies of humans (Bodo et al., 2017).

In vitro bioimpedance validations

Based on preliminary results, REG shows promise as a practical, noninvasive, and continuous monitoring modality of brain injuries. However, REG literature reflects uncertainty about whether the signal reflects flow or volume. Presented here are results of *in vitro* studies manipulating flow/volume to model clinical conditions (such as brain ischemia and vasospasm) while recording the electrical impedance signal. A loop was created using tubing filled with 0.9 % NaCl. This loop was comprised of a Doppler in-line flow probe connected to an ultrasound flow meter, a peristaltic pump, a pressure transducer, and home-made electrical impedance measuring cell, incorporating a balloon catheter. Bipolar impedance amplifiers were used to measure the impedance pulse waves. Data were stored on a PC and processed off-line. This *in vitro* study confirmed that 1) Doubling flow rate influenced the pulse amplitude and mean flow of the Doppler signal; 2) Doubling flow rate had no influence on the amplitudes of the pressure or electrical impedance signals; 3) An increase in amplitude was observed in the pressure and electrical impedance signals when the first derivative was taken.

Figure 6. PRx – REGx comparison during vinpocetine injections in rat. PRx – REGx comparison during vinpocetine injections in rat. Upper panel: SAP (red) and ICP (blue) traces. Blue ICP peaks indicate time of vinpocetine injections (n=3).

4) Balloon inflation decreased electrical impedance and Doppler flow pulse amplitudes; 5) With balloon inflation, Doppler and electrical impedance signals showed an identical relationship to decreased flow ($R^2 = 0.966$) (Bodo, 2010).

***In vivo* animal studies**

Microwave exposure on rats: REG pulse wave amplitude increased after 10 min, 10 mW cm⁻², 2450 MHz microwave exposure (Thuroczy et al., 1992).

CBF manipulations on rats (Figure 6): Several groups were used for measuring REG pulse amplitude change during electrical stimulation, carotid clamping, hemorrhage, CO₂ inhalation, vinpocetine injection. REG was compared to carotid flow, laser Doppler flow, ICP, SAP, and spreading depolarization (Bodo et al., 2003, 2004, 2005, 2010, 2015, 2016).

CBF manipulations on pigs

Several groups were used for establishing REG pulse waveform change during aortic compression, progressive hypotension, Doxil injection, hemorrhage, CO₂ inhalation, positive end expiratory pressure (PEEP). REG was compared to carotid flow (CF), laser Doppler flow, ICP, SAP, absolute CBF, and pulse oximeter signal. Additionally, REGx was compared to PRx (Brady et al., 2010; Popovic et al., 2013; Bodo et al., 2015, 2018). During aorta compression, systemic arterial pressure increased ($p = 0.008$), and REG amplitude decreased. Doxil injection caused a

transient brain vasospasm, prior to systemic cardiorespiratory changes, which may explain symptoms in patients during Doxil infusion (Bodo et al., 2005). When CBF AR was present, it was detected by both REG and carotid flow. Following hemorrhage, CBF AR was lost; CF and REG passively followed SAP (Bodo et al., 2007). PEEP after hemorrhage caused loss of CBF AR, may occur during hypotensive resuscitation. REG and carotid flow showed strong linear relationship (Bodo, 2010).

CBF manipulations on rabbits

Rabbits were used for establishing REG correlations during hemorrhage, CO₂ inhalation, acetazolamide injection, hyperventilation, PEEP, and SAP changes. REG was compared to laser Doppler flow, ICP, SAP, absolute CBF, brain tissue temperature, pulse oximeter signal, and exhaled CO₂ level. Visual inspection suggests correlation among CBF, ICP, brain tissue O₂, temperature, LDF and REG during challenges. In total, 47 correlations (positive and negative together) were established. CBF AR was active in 6 animals and passive in 7 animals. Demonstrated CO₂ decreasing effect of acetazolamide has a potential clinical application in neurosurgical care that demands strict avoidance of hypercapnia and hypocapnia (Christy et al., 2014). We present correlations among various modalities. Though statistical analysis has not been completed, continuous non-invasive measurement of CBF appears to correlate with invasive measurements (Bodo et al., 2014).

Figure 7. The physiological basis of REGx calculation: identical changes of ICP and REG. Slow waves of arterial blood pressure (ABP), ICP are compared with a trend of pulse-frequency amplitude changes in REG (FundA). Slow waves of ICP

Figure 8. Electrode and sensor location.

Figure 9. Invasive CBF Modalities (rabbit): Demonstration of CBF heterogeneity during CO₂ inhalations (n=5 and Diamox injection. Rabbit Aug 21.

Discrepancy of CBF measuring modalities can be explained by brain tissue heterogeneity of CBF and different locations of sensors. Additionally, REGx documented the overdose of anesthesia; PRx values showed passive or absence of CBF AR (Felbaum et al., 2015, Felbaum et al., 2015).

CBF manipulations on monkeys

We developed a software module (DataLyser), which was able to determine the lower limit of CBF AR in monkey experiments (Bodo et al., 2010). The importance of this statement is that REG electrodes were on the skin of skull. Meaning, that REGx calculation is operational in noninvasive manner (Popovic et al., 2013).

Neurocritical Care patients

ICP is more than a number. This slogan may mean that apart from its mean value, ICP contains many transients and waves, which are useful for describing intracranial pathology (Czosnyka and Czosnyka, 2020). Fortunately, such information is present in REG waveform. REG and lower arm bioimpedance were measured to calculate REGx. REGx reflected 1) status of intracranial compliance; 2) healthy or sclerotic brain arterioles; and 3) level of ICP – indirectly, by identical pulse wave change as ICP pulse wave

(McHenry, 1965, Jenkner, Canizzarro et al., 2019; Czosnyka and Czosnyka, 2020).

Discussion

Cardiovascular disease

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels of brain; CVDs are the number one cause of death globally: more people die annually from CVDs than from any other cause. An estimated 17.9 million people died from CVDs in 2016, representing 31% of all global deaths. Of these deaths, 85% are due to heart attack and stroke. Over three quarters of CVD deaths take place in low- and middle-income countries. Heart attacks and strokes are usually acute events and are mainly caused by a blockage that prevents blood from flowing to the heart or brain. The most common reason for this is a build-up of fatty deposits on the inner walls of the blood vessels that supply the heart or brain. Strokes can also be caused by bleeding from a blood vessel in the brain or from blood clots. The cause of heart attacks and strokes are usually the presence of a combination of risk factors, such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol, hypertension, diabetes, and hyperlipidemia [WHO]. The etiology of CVD/stroke is arteriosclerosis/atherosclerosis.

Jan 17, 2020

Figure 10. REG waveform comparison. Upper trace: REG waveform at the beginning of recording. Note: second peak (P2) is higher than first (P1) – reflecting elevated ICP and decreased IC compliance. Middle trace: REGx during recording. Time window for REGx: 36 min. At beginning REGx is closer to 1; during second half it is decreasing, trending to -1. Note: second peak is lower than first - reflecting decreased ICP and normal IC compliance. Mean REGx was 0.61 at start and -0.49 at end (average of 4 min). NB: +1: passive; -1: active CBF AR. No sing of arteriolar arteriosclerosis; REG anacrotic/ rising time is $102.56 \pm \text{msec}$; $n=10$.

Stroke

The etiology of stroke is multifactorial. Stroke is the leading cause of death worldwide and a leading cause of disability (Anonymous 7). There is a current lack of large-scale adequate screening programs designed to date to detect people with hypertension before inevitable complications of heart disease, strokes, kidney disease, or visual problems occur (Anonymous 8). A radical decrease in stroke death (80 %, Anonymous 9; de Freitas, Bogousslavsky, 2001) can be obtained by the introduction of primary prevention, i.e., screening the general population from age 40 to find high risk population. Cerberus system was created for this purpose. REG measurement is more sensitive at detecting brain arteriosclerotic status than carotid Doppler measurement (Bodo et al., 1998; 2008). This suggests that it may be a significantly improved means for the differential diagnosis of neurological disease and the screening of subjects for arteriosclerosis, TIA, and stroke prevention to be offered at the lowest level of medical service. COVID-19 infection itself has also been described as a risk factor for stroke (Markus and Brainin, 2020). History of stroke increases the risk of death caused by COVID-19, by a factor of 3. COVID-19 currently seems to be one of the main complications of stroke and CVD (Trejo, 2020).

Pathophysiology

Arteriosclerosis has been described as a progression that occurs in two phases. The first phase proceeds at a slow rate, related to accumulation of foam cells, creation of fatty streak, transformation of lipoid accumulation to crystalline cholesterol, and accumulation of cellular components such as smooth muscle cells and fibroblasts. During this phase, changes occur in the elasticity of the artery wall, but not in the lumen, and there is generally a form of compensatory remodeling of the external elastic lumina and muscular wall that allows preservation of the luminal to conduct blood flow. The second phase of arteriosclerosis occurs at “a rapid rate” (related to plaque fissuring and/or hemorrhaging leading to platelet rich thrombus accumulation (Mancini, 1995). During this phase, there are changes in the lumen and in the artery wall, as well (Yatsu and Fischer, 1989). These two phases may correspond to the known stages of prevention levels of chronic disease, called “upstream” (prevention level 1-2) and

“downstream” (prevention level 3-4) (Mausner and Kramer, 1985).

Cerebral Blood Flow Autoregulation

In the brain, CBF, metabolism, and function are strongly interrelated. Although the mechanism of this complex system is not well known, there is satisfactory scientific and clinical evidence supporting the use CBF AR (cerebrovascular reactivity) for diagnostic monitoring purposes. CBF AR is defined as the phenomenon that makes blood flow constant despite variations in SAP (Strandgaard and Paulson, 1984). CBF reacts to changes in perfusion pressure (SAP-ICP), due to adaptation of the vasculature of the brain. Cerebral vascular resistance varies in response to variations of SAP. Blood vessels in the brain constrict or dilate in response to changes in SAP between about 50-150 mmHg SAP. Below and above this limit or in pathological cases, CBF passively follows SAP. Without autoregulation, CBF would increase or decrease, with possible cerebral ischemia or edema, whenever the perfusion pressure increases or decreases. Thus, CBF AR in the cerebral circulation may be defined more pragmatically as the mechanism that protects the brain against the dangers of hypoxia, at low perfusion pressures, and against the risks of brain edema, at high arterial pressures. Based on this definition, CBF AR may be thought of as a homeostatic mechanism that is superimposed over and above the baroreceptor reflexes. The anatomical background of CBF AR is the arteriole. Arterioles represent the last small branches of the arterial system, and they act as control valves through which blood is released into the capillaries. The arteriole has a strong muscular wall, capable of closing the arteriole completely or of allowing it to be dilated severalfold, thus having the capability of vastly altering blood flow to the capillaries in response to the needs of tissue (Guyton, 1991, Kontos et al., 1978).

Neuromonitoring

The goal of neuromonitoring is to prevent secondary brain damage. CBF AR is pivotal to the maintenance of appropriate CBF. Impaired AR may lead to secondary damage from neuroexcitotoxicity and is an independent predictor of poor outcome following traumatic brain injury (TBI). The goal of ‘real-time’ continuous CBF AR monitoring is to be able to optimize treatment strategies according to evolving physiologic parameters.

Traumatic brain injury (TBI) is a major cause of death and disability among soldiers and young individuals. A worse outcome is associated with ongoing secondary insults. Current Brain Trauma Foundation guidelines (Carney et al., 2017) regarding the management of patients after TBI include the reduction of ICP below 20 mmHg and maintenance of cerebral perfusion pressure (CPP) between 50 and 70 mmHg. Bedside assessment of CBF AR may help to optimize individual CPP-guided treatment. A new method of autoregulation-guided treatment is based on continuous evaluation of cerebrovascular reactivity (PRx).

CBF AR (cerebrovascular reactivity) is tested, whether it is passive or active. Such tests are breath holding, hyperventilation, CO₂ inhalation, and acetazolamide/Diamox injection (Ringelstein et al., 1992). Mild brain trauma in the setting of polytrauma may cause cerebrovascular dysregulation. Hemodynamic manipulation in polytrauma, e.g., hypotension, may be damaging to the brain, because of loss of AR.

A continuous monitoring of CBF AR status (active/passive) is possible with a program, called ICM+ (Anonymous 6). The fundamental relationships between SAP, vessel tone, cerebral blood volume, and ICP form the basis for the pressure reactivity index (PRx) (Czosnyka, et al., 1997). PRx is analogous to other time domain AR indices and is calculated as the continuous correlation between 30 consecutive time-averaged (10 s) SAP and ICP values. A positive index (positive correlation) implies impaired/passive cerebral autoregulation, while a negative index (inverse correlation) implies intact/active AR.

Previous studies documented that 1) REG reflects cerebrovascular reactivity/CBF AR; 2) REGx and PRx are correlated to detect the lower limit of CBF AR; the area under the receiver-operator curve for the REGx is 0.86 (Brady et al., 2010); and 3) REGx can be measured with skin/scalp electrodes [Bodo et al., 2010].

Neurocritical care society (NCS) guidelines and consensus statements are detailed elsewhere (NCS). Ideally, neuromonitoring would be noninvasive and continuous. Bioimpedance/REG can accomplish this task.

Space research and REG

It has been documented that space flight damages astronauts' CBF AR. Symptoms of increasing intracranial volume/pressure (ICP) and impaired CBF AR have been linked to space flight-associated neuro-ocular syndrome, orthostatic intolerance, headache, and impaired

neurocognitive performance (Yegorov, 1979; Blaber et al., 2011; Law et al., 2014; Hughson et al., 2016; Iwasaki et al., 2007; Zuj et al., 2012; Taylor et al., 2013; Arbeille et al., 2016; McDonald, 2009; Klein et al., 2019).

Although NASA has sought 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 measurements are invasive, they are not performed in real time on astronauts, while on the ISS, but only after they return from the space mission. Transcranial Doppler is then used to determine CBF in the middle cerebral artery, but CBF AR, a function of smaller vessels arterioles, is not measured. After studies by the US Army proved that a real-time measuring technique, REG, reflects both CBF AR and ICP, the US Department of Defense supported development of a noninvasive, continuous brain monitor, using REG technology (Meghdadi et al., 2019). Unit dimensions are: 85 x 58 x 16 mm; mass: 102.06 g [ABM]. This operator-independent device calculates REGx in real time, utilizing regular ECG electrodes, dry electrodes, or reusable conductive fabric, placed on the forehead and lower arm.

A recent publication details impacts of spaceflight and spaceflight analogs on CBF AR (Kermorgant et al., 2020).

Additionally, such monitors can be used in military aviation. Modern jet planes fly under computer control and can do maneuvers that a pilot cannot tolerate, because of CBF decrease. Unfortunately, this physiological variable is not stored in black box. However, REG (or other noninvasive) sensors can be placed in helmet and offer earliest signal of losing consciousness and urgent need to switch to autopilot mode.

Conclusions

Results indicate that REG accurately reflects cerebrovascular reactivity (CBF AR), similarly to ICP, carotid flow, etc. Bioimpedance/REG pulse amplitude change reflects blood and cerebrospinal volume change, rather than absolute CBF (Bodo et al., 1986; Bodo 1990, 2010). Clinical importance of these findings is that REG can be measured noninvasively, conveniently, and continuously in humans. It has been demonstrated that REG is able to identify cerebrovascular arteriosclerosis caused by decreased (Windkessel effect) brain vasospasm during Doxil injection, passive CBF AR during PEEP and anesthesia overdose. Therefore, measurement of CBF AR/REG has potential for

use as a life sign monitoring modality in civilian, military medicine, and in military aviation and space research, as well. Specifically, since the REG device was miniaturized and computerized (Meghdadi et al., 2019), NB: CO₂ level on ISS (4.0 mmHg), requires validating a practical test of 30 s breath holding. Previous study (Bodo et al., 2017) demonstrated usefulness of this test, but only on Earth (0.3 mmHg). Future studies need to clarify REGx normative in healthy persons (does not exist) and threshold for alarm in vital sign monitor. The initial alarm can be raised, when there is a loss of CBF AR by REGx, while the second can be the cessation of EEG for 2 s, and respiration (Bodo et al., 2013).

Either in spaceflight or in ground-based model of microgravity, most of short-term studies show a preserved or even an improved CBF AR. Nevertheless, long-term studies depict an impairment in CBF AR. One of the main reasons of the discrepancy may depend on baseline orthostatic tolerance. Indeed, subjects who are orthostatically tolerant have a preserved or even an enhanced CBF AR. In contrast, orthostatically intolerant subjects would present an impaired CBF AR (Kermorgant et al., 2020). In present an adequate device is already available to measure CBF AR on ISS.

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