

REG can be used to detect cerebrovascular alteration caused by alcoholism

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Despite recent evidence of the beneficial effects of moderate alcohol consumption in arteriosclerosis prevention, the neurotoxic effects of alcohol abuse are well known. Our hypothesis was that uncontrolled alcohol consumption may cause cerebrovascular damage detectable by rheoencephalography (REG), a noninvasive bio-impedance technique for estimating cerebral blood flow.

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.

ANOVA showed that daily alcohol consumption and smoking were significantly higher in alcoholics than in 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.

The correlation of increased REG anacrotic time and daily alcohol consumption supports the hypothesis that REG detects accelerated cerebrovascular aging (arteriosclerosis) in alcoholic subjects.

Keywords: alcohol abuse, cerebrovascular aging, rheoencephalogram, REG

The nervous system is particularly susceptible to the harmful effects of alcohol. It has been shown conclusively that cerebral blood flow (CBF) measured by the ¹³³Xe inhalation method is decreased in chronic alcoholism, correlating well with the amount of alcohol consumed. With abstinence, CBF returns toward normal levels provided the neurotoxic effects of chronic alcoholism are of recent onset (37). For most people who

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drink alcohol, the substance is viewed as a pleasant accompaniment to social activities. Moderate alcohol use (less than 20–50 gr/day, in general, two drinks per day for men and one drink per day for women and older people) is not harmful and protects against arteriosclerosis (3, 19). However, uncontrolled alcohol consumption causes mental and somatic problems (3, 25, 51).

Psychological and somatic variables were measured to establish possible correlations with cerebrovascular alterations due to alcoholism. Cerebrovascular alteration was estimated by rheoencephalography (REG), a noninvasive bio-impedance technique acknowledged by the U.S. Food and Drug Administration as a tool for estimating CBF (2). The Cerberus system (6, 8, 31) was used for REG measurement. Under normal physiological condition, REG peak amplitude increase or decrease reflects cerebral volume change caused by arteriolar vasodilatation or vasoconstriction. Under pathological condition (arteriosclerosis), increased REG peak time reflects decreased elasticity of the arteriolar wall. The term “REG cerebrovascular alteration” or “arteriosclerotic standard” was used in this article on the basis of Jenkner’s work (28, 29). On the basis of his work we can hypothesize that there were both structural and functional alterations; he stated that the alteration was verified with arteriography (i.e. *structural*). Additionally, we can hypothesize that patients were hospitalized because of having *functional* cerebrovascular problems, such as TIA symptoms. Jenkner’s data served as point of relativity in this case, too, since alcohol abuse is a known risk factor for stroke and cardiovascular disease (decreased elasticity of the artery wall).

Our hypothesis was that uncontrolled alcohol consumption may cause cerebrovascular damage, identical to arteriosclerosis, and will be detectable by REG.

Materials and Methods

The Cerberus system involved the measurement of pulsatile electrical impedance in the brain (REG), detailed elsewhere (6, 8, 31). Briefly, Cerberus, a computer-based system, can detect individuals at high risk for stroke years before the first symptoms of arteriosclerosis occur. The Cerberus system detects and measures lost elasticity of cerebral arteries by means of the electrical impedance method of measurement. The system incorporates questionnaires related to risk factors for arteriosclerosis, stress, and symptoms of TIA for each subject, then combines this information with data obtained by polygraphic monitoring of the subject. Data processing is focused on electrical impedance waves of the head (REG) and the extremities. EEG and ECG are also recorded by the system. Processing of the physiological data includes Fourier analysis, signal averaging, determination of pulse wave minimum and maximum values, pulse wave transit time, and measurement of the asymmetry of these values comparing the right and left sides of the body. REG electrodes (four 15 mm diameter tin discs) were incorporated into the ECI Electro-Cap Electrode System (Electro-Cap International, Inc, Eaton, OH). Electrode arrangement within the cap was: EEG: T5-O1, T6-O2 recording in bipolar configuration. EEG ground was: Fz; REG: Fp1-F7; Fp2-F8. Localization was

given according to the International 10–20 system of EEG. Measurements were performed similarly to an EEG recording. Analog digital (AD) conversion was made by a 12 bit resolution card; sampling rate was 275 Hz (Advantech, Sunny Vale, CA). A one minute REG recording was used for signal averaging, triggered by the ECG R wave. The left and right side REG data were averaged for each person (Fig. 1). REG anacrotic time was measured and evaluated as a symptom of cerebrovascular alteration; a REG anacrotic time above 180 ms was considered pathological (29).

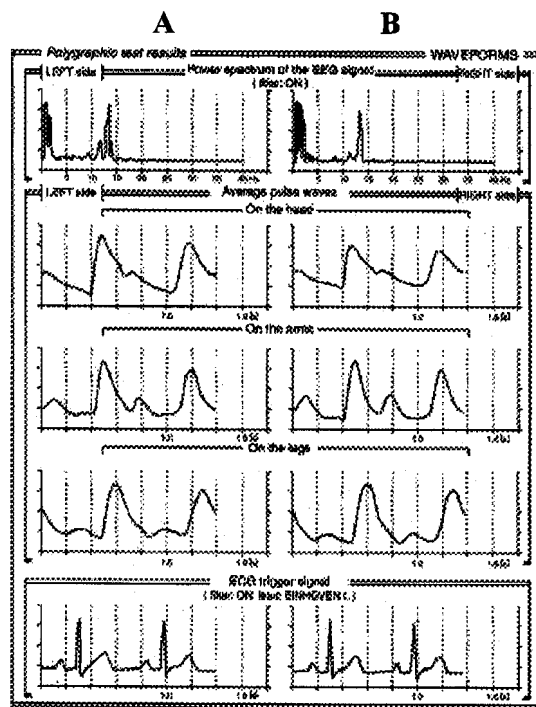


Fig. 1. Printout of an original Cerberus polygraphic test. A (left) and B (right) columns represent homologous brain areas; the top four traces represent averages for one minute of recording time. The uppermost trace shows the power spectrum of an EEG with alpha dominant frequency; the second trace from the top shows the REG pulse waves of a healthy young adult. The REG pulse amplitude was lower right side. The asymmetry was within normal physiological range. The third and fourth traces show symmetrical peripheral blood flow (wrist: trace #3; ankle: trace #4). The bottom trace shows an original, unaveraged ECG recording, identical for both right and left sides. The following numeric values of above printout are calculated and stored in Cerberus: dominant frequency and amplitude of EEG power spectrum, bioimpedance pulse variables, detailed in Fig. 2, and the percentage of their asymmetry

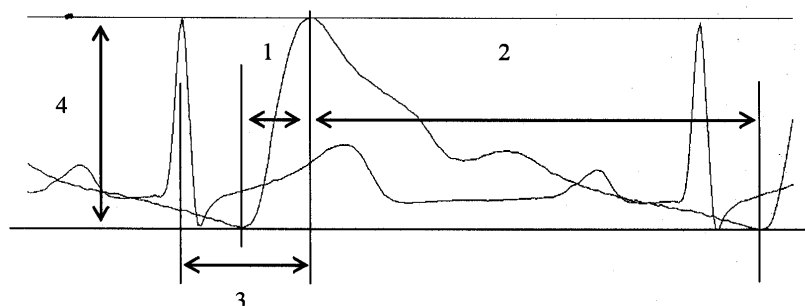


Fig. 2. REG pulse curve and its relationship to Electrocardiogram (ECG) and basic variables of REG. The pulse wave transmission time is defined as the time between the peak of the R-wave of the ECG signal and the peak of the bio-impedance pulse. Peak time is the time from the start of the pulse until its peak, called anacrotic time. The descending pulse wave is called catacrotic time. Pulse amplitude is the difference between the minimum and the maximum value of a pulse. 1: anacrotic time (81.1 ms), 2: catacrotic time, 3: pulse wave transmission time (152 ms), 4: pulse amplitude, Period: $1 + 2 =$ peak-to-peak interval: 618.4 ms. Typical healthy REG curve (Cerberus record ID # 1). Fragment of original trace; time window 934.5 ms (X axis is ms, Y axis arbitrary unit – units of AD conversion) ECG trace also presented

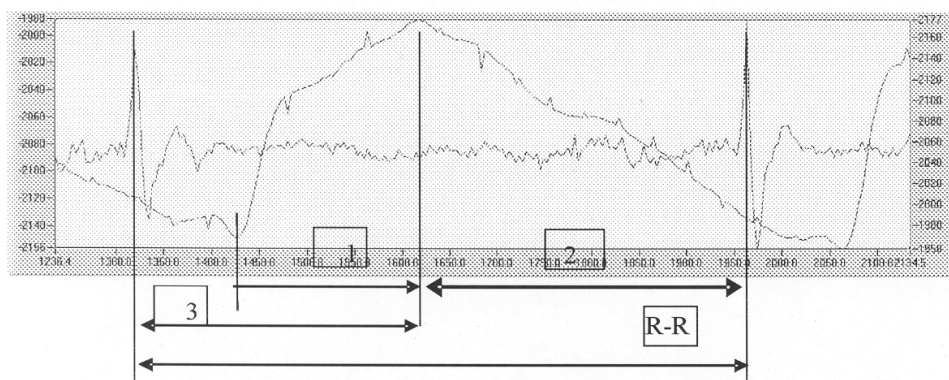


Fig 3. Typical pathologic REG (Cerberus record ID # 294/2). Fragment of original trace, not an averaged curve; time window 898.2 ms (Note: the time window start not with 0 but 1236.4 ms). This data may differ from data used in statistics: the signal averaging of a one minute recording reduces the noise visible here and also eliminates the respiratory subharmonic and physiologic arrhythmia. The elongated REG anacrotic time (1–191.3 ms) indicates the pathologic alteration, i.e. decreased vessel wall elasticity; 2: catacrotic time; 3: Pulse wave transmission time – 298 ms; R-R: ECG R – R interval – 643 ms (X axis is ms, Y axis arbitrary unit – units of AD conversion); ECG trace also presented

The Cerberus system generated an ASCII (American Standard Code for Information Interchange) file, containing automatically calculated average of REG anacrotic time values (which was exported and used for this study) and a binary file, containing the

one minute recording of analog physiological signals. In case of artifact contaminated files, original Cerberus binary (Redirec) (23) files were exported and picked up with a proprietary software (DataLyser), and 10 REG anacrotic times were measured with cursor operation and averaged in Excel (Microsoft, Redmond, WA) spreadsheet for statistical summary (Figs 2, 3). For the measurement of IQ, the Hungarian version of the Wechsler Adult Intelligence Scale (MAWI) (59) was used; for anxiety measurement, the short form of State-Trait Anxiety Inventory (STAI) (22, 8) was used twice for each subject. The ANOVA and Student's *t*-test were used for statistical evaluation. $P < 0.05$ was considered significant.

Subjects

1) Sample from Kecskemet, Hungary. Three groups of hospitalized psychiatric patients were compared: those with drug abuse, alcohol abuse or depression. The alcohol-abuse patients were middle-aged inpatients identified as having alcohol problems for more than ten years (56) ($n=44$, mean age, 41), who were participating either in detoxification (Dg: F10.30: Withdrawal state, uncomplicated; F10.40: Withdrawal state with delirium, without convulsions) or abstinence treatment programs (Dg: F10.10: Alcohol Abuse; F10.20: Alcohol Dependence; F10.80: Other mental and behavioral disorders due to use of alcohol). Ages varied from 27 to 54 years for males and from 27 to 56 years for females. The drug abuse patients were two subjects with dependency (F12: Mental and behavioral disorders due to use of cannabinoids; F13: Mental and behavioral disorders due to use of sedatives or hypnotics), and four subjects with a diagnosis of abusive disorders (F11: Mental and behavioral disorders due to use of opioids; F18: Mental and behavioral disorders due to use of volatile solvents; F19: Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances) ($n=6$, mean age: 31). The youngest and oldest subjects were males 19 and 49 years of age. There were two female drug-addicted patients, aged 25 and 31. The depressive subjects were non-psychotic ($n=6$, mean age: 51.33) (F32.00, Mild depressive episode without somatic symptoms; F32.20: Severe depressive episode without psychotic symptoms; F33.2: Recurrent depressive disorder, current severe episode without psychotic symptoms). Four additional subgroups were formed according to smoking habits and average daily alcohol dose. The male/female ratio for patient groups mirrored the general tendency of gender distribution for their disorders: alcoholic patients, 32:12; drug patients, 4:2; and depressive patients, 1:5.

2) Sample from Silver Spring, Maryland, (USA): The control group consisted of 13 healthy male subjects, who were tested for REG comparison with the alcoholic sample only. Both REG samples also were analyzed dividing into subgroups according to age: young (= below age 40) and old (= above age 40). Blood pressure, body mass index (BMI) and modified vegetative balance were measured and calculated by Kerdo/Sipos (8).

Results

The most important result of this study was that the longer REG anacrotic time was parallel to the higher quantity of daily alcohol consumption in the MAWI subgroup ($n=12$). BMI and MAWI dementia % showed a statistically significant positive correlation ($r=0.599$; $p=0.020$) in the same subgroup. The daily alcohol consumption correlated to 1) REG anacrotic time $r=0.683$; $p=0.007$; dementia % vs. BMI: $r=0.599$; $p=0.020$; Kerdo-2 index vs. risk factors: $r=0.610$; $p=0.018$; anxiety-2 vs. risk factors: $r=0.538$; $p=0.036$.

Alcoholic – Drug – Depression Groups

Significant differences were found for age between the drug-addicted group (31.33 ± 11.88 y) and the depression group (47.75 ± 10.36 y, $p=0.017$) and for the alcoholic (42.44 ± 7.72 y) and drug-addicted groups ($p=0.003$). The REG anacrotic time was significantly different for the drug-addicted (79.75 ± 59.05 ms) and alcoholic (108.38 ± 61.85 ms) groups ($p=0.025$). The systolic arterial pressure, BMI, Kerdo index values showed no significant differences among the 3 groups.

Healthy vs. alcoholic groups

The age difference of REG anacrotic time in the male and female alcoholics was not significant; therefore, males and females were placed in a single group. In young subjects tested, no significant differences in REG and age were observed for alcoholic and healthy subjects. Between older groups, however, significant differences both in age and in REG anacrotic time were observed (Table I). The REG anacrotic time in the alcoholic group had a dual peak distribution – around a lower mean anacrotic time (99.43 ± 56.56 , $n=33$) and a higher one ($133 \text{ ms} \pm 71.39$, $n=12$). Between these groups the significant difference was the REG time ($p<0.0001$) and the systolic arterial pressure ($p=0.0159$). The Kerdo vegetative index, diastolic arterial pressure, heart rate, symptoms of transient ischemic attack, incidence of stroke risk factors, level of anxiety, BMI, and age difference were not significant.

Table I

Numeric characteristics of alcoholic and healthy groups

	Young alcoholic		Young healthy		Older alcoholic		Older healthy	
	Age year	REG ms	Age year	REG ms	Age year	REG ms	Age year	REG ms
Mean	24.00	64.35	22.33	65.50	43.88	111.28	47.57	60.71
SD	4.04	13.73	4.37	8.34	2.92	61.32	4.58	5.65
Count	7	7	6	6	34	34	7	7
P							0.008*	0.037*

* P value of a *t*-test between older alcoholic and older healthy groups.

A striking difference was observed between the older healthy and the older alcoholic subjects. In our study, 11 subjects in the alcoholic group surpassed the REG anacrotic time above 180 ms level (Fig. 4).

For all healthy subjects, physiological cerebrovascular aging was expected to show an identical slope with age. In the alcoholic group, the steeper REG slope: 36.68 vs. age: 0.56 (ratio: 64.39) reflected the pathological impact of alcohol abuse (Fig. 4). The U.S. control sample showed a nearly identical slope for both REG (1.79) and age (3.45; ratio: 0.52) (Fig. 5). The sorted REG anacrotic time (<100 ms and >140 ms) in alcoholic group showed that there was no significant age difference between these two subgroups (Fig. 6).

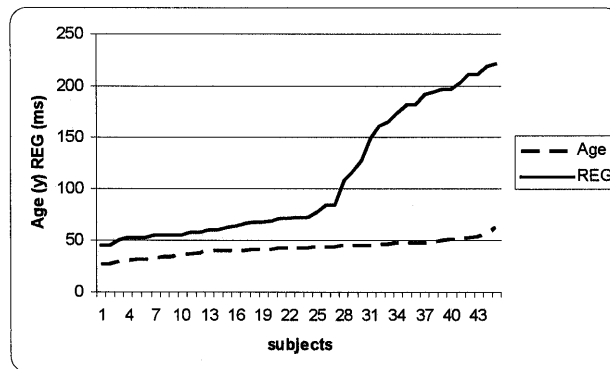


Fig. 4. Sorted age and REG anacrotic time in alcoholic group: the steeper REG anacrotic time slope reflected the pathological impact of alcohol abuse. After being sorted independently for REG anacrotic time and for age, these variables showed the following regression values: age, $y=0.5697x+29.341$ $R^2=0.9398$ (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) (55)

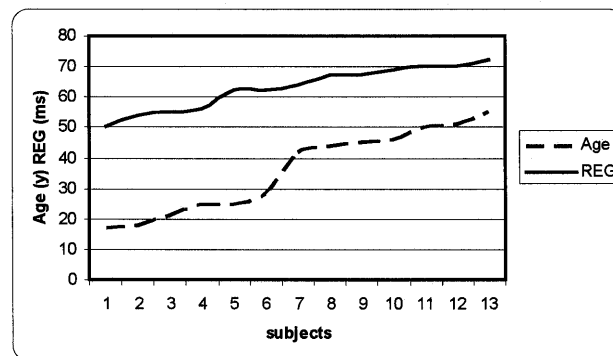


Fig. 5. Sorted age and REG anacrotic time in healthy group: physiological cerebrovascular aging. REG anacrotic time showed an identical slope with age. Age and REG regression values (calculated as one group, $n=13$) are as follow: Age: $y=3.4505x+11.769$, $R^2=0.9509$, and REG anacrotic time: $1.7912x+50.385$, $R^2=0.9527$ (both linear) (55)

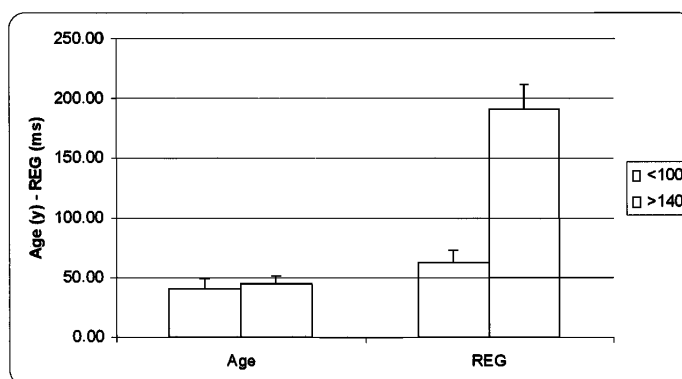


Fig. 6. Relationship of age and REG anacrotic time in alcoholic group, sorted by REG anacrotic time: <100 ms (n=27) and >140 ms (n=15). The <100 ms subgroup mean age was: 40.37 ± 8.16 ; 140 ms mean age was 44.93 ± 5.89 . The difference was not significant ($p=0.0641$). The <100 ms subgroup mean REG anacrotic time was 62.00 ± 10.54 ms. The >140 ms mean REG anacrotic time was 190.19 ± 21.71 ms. The difference was significant ($p<0.00001$). This comparison was not applicable for the healthy group; there were no significant differences

Discussion

Clinical and pathological studies show significant loss of brain volume with ventricular dilatation after alcohol abuse even among young “social” drinkers. This toxic effect of alcohol is accompanied by varying degrees of cognitive impairments ranging from slight memory loss to frank dementia. Both the decrease in brain volume and the cognitive impairments, which occur with or without nutritional deficiency, are to a large extent reversible with abstinence and nutritional supplementation. Alcohol appears to accelerate age-related declines in CBF while nutritional deficiencies enhance the neurotoxic effects of alcohol. Among chronic alcoholics, there are significant and diffuse reductions in cortical and subcortical gray matter CBF that are especially remarkable in hypothalamus and substantia innominata, which includes the nucleus basalis of Meynert, a major source of cholinergic input to neocortex and hippocampus (37).

Light-to-moderate alcohol consumption seemed to decrease the risk of ischemic stroke by reducing atherothrombotic events, but the underlying mechanism is still unclear. Heavy drinking increased the risk for both hemorrhagic and ischemic strokes (25). It is known that the nervous system is particularly susceptible to the harmful effects of alcohol, which can affect both neuronal tissue and the cerebral arteries (37).

In this study we used various methods to measure the effect of regular alcohol consumption on the nervous system, including vascular, psychological and cognitive deterioration and somatic co-morbidity (prevalence of arteriosclerosis risk factors). This result may be partially explained by higher Hungarian cardiovascular risk and stroke mortality compared to U.S. data (9, 10, 52). The correlation of increased REG anacrotic time and daily alcohol consumption supports the hypothesis of accelerated cerebrovascular aging of the alcoholic subjects (Fig. 6) (37). Here we present related information on arteriosclerosis, CBF autoregulation and REG in order to offer a potential insight to the background of described findings.

Arteriosclerosis

The known risk factors of heart attack and stroke are identified from the Framingham study (14), and sorted today in the following groups: Non-modifiable: age, gender, race, heredity; modifiable: hypertension, diabetes mellitus, hypercholesterolemia, cigarette smoking, alcohol abuse, diet, oral contraceptive, atrial fibrillation; emerging: fibrinogen, homocysteine, inflammation/infection (16, 50).

Atherosclerosis involves structural change to the intima and media of medium- and large-sized arteries (13). Although an atherosclerotic plaque may remain clinically silent, it is prone to disruption, leading to local platelet activation and aggregation. Therefore, the major complication of atherosclerosis is thrombosis, with local occlusion or distal embolism – a generalized disease process known as atherothrombosis. The three main clinical manifestations of atherothrombosis are coronary heart disease (myocardial infarction and angina), peripheral arterial disease and cerebral ischemia. Atherothrombosis is a leading cause of mortality, and stroke is the leading cause of disability in adults, the second most important cause of dementia and the third most common cause of death in industrialized countries. Ischemic stroke accounts for 80% of strokes and atherothrombosis accounts for approximately 20% of all strokes (33).

The atherosclerosis progression has two rates of progression:

- 1) *slow rate* (related to accumulation of foam cells, creation of fatty streak, transformation of lipid accumulation to crystalline cholesterol and accumulation of cellular components such as smooth muscle cells and fibroblasts);
- 2) *rapid rate* (related to plaque fissuring and/or hemorrhaging leading to platelet rich thrombus accumulation. The second is that in the early stages, the process affects the wall, not the lumen, and generally includes a form of compensatory remodeling of the external elastic lumina and muscular wall that allows preservation of the luminal to conduct blood flow (38). Arteriosclerosis is called “the silent killer” because of conditions during the slow rate. For primary prevention, this is the best time to discover the disease and initiate adequate countermeasures, which is specifically true for stroke (15, 40). The Cerberus system was designed as a high capacity tool for mass screening of populations in order to find subjects at high risk for cardiovascular disease, particularly stroke (20). REG can be used for this early and sensitive index role, according to the literature (28, 41).

CBF autoregulation

CBF autoregulation is a homeostatic mechanism that minimizes deviations in CBF when cerebral perfusion pressure changes. CBF autoregulation acts through vasomotor effectors that control cerebrovascular resistance (11, 54). It is possible to evaluate CBF autoregulation practically, that is, to record systemic arterial pressure (SAP) and CBF modalities simultaneously to determine if changes are concurrent or not. If decreases in CBF, for example, coincide with SAP increases, we can state that the occurrence is a CBF autoregulatory response, and vice versa (32, 47). A CBF modality that is the most inverse to SAP change is the most accurate modality for reflecting CBF autoregulation. Brain vessel responses (CBF autoregulation) have been found to be size dependent. Small arterioles (less than 100 μm in diameter) dilated only at a pressure equal to or less than 90 mm Hg; below 70 mm Hg, their dilatation exceeded that of larger vessels (30). This difference in reactivity may explain why Doppler velocity measurements in the spastic segment when taken alone may not be a good index of the degree and effect of the spasm. These measurements must be combined with other techniques such as extracranial Doppler or CBF to assess the degree of spasm (1).

In clinical practice, mostly carotid flow is used to measure CBF autoregulation (39). However, it should be noted that the autoregulatory response is vessel-size-dependent; consequently and predictably, on the carotid the autoregulatory answer should be smaller than on the arterioles (30, 49). The main background and interesting fact here is that in clinical practice, for CBF autoregulation the less sensitive method is used instead of the more sensitive, the REG. Previous animal studies with CO_2 inhalation and hemorrhage proved that REG reflected CBF autoregulation better than carotid flow or cortical CBF measured by laser Doppler flow (4, 5, 7). CBF autoregulation is a sensitive indicator of any pathological cerebrovascular alteration.

During arteriosclerosis CBF autoregulation is damaged, a fact reflected in the elongated REG anacrotic time. This background explains why rapid and drastic changes in blood pressure are problems for elderly patients, since decreased CBF autoregulation capacity can cause ischemic damage.

REG

The main finding in the present study was that for the first time, cerebrovascular alteration caused by alcohol abuse was shown to be detectable by use of the REG method of measurement.

The physical basis of the electrical impedance method is based on the fact that blood and cerebrospinal fluid are better conductors than the brain and other 'dry' tissue (46). The electrical impedance method, that is, measuring blood flow by alternating current, is known in clinical practice but is used mainly in cardiology and in measuring peripheral circulation. The electrical impedance pulse curve looks like an arterial pressure pulse curve: the rising portion is called the anacrotic phase, and the decreasing

portion is the catacrotic phase. The pulsatile change is in the range of 0.1–1% of the total impedance (48). When used on the head, this measurement technique is called REG (28).

The REG signal reflects change in impedance: during blood inflow into the cranial cavity, electrical conductivity is increased (resistance decreased), represented by increasing REG pulse (peak-to-peak) amplitude. However, practically, in the literature, the inverted REG pulse is shown, as a convention, similarly to our figures, which occur inside the amplifier; at the output, this pattern can be seen. The same electrical impedance change occurs in generating a pulse wave on peripheral site, as previously described (45) in the parallel-column model. In the skull, the input is the volume of the arterial pulse, and the output is the venous outflow and the CSF together. The resulting impedance change – REG pulse curve – is the result of the equation, involving all mentioned factors but not detailed individually (44). The measured electrical impedance value offers the basis of several volume calculations, detailed by Jenker (28).

Usually, REG is recorded from the scalp surface in a bipolar arrangement (REG I) or in a tetrapolar arrangement (REG II) (28, 35, 36). REG studies have been conducted for research, clinical, theoretical, and modeling fields listed previously (7). Various correlations were established between electrical impedance (REG) and volume, flow, pressure or EEG (17, 21, 26, 27, 28, 45). REG pulse amplitude is quantified most frequently using its derivative or integral (26, 43, 57). Both variables detect the applied CBF manipulations (5, 7). The signal averaging, used in EEG technology, was applied here: the ECG R wave triggered the averaging of REG, which improved the signal/noise ratio (8, 12). Other potential REG processing methods have resulted in no practical application (53). One technical problem with the REG instrumentation used in this study concerns the REG device; its bipolar derivation is able to measure only ac, pulsatile impedance. The basic impedance is compensated at the beginning of the measurement in such type of impedance amplifiers, so they are unable to record the dc component as a signal. This prevents detection of changes in the dc portion of the signal, which are related to the overall brain volume. The tetrapolar devices are able to record basic impedance and consequently detect absolute volume changes, as they are used in clinical practice for venous outflow phlebography or impedance cardiography.

Use of REG to estimate CBF is rare, since the method's anatomical background is little understood (44). The main problem for REG application in clinical settings is that up to now, unlike ultrasound measurement, where internal carotid or other large artery flow is measured, no direct knowledge was available to create an analogous relationship between REG and any anatomical structure. The REG suggested classical CBF autoregulation, indicating its relationship to arteriolar changes (58). Early CBF–REG studies have not focused on this topic (21, 26, 28, 44). The CBF reaction differed, according to what was being measured: REG reflected vasoreactive aspect of CBF; LDF reflected cortical CBF; carotid flow reflected SAP change during hemorrhage. The basis of this method-dependency is the heterogeneity of CBF in physiological and even pathologic condition such as hemorrhage (57).

Arteriosclerotic REG normative was offered by Jenkner, who averaged REG pulses from 100 phases of each patient of 178 normal subjects and 246 patients with proven cerebral arteriosclerosis (29). Using these data REG anacrotic time above 180 ms was considered pathological in Cerberus system (8).

According to REG literature (12), the lost elasticity of arterial wall – decreased Windkessel function (42) – is expressed in the elongation of the REG anacrotic time (see Fig. 3). Additionally, human correlative study comparing REG and carotid Doppler ultrasound found that slope of age regression lines of REG anacrotic time and Doppler systolic velocity differed in the same population: the regression lines of male and female groups were similar, but the slope of REG was about ten times larger than that of the Doppler; furthermore the prevalence of pathologic flow values as measured by Doppler were 29.41% (male) and 39.06% (female), while pathologic flow values measured by REG were 52.78% (male) and 55.8% (female) (9).

Further correlative studies will be performed measuring peripheral vascular alteration, carotid Doppler and ECG abnormalities.

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Disclaimer

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