Physiological Measurement

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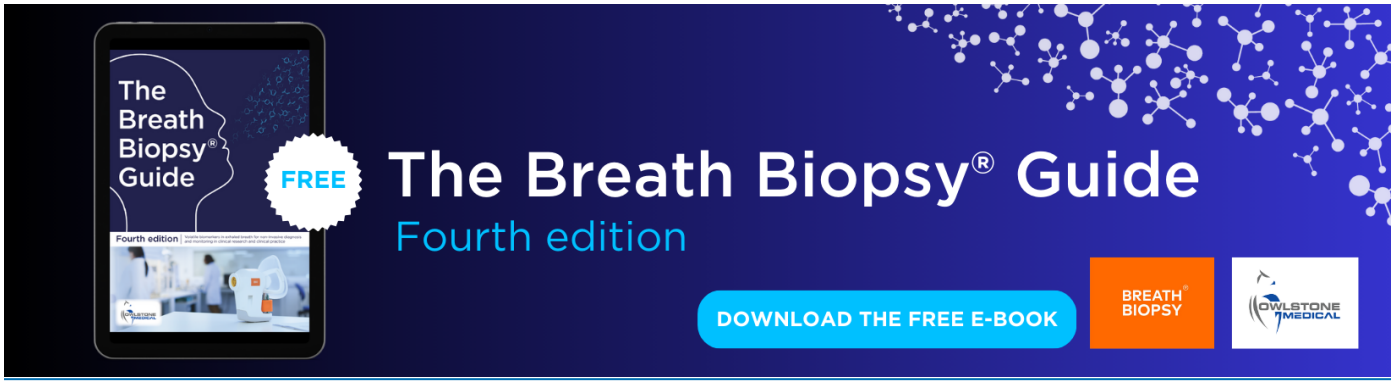

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Changes in the intracranial rheoencephalogram at lower limit of cerebral blood flow autoregulation

M Bodo[1], F J Pearce[1], L Baranyi[2] and R A Armonda[3]

[1] Department of Resuscitative Medicine, Walter Reed Army Institute of Research, Silver Spring, MD 20910, USA
[2] Department of Membrane Biochemistry, Walter Reed Army Institute of Research, Silver Spring, MD 20910, USA
[3] Division of Neurosurgery, National Capital Consortium, Section of Cerebrovascular Surgery and Interventional Neuroradiology, Walter Reed Army Medical Center, Washington, DC 20307, USA

E-mail: michael.bodo@us.army.mil

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Abstract

Cerebral blood flow (CBF) reactivity monitoring is an appropriate primary parameter to evaluate cerebral resuscitation due to a systemic or regional cerebral injury leading to possible irreversible brain injury. Use of the electrical impedance method to estimate CBF is rare, as the method's anatomical background is not well understood. Use of intracranial rheoencephalography (iREG) during hemorrhage and comparison of iREG to other CBF measurements have not been previously reported. Our hypothesis was that iREG would reflect early cerebrovascular alteration (CBF autoregulation). Studies comparing iREG, laser Doppler flowmetry and ultrasound were undertaken on anesthetized rats to define CBF changes during hemorrhage. Blood was removed at a rate required to achieve a mean arterial blood pressure (MABP) of 40 mm Hg over 15 min. Estimation of CBF was taken with intracranial, bipolar REG (REG I; $n = 14$), laser Doppler flowmetry (LDF; $n = 3$) and carotid flow by ultrasound ($n = 11$). Data were processed off-line. During the initial phase of hemorrhage, when MABP was close to 40 mm Hg, intracranial REG amplitude transiently increased (80.94%); LDF (77.92%) and carotid flow (52.04%) decreased and changed with systemic arterial pressure. Intracranial REG amplitude change suggests classical CBF autoregulation, demonstrating its close relationship to arteriolar changes. The studies indicate that iREG might reflect cerebrovascular responses more accurately than changes in local CBF measured by LDF and carotid flow. REG may indicate promise as a continuous, non-invasive life-sign monitoring tool with potential advantages over ultrasound, the CBF measurement technique normally applied in clinical practice. REG has particular advantages in non-hospital settings such as military and emergency medicine.

Keywords: rheoencephalogram (REG), cerebral blood flow (CBF), CBF autoregulation, rat

(Some figures in this article are in colour only in the electronic version)

1. Introduction

1.1. Pathophysiology

The most common cause of death following serious injuries in both military and non-military settings is hemorrhage (Bellamy *et al* 1996). During hemorrhaging, the first monitored life sign to disappear is respiration, followed sequentially by brain activity as measured by cerebral blood flow (CBF) and electroencephalography (EEG), then systemic arterial pressure (SAP) and, finally, heart beat, as measured by the electrocardiogram (EKG) (Bodo *et al* 2004b). Therefore, the optimal life-sign monitor would be one that detects the earliest pathological change. This concept was concisely summarized in the statement 'cardio-pulmonary resuscitation should be brain-oriented' (Safar 1998). However, use of the EKG for life-sign monitoring is common in both civilian and military medicine as well as in air and space research, because of its ease in application—placement of three electrodes on the patient. Another life-sign monitoring method is the electrical impedance method or rheoencephalography (REG), which estimates CBF by placement of electrodes on the patient's head. However, use of REG for this purpose is rare, as the method's anatomical background is not well understood. REG was not mentioned among the vital sign monitoring techniques listed by Shoemaker *et al* (1996), and there are few comparative studies of life-sign monitoring techniques (Cartheuser 1988). The present study defined CBF changes during hemorrhage by comparing intracranial rheoencephalography (iREG), laser Doppler flowmetry and Doppler ultrasound. Our hypothesis was that iREG would reflect early cerebrovascular alteration (CBF autoregulation).

CBF autoregulation is a homeostatic mechanism that minimizes deviations in CBF when cerebral perfusion pressure (CPP) changes. Arterial hypotension and intracranial hypertension are detrimental to the injured brain. Intracranial hypertension and cerebral ischemia are the two most important secondary injury processes that can be anticipated, monitored and treated in the intensive care unit. Prompt detection and treatment of these conditions may eliminate potential secondary insults before they cause severe and irreversible injury to the brain (Hlatky *et al* 2003).

CBF autoregulation acts through vasomotor effectors that control cerebrovascular resistance (Strandgaard and Paulson 1984, Chillon and Baumbach 2002). It is possible to evaluate CBF autoregulation practically, that is, to record 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 (Panerai 1998, Lang and Chesnut 2000). 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 (Kontos *et al* 1978). 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 (Aaslid 1999).

The concept of CBF thresholds of ischemia was introduced in the 1970s, when it was observed that a dense zone of ischemia exists within the central core of the ischemic zone; however, in the peripheral zones, where electrical silence may pertain, there is a zone of intact ionic homeostasis, which has been termed the 'ischemic penumbra'. The flow threshold for maintenance of electrical activity in the cortex is 15–20 ml/100 g/min, measured on primate, cat and human (Astrup *et al* 1977, Symon 1986, Back 1998). The ultimate goal for vital sign monitoring and resuscitation is to maintain CBF above this level.

1.2. CBF monitoring

CBF reactivity monitoring is an appropriate primary parameter to evaluate cerebral resuscitation due to a systemic or regional cerebral injury leading to possible irreversible brain injury. Unlike CBF monitoring, this technique of CBF reactivity is being proposed as a non-invasive, mobile and non-operator dependant means of evaluating an unconscious patient.

In order to evaluate CBF autoregulation, there is a need to record a CBF modality and describe its relationship to SAP. This is the main evaluation criterion that should apply to decide whether a change is CBF autoregulatory or not. Since the CO_2 level has influence on CBF, CO_2 should be recorded in order to clarify this relationship or the role of CO_2 level in CBF change. Other vital signs such as EKG or EEG do not provide information to evaluate CBF autoregulation. Consequently, the assertion in the text about the greater accuracy of CBF autoregulation refers to the CBF modality that reflects the inverted trace of SAP during the applied manipulation causing CBF increase or decrease.

In clinical practice, CBF autoregulation is measured as a routine test using Doppler ultrasound (Aaslid 2002, Gur and Bornstein 2001). Our previous findings (Bodo *et al* 2003, 2004a) and the REG literature (Moskalenko 1980, Jenkner 1986) indicate that iREG reflects the functioning of arterioles and may offer better CBF monitoring than the Doppler technique since Doppler measures CBF autoregulation in larger arteries.

Also, the Doppler ultrasound method has limitations for field applications as described earlier (Bodo *et al* 2003). Monitoring of CBF or cerebrovascular reactivity is performed in neurosurgical clinical practice in order to evaluate the status of the patient after brain injury or operation. The clinical background was detailed elsewhere (Schmidt *et al* 2002, Lang *et al* 2003ba, 2003b, Steiner and Czosnyka 2002, Beaumont and Marmarou 2002, Mayberg 1998, Rosner 1995, Wood 1987, Vespa 2003). In other words, reactive brain vessels offer a positive prognosis; non-reactive vessels are a bad prognosis and call for medical intervention.

Technical aspects of CBF monitoring by REG and comparison to the Doppler ultrasound probe were detailed earlier. Use of REG for continuous non-invasive monitoring has potential advantages to Doppler (Bodo *et al* 2003), particularly in non-hospital settings, such as military and emergency medicine, where technical challenges of CBF monitoring are much greater than in the normal civilian hospital milieu (Bellamy *et al* 1996, Shoemaker *et al* 1996).

1.3. REG

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 (Nyboer 1970). 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 part is the catacrotic phase. The pulsatile change is in the range of 0.1–1% of the total impedance (Patterson 1995). When used

on the head, this measurement technique is called rheoencephalography (REG) (Jenkner 1986). The Food and Drug Administration 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 1997). REG is based on monitoring pulse-synchronous variations in cranial electrical impedance over time. Usually, REG is recorded from the scalp surface in a bipolar arrangement (REG I) or in a tetrapolar arrangement (REG II) (Lifshitz 1963a, 1963b, Jenkner 1986). REG studies have been conducted for research, clinical, theoretical, and modeling fields (Basano *et al* 2001, Benabid *et al* 1978, Bertemes-Filho *et al* 2003, Borisenko *et al* 1993, Hatsell 1991, King *et al* 1996, Laitinen and Johansson 1968, Lechner *et al* 1968, Livshitz *et al* 2001, Markovich *et al* 1967, Moskalenko *et al* 1996, Oostendorp *et al* 2000, Perez *et al* 2000, Rush and Driscoll 1968, Seipel 1967, Schuhfried *et al* 1974, Vainshtein and Iripkhanov 1980, Vainshtein and Vorob'ev 1992, Weindling *et al* 1982).

Various correlations were established between electrical impedance (REG) and volume, flow, pressure or EEG (Nyboer 1960, Hadjiev 1968, Demchenko and Burov 1971, Jacquy *et al* 1974, 1980, Jenkner 1986). REG pulse amplitude is quantified most frequently using its derivative or integral (Montgomery *et al* 1989, Jacquy *et al* 1974, Vainshtein *et al* 1978). Both variables detect the applied CBF manipulations (Bodo *et al* 2003, 2004a, 2004b). The signal averaging, used in EEG technology, is applied here the way that EKG R wave triggered the averaging of REG, also one form of quantification of REG signal, furthermore improving the signal/noise ratio (Cooper *et al* 1980, Bodo *et al* 1995). Other potential REG processing methods have resulted in no practical application (Sokolova and Iarullin 1982).

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 the 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 (Moskalenko 1980). However, REG has potential as a valuable tool for non-invasive, continuous life-sign monitoring. Our hypothesis was that iREG amplitude would reflect CBF autoregulation.

In order to avoid any potential interference with extracranial circulation, in this study we used only intracerebral (invasive) REG derivations (iREG). We plan to study the relationship of intracerebral and surface derivations separately in the future.

The objective of this work was to monitor and compare using three measurement techniques: CBF using iREG, local CBF by laser Doppler flow and carotid flow by ultrasound during hemorrhage known to produce predictable change in CBF, i.e. transient autoregulatory CBF increase.

2. Methods

This research conducted in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals adheres to principles stated in the Guide for the Care and Use of Laboratory Animals (NRC Publication 1996 edition).

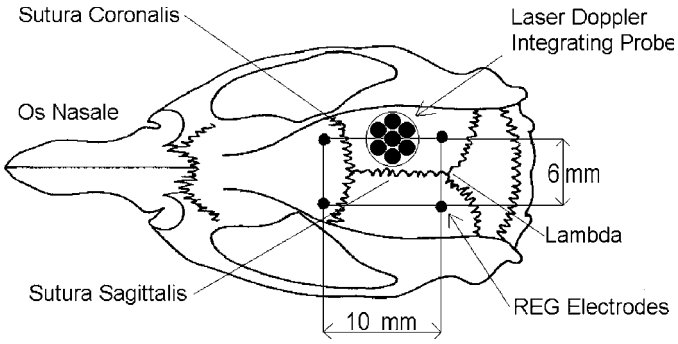

Figure 1. Rat skull with iREG electrode and laser Doppler probe localization. In one measurement, two iREG electrodes were used with the bipolar derivation within one hemisphere, the others were used for EEG derivation. Four electrodes were implanted identically; iREG derivations were alternated but have same lateralization as LDF or carotid flow probe. The electrodes were placed at a 5 mm depth perpendicular to the surface of the skull. The electrode diameter was 0.35 mm at the uninsulated tip (5 mm). The active (5 mm uninsulated) surface of the electrode covered not only the cortex, but subcortical sources as well; the cortex (approximately 1 mm) and subcortical white matter (4 mm) in rat brain.

Sprague-Dawley rats (250–350 g) were anesthetized with sodium pentobarbital IP (50 mg kg^{-1}), tracheotomized and heparinized (50 IU/100 g, IV); body temperature was maintained with a heating pad-rectal thermometer system (Homeostatic Blanket Control Unit, Harvard Apparatus, Edenbridge, KT). One femoral artery was used for monitoring SAP with disposable transducer (Maxxim Medical, Athens, TX) and Digi-Med Blood Pressure Analyzer (Micro-Med, Louisville, KY), and the other was attached to a computer-controlled peristaltic pump for hemorrhaging the animal. Both left and right femoral arteries were alternately used for monitoring SAP.

A Wiggers type of isobaric hemorrhage was used (Wiggers 1950). The peristaltic pump (model P720, Instech Laboratories, Plymouth Meeting, PA) was adjusted via the digital/analog converter (PC-LPM-16, National Instruments, Austin, TX). The blood withdrawal was not constant but was automatically adjusted by the software to the slope of the targeted MABP. Blood was removed at a rate required to achieve a mean arterial blood pressure of 40 mm Hg over 15 min (figures 3 and 4, trace SAP), for further details see Johnson *et al* (1995). The experiment was performed using a computer-based data acquisition system (OptiPlex GX1p, Dell Computer Co, Round Rock, TX), running a program written in LabVIEW (National Instruments, Austin, TX).

Intracranial REG I (iREG) was measured with intracranial electrodes (E 363/1, Plastics One, Roanoke, VA) in intra-hemispherial, bipolar derivation; measuring frequency was 45 kHz (KR-Ea Rheography Preamplifier, Carlo Erba/Galileo, Italy). Four electrodes were implanted identically; iREG derivations were alternated but had the same lateralization as LDF or carotid flow probe. The electrodes were placed at a 5 mm depth perpendicular to the surface of the skull. The electrode diameter was 0.35 mm at the uninsulated tip (5 mm) (figures 1 and 2). The electrodes were fixed to the skull with dental acrylic cement (Plastics One, Roanoke, VA) and the electrical contacts were placed in a plastic electrode pedestal (MS 363, Plastics One, Roanoke, VA). The typical iREG resistance was about 10 ohms.

The EEG was recorded using the same type of electrodes on the contralateral hemisphere; the amplifiers used were a 7P5B Wide band EEG pre-amplifier and a 7DAG Polygraph DC driver amplifier Grass (Quincy, MA). Measurement of CBF was taken with iREG, laser Doppler flowmetry (Integrating probe, Periflux System 4001, Perimed Sweden) and carotid

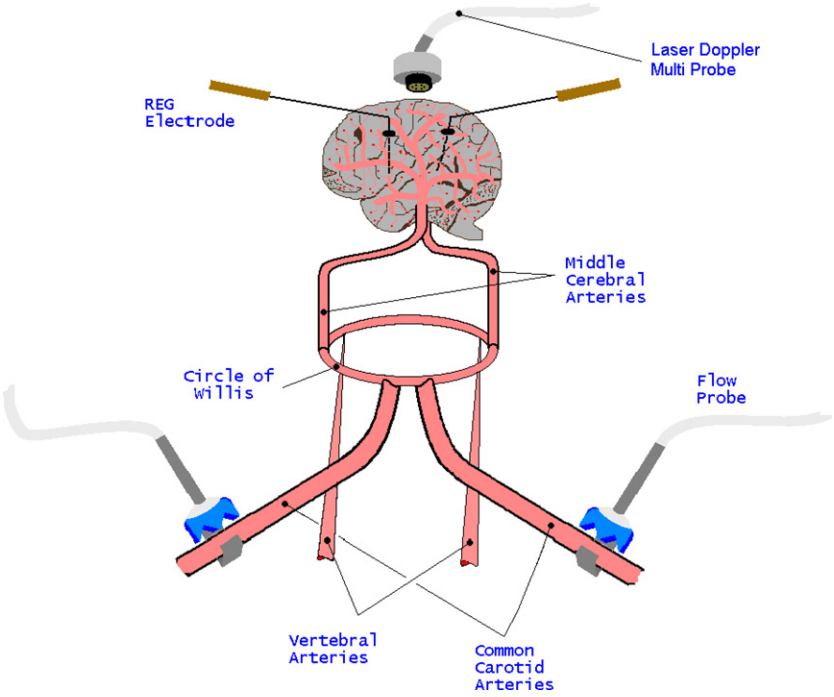

Figure 2. Schematics of CBF and probe for electrode localization. CBF was measured by iREG, local CBF by LDF (Multi Probe: 7 fibers in a 6 mm diameter circle) and carotid flow by Doppler ultrasound. The iREG electrode active surface was a cylinder (5 mm long, 0.35 mm diameter).

flow by an ultrasound device (T201 Ultrasonic Bloodflow Meter, Transonic Systems, Ithaca, NY). Further details are described earlier (Bodo *et al* 2004a, 2004b). The electrocardiogram was recorded by Lead (Einthoven) II with ECG/Biotach amplifier, Model 20-4615–65, Gould Electronics (Valley Road, OH); wide band ac preamplifier & integrator with polygraph dc driver amplifier (Grass Instruments, Quincy, MA). Respiration was recorded by MT-29/1 Needle microprobe, diameter: 29 ga BAT-12 Microprobe Thermometer, PhysiTemp (Clifton, NJ) and with a Transducer preamp, Kent Scientific (Torrington, CT). The exhaled CO_2 was recorded by a Carbon Dioxide Analyzer (CD-3A, Ametek, Pittsburgh, PA). The settings of the filters were as follows: EEG: 3–35 Hz; iREG (time constant): 3 s; EKG: 1–500 Hz (Grass), 0.5–30 Hz (Gould); Doppler ultrasound: dc—100 Hz, respiratory sensor (time constant): 0.125 s.

The difficulty in measuring the three CBF modalities simultaneously concerned the placement of sensors on the rats. The animal was placed in a stereotaxic frame (David Kopf Instruments, Tujunga, CA) in a sphinx position for recording LDF; during measurement of carotid flow, the rat was in a supine position; iREG was measured in both the cases. Therefore, the iREG number covered both groups, and the LDF and carotid flow were measured in different subgroups. The number of rats used was as follows: LDF ($n = 3$), Doppler ($n = 11$) and iREG with both, i.e. ($3 + 11 = 14$) (table 1).

2.1. Data acquisition

Intracranial REG and other modalities were measured continuously before and during hemorrhage. An IBM compatible PC performed the data collection (polygraphic signals) with a PCL-718 AD card (Advantech, CA). The A/D sampling rate was 630 Hz; the resolution

Table 1. iREG, LDF and carotid flow changes during hemorrhage. The iREG data had higher CV, figure 5. The first column is the identification of rat and file. iREG data are on the left side of table, the right side are the LDF (upper) and carotid flow (lower) data. The second column contains the control (baseline—BL) iREG values; the third column shows iREG values (MABP was about 40 mm Hg). The differences were expressed as percentages of the baseline values in the case of iREG (increase BL%) and in the case of LDF and carotid flow (decrease BL%). The increase of iREG amplitude ($p = 0.002$) and decrease of carotid flow ($p = 0.005$) were significant. The overall iREG increase was 80.94% ($n = 14$). Negative iREG value (rat 164) was neglected, meaning that the maximal vasodilatation did not reach the BL level but autoregulatory response was present. Amplitude values were presented here in arbitrary units (units of analog digital conversion). Individual values may differ due to different gain settings of REG amplifier. CV%: coefficient of variability (mean/SD). Probability was calculated for REG versus LDF and REG versus carotid flow data using student *t*-test in Excel software. For other details see table 2 and section 2.

Rat/file ID	BL	MABP 40 mm Hg	Increase (BL%)	BL	MABP 40 mm Hg	Decrease (BL%)
		REG			LDF	
R 7–25–1	56.7	79.24	39.75	1006.15	806.42	80.15
R 8–1–3	247.12	469.28	89.90	1976.85	1368.61	69.23
R 8–6–3	17.28	51.8	199.77	1987.34	1676.7	84.37
Group mean	107.03	200.11	109.81	1656.78	1283.91	77.92
Probability		0.143			0.046	
		REG			Carotid flow	
156 H20	367.13	546.5	48.86	3256.05	2436.73	74.84
157 H5	440.94	937.12	112.53	6371.91	3059.22	48.01
160 H1	63.83	120.89	89.39	2320.28	2053.22	88.49
164 32	143.66	115.86		488.75	360.72	73.80
165 H25	187.32	207.86	10.96	294.91	61.51	20.86
166 CO_3	517.77	1155.08	123.09	1347.4	260.16	19.31
168 H20	80.71	103.86	28.68	1736.46	879.87	50.67
169 H20	278.1	559.09	101.04	849.07	371.79	43.79
171 H19	583.65	934.59	60.13	1910.59	1023.15	53.55
172 H17	624.6	970.25	55.34	779.59	610.56	78.32
174 CO_3	415.44	800.88	92.78	1754.02	364.31	20.77
Group mean	336.65	586.54	72.28	1919.00	1043.75	52.04
Total mean			80.94			57.58
Total CV%			60.77			57.83
Probability		0.002			0.005	

was 12 bits. The input setting of the card was ± 1 V, which was optimized for the card using preamplifiers for preconditioning (DC Amplifier; Universal Amplifier; Gould Electronics, Valley Road, OH and polygraph DC driver amplifier, Grass Instruments, Quincy, MA).

For analog physiological data acquisition, proprietary softwares (Heilig *et al* 1998) and DataLyser (Baranyi) were used on a PC, data were processed offline. The REG, LDF and carotid flow calculations and comparisons were analyzed quantitatively, based on amplitude (minimum–maximum distance of pulse amplitude) measurement of 5 s time-windows in the time of maximal vasodilatation during the first 15 min of hemorrhage, typically close to MABP 40 mm Hg. In the REG literature, the mean value—contrary to SAP—is not used. Similarly, in the CBF autoregulation literature, mean value is method dependent, whether it is measured or calculated as an average value of multiple measurements (Chillon and Baumbach 2002). The calculation was executed using two cursor readings. Data are given as units of AD converter (table 1). Since neither LDF nor iREG is an absolute flow measurement, a control segment of recording was chosen from the period (baseline) before hemorrhage, and the changes were expressed as a percentage of the baseline. In order to decrease the respiratory interference with iREG, data were digitally filtered ('Chebyshev' filter order = 5, band pass, 0.3–60 Hz)

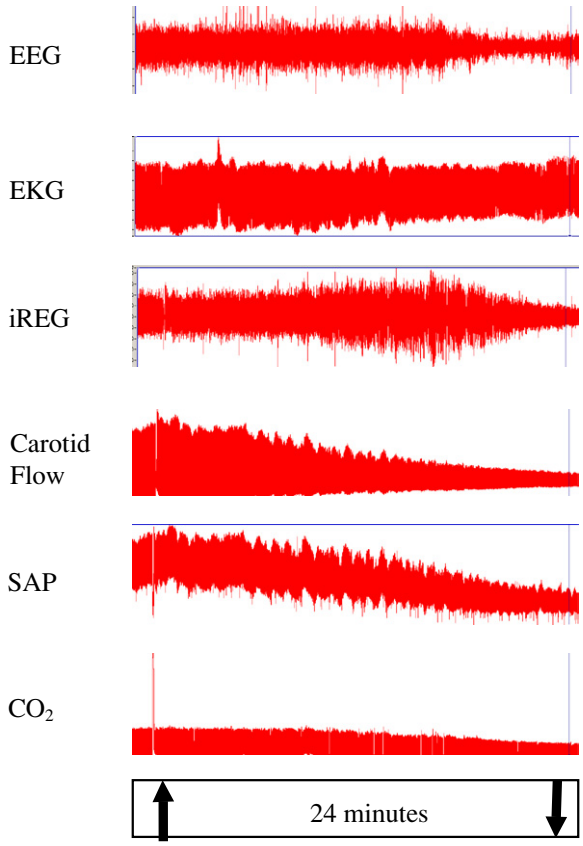

Figure 3. Typical intracranial REG pulse amplitude increases during hemorrhage. Arrows indicate start and end of SAP decrease to 40 mm Hg. Carotid flow decreased similarly to SAP without suggesting any sign of CBF autoregulation. iREG amplitude transiently increased and then decreased, suggesting CBF autoregulation and indicating its lower limit before 40 mm Hg MABP. The EEG amplitude decrease coincides with the disruption in brain activity coincident with the diminished CBF status. EEG: electroencephalogram; iREG: left side, after removal of respiratory subharmonic; Carotid flow: left side; SAP: systemic arterial pressure; CO_2: exhaled carbon dioxide. Time window: 24 m. The rat/file ID was 174—CO_3.

with a software module integrated into the DataLyser. Two correlation coefficients (Pearson's product-moment correlation and Spearman's rank correlation) and two statistical tests (the paired *t*-test and the Wilcoxon signed-rank test) were examined. Student *t*-test was used for comparison of CBF changes: data were available and suggest that the change is only one directional (non-symmetric) compared to the baseline, i.e. iREG amplitude increased. The tests were performed using GraphPad Prism version 3.00 for Windows (GraphPad Software, San Diego CA, USA, www.graphpad.com). $p < 0.05$ was considered significant.

3. Results

When MABP was decreased from its normal level to 40 mm Hg during 15 min, the following events occurred: intracranial REG amplitude transiently increased (72.3%, $p = 0.002$), and then decreased. Carotid flow decreased (52.04%, $p = 0.005$). Exhaled carbon dioxide also decreased (figure 3).

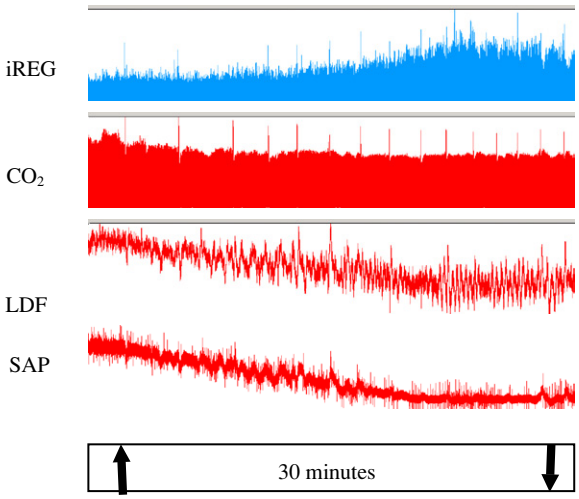

Figure 4. Typical LDF and iREG changes during hemorrhage. iREG indicated CBF autoregulation (arteriolar vasodilation), local cortical CBF passively follows SAP, with increased pulse amplitudes, CO_2 slightly decreased. Left side: baseline; MABP decreased to 40 mm Hg during 15 min; right side plateau: 40 mm Hg, time window: 30 min. CBF by iREG; Cortical CBF by Laser Doppler flow (integrating probe: 7 sensors in a 6 mm circle array). The rat/file ID was 8-6-02—3.

Similarly, when LDF was used instead of carotid flow to compare iREG change, iREG amplitude transiently increased and then decreased. LDF decreased similarly to SAP with slightly increased rhythmic oscillations in time of 40 mm Hg MABP. Exhaled carbon dioxide also decreased (figure 4). The comparison of the baseline and 40 mm Hg states suggests that during hemorrhage, iREG amplitude increased (109.81%) and LDF decreased (77.92%) (table 1). The total REG group increase was 80.94% and the total non-REG group (LDF + carotid flow) decrease was 57.58%. The observed changes were biologically relevant and partially statistically significant (table 2).

4. Discussion

The purpose of the study was to establish the behavior of iREG during hemorrhage and to evaluate its nature from the point of view of CBF autoregulation as well as to compare various CBF modalities. In order to perform evaluation on CBF autoregulation, it was necessary to record other modalities, such as SAP and exhaled CO_2. Because of the CBF heterogeneity (Waschke *et al* 2004), local CBF or one, unable to show CBF autoregulation it would not be acceptable for vital sign monitoring purposes.

The CBF autoregulation was tested by hemorrhage, which caused blood pressure to decrease, resulting in brain vasodilatation. There is no previous publication reporting use of iREG during hemorrhage or comparing iREG to other CBF measurements. The iREG may indicate classical CBF autoregulation during hemorrhage. As has been reported previously, iREG also suggested CBF autoregulation during CO_2 inhalation and aortic compression (Bodo *et al* 2003, 2004a). Both cortical flow (LDF) and carotid flow coincided with a transient SAP decrease, but iREG increased transiently (figures 3 and 4). This result suggests that iREG reflects CBF autoregulation. If only cortical CBF or carotid flow were measured, without measuring iREG, one might conclude that CBF autoregulation does not exist during hemorrhage. In clinical practice, mostly carotid flow is used to measure CBF autoregulation (Manno 2004). However, it should be noted that the autoregulatory response is

Table 2. Summary of the statistical analysis. To test for statistically significant differences between mean baseline (BL) measurements and SAP (40 mm Hg) measurements for iREG, LDF and carotid flow (CF), two statistical tests (the paired *t*-test and the Wilcoxon signed-rank test) were found. When only three pairs of observations were examined, all *p*-values exceeded the 0.05 level; however, when 11 pairs of observations were examined, all *p*-values were less than 0.05. To determine if iREG per cent changes were correlated with LDF and carotid flow per cent changes, two correlation coefficients (Pearson's product-moment correlation and Spearman's rank correlation) were examined. None of the four correlations were statistically different from zero (i.e. we failed to reject the hypothesis that each correlation was equal to zero).

Comparison of interest	Group size	Two-sided stat. test	*p*-value	Comments
		Summary of *p* values		
ireg BL versus iREG 40	3	Paired *t*	0.29	Small sample size
iREG BL versus iREG 40	3	Signed-rank	0.18	Small sample size
LDF BL versus LDF 40	3	Paired *t*	0.09	Small sample size
LDF BL versus LDF 40	3	Signed-rank	0.18	Small sample size
iREG BL versus iREG 40	11	Paired *t*	0.003	
iREG BL versus iREG 40	11	Signed-rank	0.004	
CF BL versus LDF 40	11	Paired *t*	0.01	
CF BL versus LDF 40	11	Signed-rank	0.004	
Comparison of interest	Group size	Correlation coefficient	Value of correlation	H_0: $r = 0$, *p*-value
		Summary of Pearson and Spearman correlations		
iREG% versus LDF%	3	Pearson	0.47	0.69
iREG% versus LDF%	3	Spearman	0.50	0.67
iREG% versus CF%	10	Pearson	−0.13	0.72
iREG% versus CF%	10	Spearman	−0.38	0.28

vessel-size-dependent; consequently and predictably, on the carotid the autoregulatory answer should be smaller than on the arterioles (Kontos *et al* 1978). 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. The main point that we would like to emphasize is that this is the first study to compare the three methods for monitoring purposes and describe the differences.

4.1. CBF and hemorrhage

The vital functions of the brain, in spite of its well-developed autoregulation, are impaired during prolonged hypovolemic conditions as the CBF autoregulatory reserve is exhausted. Afferent neural input to the brain seems to be elevated during shock. It may be presumed that this leads to increased tissue metabolism and the accumulation of metabolites. The low flow combined with elevated neuronal activity and cellular metabolism produces an imbalance between oxygen delivery and oxygen utilization leading to neuronal damage (Kovach 1988).

Cerebrovascular responses to hemorrhage reflect the balance between autoregulatory vasodilatation and sympathetic vasoconstriction (Pearce and D'Alecy 1980). During hemorrhage, CBF heterogeneity and hypovolemic cerebral hyperemia were observed (Komjati *et al* 1996, Waschke *et al* 2004). In hemorrhagic hypotension, the shift of CBF autoregulation is described (Chillon and Baumbach 2002). In our experiments during hemorrhage, only iREG suggested the classical CBF autoregulation: LDF and carotid flow followed SAP decrease during hemorrhage. It would appear from these responses that the iREG responses may be best explained if the iREG signal is a vascular volume measurement as opposed to a measure of blood flow. This would explain why the iREG and LDF measures may

change in apparently opposite directions, such as that encountered in the case of hemorrhagic hypotension. To clarify the increased rhythmic oscillation of LDF during hemorrhage requires a separate study. The vasomotion measured by LDF possibly increased indicating the early arteriolar endothelial dysfunction—but the LDF downward shape can reflect the decreased SAP and carotid flow, in other words the decreased number of red blood cells (Nilsson and Aalkjaer 2003, Landmesser *et al* 2004).

4.2. Monitoring

The use of clinical information systems has increased exponentially over the last few years, especially in critical care settings, where computers have been routinely integrated into patient monitoring, bedside calculations and life-support devices (Levy and Sibbad 2004, Gupta 2002). Specifically, the continuous monitoring of CBF autoregulation has a lifesaving importance (Czosnyka *et al* 2000, Steiner and Czosnyka 2002).

The brain, which is the most sensitive sensor of hypoxia and ischemia, is the optimal organ for use as a feedback modality for life-sign monitoring and resuscitation. The potency and maximum feedback gain of various arterial pressure control mechanisms (baroreceptor, chemoreceptor and central nervous system ischemia) are different, the most potent being the central nervous system (Guyton and Hall 2000). One potential monitoring modality is the electrical activity of the brain (EEG). However, the EEG is an indirect mirror of brain functioning. This is why EEG monitors, even those with advanced computational support, such as the bispectral index (Aspect Medical Systems, Newton, MA), cannot be used for CBF evaluation alone but also for anesthesia control. The EEG has about a 10 s delay to indicate a decrease in CBF because of its glucose and oxygen store (Moskalenko 1980, Shulman *et al* 2002). In the case of brain ischemia (hypoxia, traumatic brain injury, stroke, increased intracranial pressure, systemic hypovolemia), the tight coupling of function (EEG), metabolism and CBF are disconnected. Monitoring of CBF or its reactivity is essential and has life-saving potential (Bouma and Muizelaar 1995). Interpretation of the REG signal alone, without knowledge of CPP, intracranial pressure (ICP) or SAP is difficult. In the future, monitoring of CBF reactivity may involve other modalities, such as EEG, in order to overcome methodological limitations and to obtain an improved picture of the pathophysiological status of a patient. Studies covering various aspects of this problem were detailed elsewhere (Lang and Chesnut 2000, Panerai 1998, Vespa 2003, Weyland *et al* 2000, Wilson *et al* 2003, Yonas and Pindzola 1994, Sandor *et al* 2003, Rosner 1995).

In the case of subarachnoid hemorrhage, the recent clinical practice for treatment cerebral vasospasm involves ‘check transcranial Doppler flow (TCD) velocities every day’. Also, ‘TCD flow velocities may need to be supplemented with another form of CBF evaluation’ (Manno 2004). The continuous REG monitoring offers an advantage to this practice.

Additionally, recent results suggest that non-invasive cerebral impedance measurements reflect intracranial events and are able to detect cerebral edema following hypoxia-ischemia (Lingwood *et al* 2002). Characteristic changes in the REG wave with increased ICP in humans and in animals have been reported previously (McHenry 1965, Bodo *et al* 1986). Because of the vital importance of CPP (CPP = SAP − ICP), potential REG application can be very useful either as an indicator of CBF autoregulation, CPP or non-invasive ICP monitoring since ICP elevation is a common consequence of traumatic brain injury (Bakay and Lee 1965, Marmarou 1994, Manz 1979, Moskalenko 1980, Pronk 1986, Rosner *et al* 1995, Roffey *et al* 1999).

CBF and its reactivity were influenced by anesthesia (Szabo *et al* 1983, Kirsch *et al* 1996, Roberts 2000). The start of the hemorrhage was not precisely timed from the start of the first

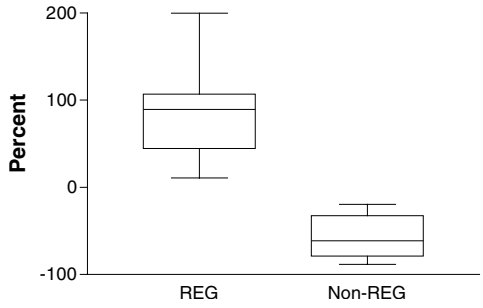

Figure 5. Comparison of data of iREG group and non-iREG (LDF and carotid together) groups. The groups were significantly different ($p < 0.0001$). Confidence intervals for iREG were as follows: lower 95%—51.22 and upper 95%—110.7; for non-iREG group lower 95%—71.75 and upper 95%—43.42 (see figure 5 and table 1), iREG, column 4; non-iREG, column 7; data for rat 164 were excluded as a negative value; $n = 13$. Both groups passed the normality test. The tests were performed using GraphPad Prism (version 3.00 for Windows, GraphPad Software, San Diego, C, USA, www.graphpad.com).

anesthesia; consequently, the blood concentration of pentobarbital was different depending on when it was measured. Consequently, the time of iREG amplitude maximum during hemorrhage was different, which explains the higher dispersion of iREG data (table 1 and figure 5). To measure CBF variations with anesthesia would require a different protocol than that used in this study. We plan to perform such a study in the future, using precise timing and anesthesia depth control by EEG monitoring (Bispectral index, Aspect Medical Systems, Newton, MA), furthermore REG measurement in awake animals.

4.3. REG

The REG signal reflects the impedance change: during blood inflow into the cranial cavity, electrical conductivity is increased (resistance decreased), represented by increasing REG pulse amplitude. The same electrical impedance change occurs generating pulse wave on peripheral site, as it was first described by Nyboer (1970) 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 curve—is the result of the equation, involving all mentioned factors but not detailed individually. The measured electrical impedance value offers the basis of several volume calculations, detailed by Jenker (1986).

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 iREG suggested classical CBF autoregulation, indicating its relationship to arteriolar changes (Ganong 2001). Early CBF–REG studies have not focused on this topic (Hadjiev 1968, Jacquy *et al* 1974, Moskalenko 1980, Jenkner 1986). The CBF reaction differed, according to what was being measured: iREG reflected vasoreactive aspect of CBF; LDF reflected cortical CBF; carotid flow reflected SAP change during hemorrhage. The relationship between CBF and CO_2 gas concentration is known (Hurn and Traystman 2002) and was validated by iREG previously (Bodo *et al* 2003, 2004a). In these experiments, the CO_2 served to establish that the observed CBF change was unrelated to the CO_2 change. In other words, CO_2 increase can cause CBF increase, independent of SAP decrease.

The estimated distance (vertex–basis) of the rat brain is less than 10 mm. It would be better to use iREG electrodes with a 10 mm active surface instead of a 5 mm surface. However, at the base of the brain are the major arteries, and the longer electrode may cause bleeding. The current goes non-parallel between the two cylinders, but with a wider path (King *et al* 1996). A major theoretical problem is the electrical and CBF heterogeneity within the brain, the subject of a different article (Malmivuo 1992, Perez *et al* 2000, Waschke *et al* 2004). However, 'attempts are made to calibrate the pulsatile impedance signal in terms of blood flow in the field between the electrodes' (Geddes and Baker 1989). Intracranial REG is likely to reflect CBF around the electrodes, that is, regional CBF. However, in the case of this study, this region comprises most of the brain volume. There is no scientific knowledge or terminology to quantify and name the iREG-covered area today (see Moskalenko (1980)).

As an illustration of potential REG monitoring application and its advantage, it is worth to mention a study using PET scan for measuring CBF autoregulation reserve during CO_2 inhalation in cerebrovascular patients (Herold *et al* 1988). The price difference between PET scan and a much cheaper REG device explains why REG monitoring has a potential in diagnosing cerebrovascular alterations measuring cerebral hemodynamic reserve.

A typical REG change is known to occur as a consequence of arteriosclerosis, expressed as elongation of REG pulse amplitude peak time or decreased slope of anacrotic part (Jenkner 1986). The possible cause of this alteration is the decreased elasticity of arteriolar wall, which is the most sensitive indicator of disease progression. In a population survey of arteriosclerosis comparing REG and Doppler ultrasound systolic velocity, REG was a more sensitive indicator than Doppler. The regression lines of age versus REG rise time and CF in male and female groups were similar, but the slope of REG was about ten times steeper than that of systolic velocity (Bodo *et al* 1998).

Since that time, advances in the development of microprocessors and signal processing techniques offer the possibility to reconsider the feasibility of implementing a portable or even wearable version of the REG monitoring technique to evaluate the adequacy of CBF reactivity (Bodo *et al* 1995).

Further correlative study is desirable for REG and MRI T(2) BOLD images, which also reflect arteriolar functioning (Kim and Ogawa 2002, Kavec *et al* 2001, Vainrub *et al* 2004).

4.4. Cushing reflex

The Cushing reflex or triad is a cardiovascular response to increased ICP. The consequence is decrease of CBF. Cerebral ischemia, a major complication of cerebral hemorrhage, causes a massive discharge of sympathetic outflow. The symptoms are hypertension, bradycardia and decreased or irregular respiration (Anonymous 2004). The danger of these symptoms is not only the direct life threatening condition, but also misleading information, such as increased SAP can cause increased CPP. During postoperative care following neurosurgery, traumatic brain injury or hemorrhage, patients are typically in a comatose condition. In such cases, an increase in SAP can be easily misinterpreted as an improvement in the status of the patient. Without intervention, SAP increase can lead to herniation and death (Bakay and Lee 1965). Related clinical aspects can be found elsewhere (Prall *et al* 1995, Jones 1989, Strandgaard and Paulson 1989, 1995, Griswold *et al* 1981).

5. Conclusion

In an experiment, cerebrovascular changes have been induced in rats by hemorrhaging. Two variables, related and dependent on the cerebrovascular state, have been measured before and after the induced change: iREG and carotid flow. The results show that there are statistical

differences both in iREG and carotid flow measurement, with respective probabilities of 0.002 and 0.005. Carotid flow gives a greater difference in their measurement between both states but was unable to detect CBF autoregulation. 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 (Aaslid 1999). Possibly, there is a similar situation during hemorrhage we observed.

The results indicate that iREG more accurately reflects cerebrovascular responsiveness than do the local CBF changes measured by LDF or carotid flow measured by ultrasound. The physiological background of these results was summarized as follows: 'Because the regulation of blood flow is a function of arterioles distal to the large arteries, flow through large arteries may be constant despite changes of regional flow in tissue' (Reivich and Waltz 1980).

REG monitoring may be a useful, non-invasive, continuous monitoring method of assessing cerebrovascular reactivity or capacitance for combat casualty care of victims suffering from hemorrhage and may have applicability for maintaining CBF in non-combat emergency medicine. Further work will focus on correlating brain function, such as EEG and CBF/REG assessments during hemorrhage and resuscitation, using various resuscitation fluids since their electrical conductivities are different. Additional studies are needed to test CBF autoregulation with graded increases in ICP and SAP using iREG as well as human CO_2 inhalation studies.

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