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14. ABSTRACT

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15. SUBJECT TERMS

Rheoencephalogram (REG), cerebral blood flow (CBF), CBF autoregulation, rat

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

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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.

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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

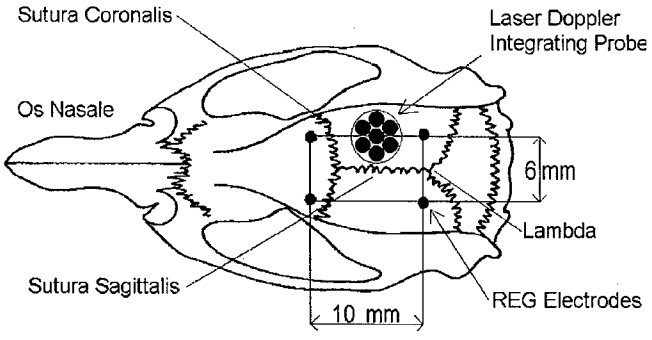

Figure 1. Rat skull with iREG electrode and laser Doppler probe localization. In one measurement, two iREG electrodes were used with the bipolar derivation within one hemisphere, the others were used for EEG derivation. Four electrodes were implanted identically; iREG derivations were alternated but 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

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)

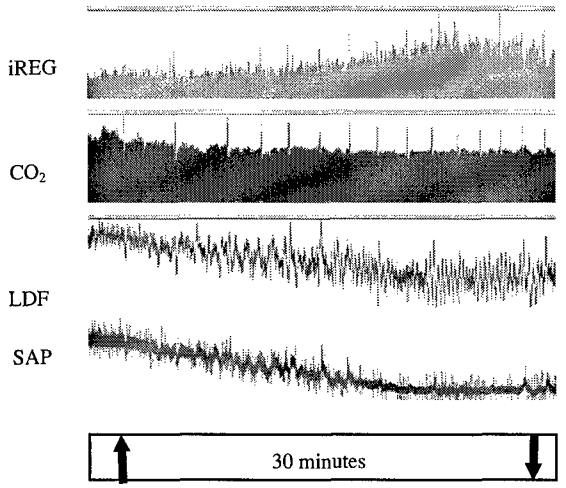

Figure 4. Typical LDF and iREG changes during hemorrhage. iREG indicated CBF autoregulation (arteriolar vasodilation), local cortical CBF passively follows SAP, with increased pulse amplitudes, CO_2 slightly decreased. Left side: baseline; MABP decreased to 40 mm Hg during 15 min; right side plateau: 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

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

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

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