

In vivo cerebral blood flow autoregulation studies using rheoencephalography

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Abstract. Acute management of patients with traumatic brain/blast injury is a challenge. To minimize secondary injury and improve outcome, it is critical to detect neurological deterioration early, when it is potentially reversible. One potential monitoring method is cerebral electrical impedance (rheoencephalography-REG) because of its non-invasiveness and good time resolution. Reported here are the results of cerebral blood flow (CBF) manipulations comparing electroencephalogram (EEG) with REG (both intra-cerebral) and measuring with surface and skull REG electrodes. Our hypothesis was that REG would reflect spreading depression and CBF autoregulation. Animal experiments were performed using one rat (four trials with intracerebral electrodes), monkeys (n=8, with surface electrodes) and pigs (n = 24 pigs with skull electrodes; 57 trials, 19 types of liposomes). Challenges included intracranial pressure (ICP) elevation, liposome infusion, and hemorrhage. Data were stored on a PC and evaluated off line. CBF autoregulation was evaluated both by visual inspection and by a Matlab script. These studies confirmed that REG reflects CBF autoregulation and that REG is useful for detecting spreading depression (SD), vasospasm and the lower limit of CBF autoregulation. These findings have clinical relevance for use in noninvasive neuro-monitoring in the neurosurgery intensive care and during transportation of patients with brain injury.

1. Introduction

The goal of neurocritical care is the prevention of secondary brain injury. Currently, there is no single modality that can monitor for hypoxia, ischemia, elevated ICP, edema, intracranial hemorrhage, vasospasm, and lack of CBF autoregulation [1]. Monitoring needs to be non-invasive, continuous and convenient. Current brain mapping methods (SPECT, PET scan, MRI) do not address these needs. Measuring brain electrical impedance is a potential technique for neuro-monitoring [2]. In previous studies we reported results of correlative studies indicating that REG has potential for use in neuro-monitoring [3-5]. Here we present results from three additional REG studies (rat, monkey, pig).

2. Methods

Animal experiments were performed using a rat (four trials under anesthesia; Ag/AgCl intracerebral electrodes; ICP elevation was by intra-cerebral probe/balloon inflation); monkeys (n=8, with surface EKG electrodes); and pigs (n = 24 pigs with skull, stainless steel electrodes; 57 trials, 19 types of liposomes). Challenges included elevation of ICP, intravenous liposome infusion, and lethal

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14. ABSTRACT Acute management of patients with traumatic brain/blast injury is a challenge. To minimize secondary injury and improve outcome, it is critical to detect neurological deterioration early, when it is potentially reversible. One potential monitoring method is cerebral electrical impedance (rheoencephalography-REG) because of its non-invasiveness and good time resolution. Reported here are the results of cerebral blood flow (CBF) manipulations comparing electroencephalogram (EEG) with REG (both intra-cerebral) and measuring with surface and skull REG electrodes. Our hypothesis was that REG would reflect spreading depression and CBF autoregulation. Animal experiments were performed using one rat (four trials with intracerebral electrodes), monkeys (n=8, with surface electrodes) and pigs (n = 24 pigs with skull electrodes; 57 trials, 19 types of liposomes). Challenges included intracranial pressure (ICP) elevation, liposome infusion, and hemorrhage. Data were stored on a PC and evaluated off line. CBF autoregulation was evaluated both by visual inspection and by a Matlab script. These studies confirmed that REG reflects CBF autoregulation and that REG is useful for detecting spreading depression (SD), vasospasm and the lower limit of CBF autoregulation. These findings have clinical relevance for use in noninvasive neuro-monitoring in the neurosurgery intensive care and during transportation of patients with brain injury.			
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hemorrhage. Data were stored on a PC and evaluated off line. Two types of REG devices were used : 1) KR -Ea Rheo Preamp, excitation frequency of 45, kHz time constant 3 s (OTE Galileo, Italy); 2) Cerberus: excitation frequency of 125 kHz, time constant 0.3 s, Quintlab, Hungary).

To calculate the lower limit of CBF autoregulation, waveform data (arterial pressure - SAP, and REG) were averaged in 10 second epochs, and the Pearson correlation coefficient was computed on 30 consecutive points (5 min) and updated every minute with a sliding window. For further details, see [6].

3. Results

3.1. Rat - Spreading depression

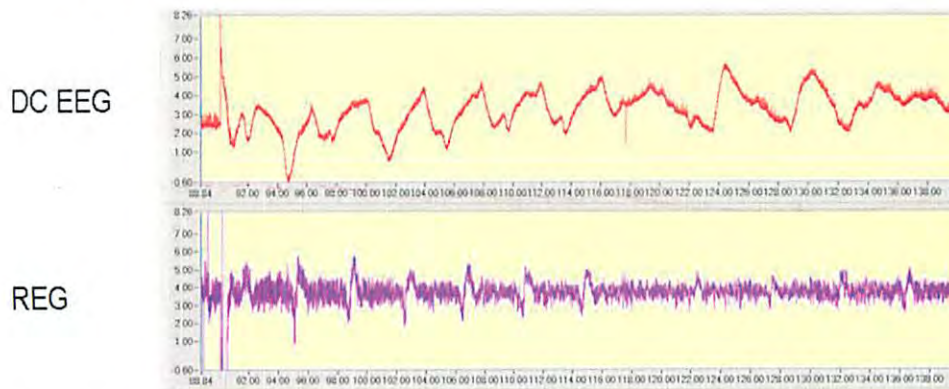


Figure 1. SD was elicited by ICP elevation. ICP elevation caused SD shown as amplitude fluctuation of DC EEG trace. REG showed close identical fluctuation.

3.2. Monkey – Lower limit of CBF autoregulation

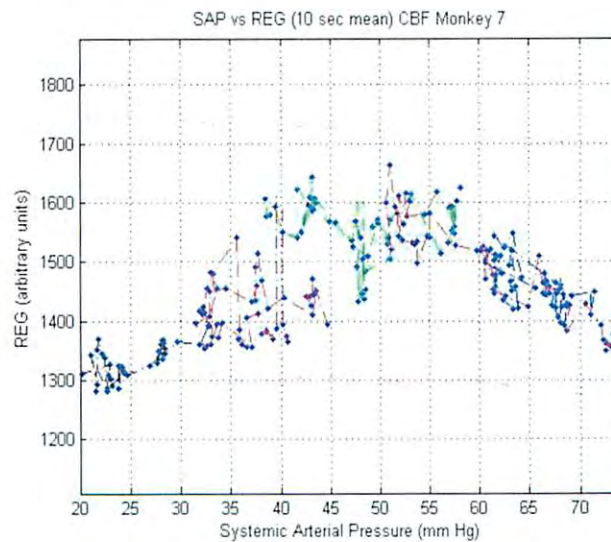


Figure 2. Relationship of REG to systemic arterial pressure during lethal hemorrhage. The lower limit of CBF autoregulation is at about 50 mmHg.

3.3. Pig – Vasospasm

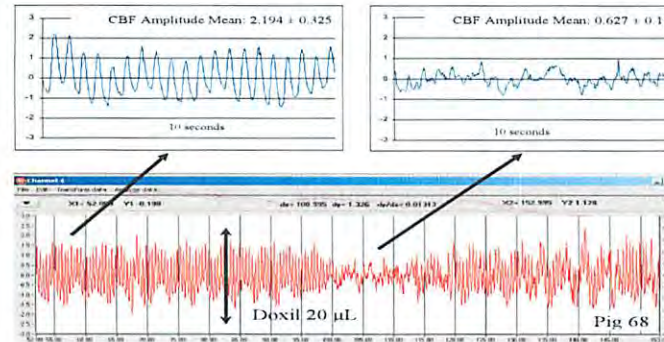


Figure 3. After the liposome injection, a transient decrease in REG pulse amplitude was observed. This result indicates the involvement of a cerebrovascular reaction during liposome/Doxil injection.

4. Discussion

Detection of spreading depression, of the lower limit of CBF autoregulation, and of vasospasm would provide clinical personnel in the ICU unit with information to prevent secondary brain damage in neurosurgery patients. The following *in vivo* studies of REG monitoring modeled these three clinical conditions.

4.1. Spreading depression

Measurement of spreading depression, an early warning sign of disturbed brain metabolism, would be ideal for neuro-monitoring if it could be measured non-invasively. In humans, EEG measurements showing SD cannot be accomplished by placing electrodes on the scalp; such measurements require intra- or epicortical electrodes with the concomitant hazard of infection. In the present rat study, REG detected spreading depression with such intra-cerebral electrodes. However, in human measurements, REG can be used to measure non-invasively with surface electrodes, thus eliminating the hazard of infection. The relationship between SD and impedance was described by Olsson et al [7].

4.2. Lower limit of CBF autoregulation

If a patient's CBF autoregulation is impaired, administering of infusion by ICU neurosurgery staff may cause secondary brain damage. Too much infusion may lead to brain edema; too little infusion may cause brain ischemia/hypoxia. The lower limit of CBF autoregulation is typically obtained invasively by measuring such modalities as ICP and SAP [8] to determine the phase relationship of slow oscillations of SAP (transfer analysis). REG conducted on monkeys with surface electrodes on the skin proved that slow wave oscillations were present in the REG signal and were not filtered out by the skull. Therefore, with a specialized algorithm developed for this purpose, REG can be used to detect the lower limit of CBF autoregulation.

4.3. Vasospasm

Vasospasm, the constriction of brain arteries, causes brain ischemia/hypoxia, which may lead to secondary brain injury [9]. Vasospasm after traumatic brain/blast injury can be present without physical impact or visible injury and may develop any time after the blast incident, even weeks later [10]. The present pig study showed that REG measurements can detect vasospasm. Cerebral vascular symptoms (nausea, dizziness, headache) have been described in humans following infusion with the cancer treatment Doxil (doxorubicin), a liposome encapsulated drug. In this study, REG detected transient vasospasm following Doxil infusion. A possible explanation is the release of vasoactive mediators causing a cerebrovascular reaction [11].

5. Conclusion

Brain injured patients are known to experience spreading depression, impaired CBF autoregulation, and vasospasm. Currently there is no non-invasive method in use to assess the risk of implementing a hypotensive resuscitation strategy in brain-injured patients. Measurements with REG can be used to identify the autoregulatory breakpoint for individual patients to determine their limit for permissive hypotension or to adequately administer infusion to increase cerebral perfusion pressure. The results reported here support the application of REG as a neuro-monitoring modality. Additional correlative studies of REG as a non-invasive modality for brain monitoring are required and are in progress.

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