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Assessment of cerebral perfusion in post-traumatic brain injury patients with the use of ICG-bolus tracking method

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ABSTRACT

The aim of this study was to verify the usefulness of the time-resolved optical method utilizing diffusely reflected photons and fluorescence signals combined with intravenous injection of indocyanine green (ICG) in the assessment of brain perfusion in post-traumatic brain injury patients.
The distributions of times of flight (DTOFs) of diffusely reflected photons were acquired together with the distributions of times of arrival (DTAs) of fluorescence photons. The data analysis methodology was based on the observation of delays between the signals of statistical moments (number of photons, mean time of flight and variance) of DTOFs and DTAs related to the inflow of ICG to the extra- and intracerebral tissue compartments.
Eleven patients with brain hematoma, 15 patients with brain edema and a group of 9 healthy subjects were included in this study. Statistically significant differences between parameters obtained in healthy subjects and patients with brain hematoma and brain edema were observed. The best optical parameter to differentiate patients and control group was variance of the DTOFs or DTAs. Results of the study suggest that time-resolved optical monitoring of inflow of the ICG seems to be a promising tool for detecting cerebral perfusion insufficiencies in critically ill patients.

Introduction

Critical alterations in brain perfusion are usually observed in patients after severe head trauma. Perspectives to reverse the effects of primary brain injury are very limited. Therefore, the aim of critical care in posttraumatic brain injury (TBI) patients is to detect, monitor and prevent secondary insults which are difficult to control (Dunn et al., 2006). Taking into account that patients treated in Intensive Care Unit (ICU) have optimal tuning of extracranial homeostasis, the emphasis is set on the monitoring of ischemic brain damage (Kim and Gean, 2011).

Several neuroimaging techniques of cerebral blood flow assessment have been introduced into clinical practice. The main imaging techniques dedicated to brain hemodynamics in head injury are perfusion-weighted MRI, perfusion CT, single photon emission computed tomography (SPECT), positron emission tomography (PET), and transcranial Doppler (TCD) ultrasonography. Cerebral perfusion pressure (CPP) monitoring is also used if intracranial pressure probe is installed. Most of the neuroimaging and neuromonitoring techniques have significant disadvantages. Perfusion-weighted MRI has a limited application in emergency settings (Petrella and Provenzale, 2000). Perfusion CT seems to be a promising method in the acute phase of head trauma but is connected with radiation exposure and necessity to use contrast agent (Kim and Gean, 2011). SPECT and PET have still limited availability and are mainly used in a research setting (Coles, 2007).

Moreover, all of the abovementioned neuroimaging techniques require the transport of the patient outside ICU to the specialized imaging facility, which remains a serious danger for those patients who are in critical condition.

Two of the above mentioned techniques can be applied at the bedside in acute brain damage treatment. Transcranial Doppler ultrasonography is a convenient tool for a bedside evaluation of hemispheric and global cerebral blood flow (CBF) but it cannot provide information about perfusion in cerebral microvascular bed. The technique for cerebral perfusion pressure monitoring is an invasive procedure that involves inserting a catheter into the intracranial compartment.

Neurological acute disorders tend to develop regionally in the brain and have high temporal dynamics especially at the early time frame. Therefore, there is an emerging need for neuromonitoring method, which should be a continuous, real time technique allowing for the assessment of regional changes in brain perfusion.

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Near infrared spectroscopy (NIRS) is a non-invasive method of estimating regional changes in cerebral oxygenation and may allow for the assessment of cerebral blood flow. The principle of the method is based on differences in the absorption of light by oxygenated and deoxygenated hemoglobin in a near-infrared wavelength range (Cope and Delpy, 1988). However, the major disadvantage of NIRS technique is the inability to distinguish reliably between intra- and extracerebral changes in oxygenation. Time-resolved NIRS (trNIRS) appears to be superior in discrimination of information on changes in oxygenation related to intracerebral tissue. This technique is based on the assumption that late photons in the distribution of time of flight have higher probability of penetration in the brain tissue than the early photons, which penetrate more superficially. This assumption was validated in a series of methodological experiments in diffuse reflectance geometry, which showed that the late photons have higher probability to penetrate the brain cortex (Aletti et al., 2012; Kacprzak et al., 2007; Liebert et al., 2004, 2005; Selb et al., 2005, 2006; Steinbrink et al., 2001).

It was proposed to use the NIRS technique during the injection of optical contrast agent in order to track inflow of the dye into the brain and assess cerebral blood flow and cerebral blood volume (Brown et al., 2002; Elliott et al., 2010; Gora et al., 2002; Habermehl et al., 2011; Keller et al., 2003; Kohl-Bareis et al., 2002; Kusaka et al., 2001; Patel et al., 1998; Roberts et al., 1998; Terborg et al., 2004). Indocyanine green (ICG) is typically used in these studies because of its relative low toxicity (Hope-Ross et al., 1994), high absorption and fluorescence emission in the near infrared wavelength region (Desmettre et al., 2000; Gerega et al., 2011; Landsman et al., 1976; Mordon et al., 1998). In recent studies, a combination of trNIRS technique with the use of ICG (Jelzow et al., 2012; Liebert et al., 2004, 2005, 2006; Steinkellner et al., 2010a) was proposed. It was also reported that trNIRS could be successfully applied in the monitoring of fluorescence light excited in the dye circulating in the brain (Gerega et al., 2012; Jelzow et al., 2012; Liebert et al., 2006; Steinbrink et al., 2008).

In the present study we investigate the potential of time-resolved NIRS used in combination with ICG-bolus tracking for brain perfusion monitoring at the bedside in ICU. The study was focused on traumatic brain injury patients with localized brain hematoma and with brain edema. Results of optical measurements of diffuse reflectance and fluorescence during the injection of ICG carried out in groups of patients were compared with the results obtained from healthy volunteers.

Materials and methods

Patients

The group of patients after traumatic brain injury is extremely heterogeneous. Occurrence of intracranial (extracerebral or intracerebral) hematomas and contusions, as well as extracranial lesions is typical for these patients. In addition, brain edema often appears as a consequence of trauma. In some cases the skull is broken or has to be removed by neurosurgical procedure. During the patient's stay in the ICU ischemic insults can occur and if they are severe enough, they result in brain death.

Two relatively homogeneous groups of patients were included in the study. The patients were examined prospectively in two clinical conditions: with intracerebral brain hematoma (hematoma group) and with posttraumatic brain edema (edema group). The inclusion criteria for the groups were: nonpenetrating TBI with abnormal findings on CT scans (intracerebral hematoma/contusion located subcortically or brain edema), age between 18 and 70 years old, and a stable hemodynamic state. The size of intracerebral hematoma had to comply with the following criteria: volume at least 2 cm^3 and the distance from the surface of the head less than 2.5 cm. The volume of the lesion was measured based on ABC/2 formula (Kothari et al., 1996). Serial CT scans were performed at the admission of the patient to the ICU and repeated within 24 h before/after NIRS measurement. Cerebral edema was represented on imaging as the loss of sulci, compression of the basilar cisterns and flattening of the ventricular margins. Typical CT scan for hematoma showed solid hyperdensity lesion. In the case of contusion, a mixed density lesion was observed. The necessity of acute neurosurgery did not lead to the exclusion of the patient from the study groups.

The general management of all patients with severe TBI was provided according to the Brain Trauma Foundation Guidelines with local modifications (Bratton et al., 2007). Patients were maintained in a euvolemic state and blood pressure maintained at a mean arterial blood pressure >90 mmHg by using volume replacement and/or vasopressor support. Studies were performed during the acute phase (corresponding to the first 20 days post-injury). The patient's discharge status was classified as discharged home, or whether the patient died. The results of the measurements were compared with the signals obtained from healthy volunteers (control group).

Ethics Committee of the Medical University of Warsaw has approved the measurement protocol. In each case, the written informed consent was obtained from the patient or the patient's legally authorized representative.

Eleven patients fit the inclusion criteria for brain hematoma/contusion measurements (mean age 47 $\pm$ 15, 8 males, 3 females), and 15 for brain edema measurements (mean age 50 $\pm$ 20, 9 males, 6 females). Five patients had a mass lesion that was evacuated (craniotomy). It should be noted that the measurements were carried out after the craniotomy but not above the area of neurosurgical intervention. In these cases we focused on hematomas or areas of brain edema that were present on CT and met the inclusion criteria. Ten patients had additional subarachnoid hemorrhage (SAH). Also in these patients measurements were not carried out above the hemorrhage area.

Glasgow Coma Scale (GCS) score ranged from 3 to 14 on admission to hospital, and study timing ranged from 0 day (the day of admission) to 14 days after injury. It was rather difficult to properly assess neurological state using GCS score on the day of measurement as in most cases analgesia and sedation was routinely used. General information and clinical data of studied patients are presented in Tables 1–3. In some cases, if different clinical conditions have occurred (for example brain hematoma and brain edema), the measurements were repeated in the same patient. The data shown in rows from 1 to 9 in Tables 1–3 describe the same patients, qualified to measurements in hematoma and edema condition.

As a control group, 9 healthy subjects (8 males and 1 female) with mean age of 32 $\pm$ 5 were examined. Healthy subjects did not suffer from any neurological disorders.

Measurement procedure

Most of the TBI intracerebral hematomas/contusions occur in the frontal and temporal lobes. During trNIRS measurements, optodes were attached on the surface of the head in locations where CT scan analysis showed intracerebral hematoma and symmetrically over the contralateral hemisphere (Fig. 1c). We assumed that this specific localization directly over the lesion would better reflect cortical perfusion insufficiencies than the optode position on the forehead used by other investigators. On the other hand, the volume interrogated by photons penetrating between source and detector could not contain any blood pool related to the extracerebral or extracranial hematoma.

For patients with brain edema and healthy subjects, the optodes were placed over C3/C4 points on the head according to the 10/20 EEG system. In the case of edema, expected changes in cortex perfusion were less localized and this standard positioning of the optodes might allow assessment of hemispheric effects.

For all patients and healthy subjects, the time-resolved diffuse reflectance and fluorescence measurements were carried out in a standardized protocol during intravenous injection of ICG (Pulsion Medical Systems SE, Germany). The dye bolus used in those experiments