行政院國家科學委員會專題研究計劃成果報告

計劃編號：NSC 88-2314-B-002-349
計劃名稱：(中文) 中度頭部外傷病人腦部質子磁共振頻譜與其預後之相關 (英文) Correlation between cerebral magnetic resonance spectroscopy and clinical outcome in moderate head injury patients
執行期限：87年8月1日至88年7月31日
主持人：杜永光
執行機構及單位名稱：台大醫學院外科

Introduction

Head injury or traumatic brain damage is one of the leading causes of death in most developed country (1). In Taiwan, head injury is the third cause of death. Approximately ten thousand patients died from this reason yearly (2). Nevertheless, ten times of this number of patients become vegetative or disable after the damage of the brain. The society has to pay a large amount of cost for taking care of these patients. A better understanding of the pathophysiological change of the brain at the initial phase after the injury will provide better stratagies in the management of this type of patients and therefore improve the outcome of the patients.

Due to the derrangement of autoregulation after head injury, cerebral blood flow and metabolism will be compromized after the increase of intracranial pressure and the decrease of cerebral profusional pressure (3). Reduction of cerebral blood flow to cause cerebral ischemia will further increase intracranial pressure and induce another vicious circle (4-6). In last year, we conducted a study to investigate the correlation between the changes of cerebral blood flow (CBF), cerebral oxygen metabolism (CMRO2), and the outcome of head injury. Our results showed a good correlation among the changes of CBF, CMRO2, intracranial pressure (ICP) and the outcome of the patients (7).

Proton magnetic resonance spectroscopy (H-MRS) is a noninvasive method of monitoring *in vivo* metabolic biochemical concentration change over a certain time interval (8). It is very sensitive in detecting the change of N-acetyl asparate (NAA), cholin, and lactate (9,10). Therefore, early detection of metabolic changes of brain cell become possible with the use of H-MRS. Most of the clinical studies focused on the subsequent changes after cerebral ischemia, and the results showed that increasing

level of lactate and decreasing level of NAA and creatine are found in the ischemia area (11,12,13). However, very few studies concerning these metabolic change after cerebral injury have been reported. Thus, we conducted this study to further elucidate the biochemical metabolism of brain following post-traumatic cerebral ischemia.

Material and Methods

From Augest 1998 to July 1999, a total of 21 patients were admitted into neurosurgical intensive care unit of National Taiwan University Hospital. All the patients had suffered from severe head injury and admitted at the first 12 hours after injury. Their Glascow coma scales were between 10 to 13, and their age between 15 to 65 years old. Standard head injury managements include the administration of hyperosmotic agent, corticosteroid, and anticonvulsant, and artificial ventilation to reduce pCO2 to 32-35 torr were given. An arterial catheter was set up for continuous blood pressure monitoring, and arterial oxygen saturation (SaO2) and arterial oxygen content (CaO2) measuring. Another central venous line was set up for the measuring of central venous pressure. Via a small burr hole, a intracranial pressure (ICP) microsensor was introduced in to the frontal lobe parenchyma. This microsensor was hooked to a HP monitor system for continuous ICP monitoring.

These measurements as well as Glasgow Coma Scale (GCS) of the patients were recorded at 24 hours, 3 days, and 7 to 10 days after the injury. Measurements of cerebral blood flow with xenon enhenced computed tomography (xenon CT/CBF) were also performed at these time intervals (14). Additional recording of GCS of the patients was done on day 14 and day 28. The outcome of the patients was evaluated with GCS at three months after the injury.

During the measurement of cerebral blood flow, the patients received the first set of CT scan with a Picker 1200SX scanner. Then, a mixture of 30% xenon, 30% oxygen and 40% room air was inhaled via a mask. Three consecutive set of CT scan were performed at 1, 3, and 5 minutes after the starting of the inhalation of this gas mixture. Four constant cuts of the CT scan were chosen for the measurement of cerebral blood flow. On each chosen cut of the CT scan, regions of interest (ROI) with a diameter of 1 cm were selected from the territories of anterior, middle and posterior cerebral arteries. Concentration of xenon in the brain parenchyma was determined by the CT number of these ROIs, and concentration of xenon in the blood was determined by end-tidal xenon concentration measured from the expired gas in the mask and connected to a thermoconductivity gas analyzer. Cerebral blood flow was then calculated by Kety-Schmidt equation (15).

Proton magnetic resonance spectroscopy was performed by our GE signa 1.5T MRI system in combination with the software Proton Brain Exam PROBE Spectroscopy and a low-pass birdcage resonator. A self-shielded gradient coil was applied to the patient's head. Before the measurement of H-MRS, a set of T2 weighted MRI image was obtained to detect any pathological change of the brain. Then, eight areas of interest (ROIs) were selected over frontal, parietal, temporal, and occipital lobes of both hemispheres (in symmetrical location) for H-MRS analysis. These ROIs had a volex of 2x2x2cm3 and contented the correspondent ROIs in the xenon CT / CBF measurements. In order to ensure that same ROIs were selected in these two different studies on the same patient, three markers from neuronavigation system were applied to the patients' nasium and zygomatic arches as the basal reference point. Two acquisition techniques were used in H-MRS analysis: (1) Long

TE acquisition (TR1 sec, TE 270 msec) for choline, creatine, lactact and NAA. (2) Short TE acquisition (TR1sec, TE 30 msec) for glutamine and glutamate. Measured H-MRS from each voxel of ROIs were analyzed by Semiautomated Line-fitting soteware to plot out resonance waveform of each chemicals. The wave of lactate was defined at 1,34ppm, NAA at 2.02 ppm, creatine at 3.03 ppm, choline at 3.2ppm, asparate at 2.68 ppm, glutamine at 2.49 ppm, and glutamate at 2.35 ppm.

Data was presented as mean + SEM. The correlations between ICP, CBF, and amplitude of waves presenting each chemicals from H-MRS studies were analyzed by ANOVA. The relations between CMRO2, coma scale, and outcome scale of the patients were tested by Wilcoxan rank sum test.

Results

There were 11 male and 10 female patients enrolled in this study. There age ranged from 19 to 61 years (mean 36.4 + 8.4 years). Their GCSs ranged from 10-13 (mean 12.3 + 1.2). Mean ICP of the patients was 36.5+9.8 torr. Mean CaO2 of the patients was 96.5+6.5 %. Mean cerebral blood flow of 8 ROIs from each of the 4 CT scan cuts were as the following: right anterior cerebral artery (ACA) territory gray matter 41.3 + 7.9 ml/100gm/min, right ACA territory white matter 27.3+6.2 ml/100gm/min, left ACA territory gray matter 44.3+4.6 ml/100gm/min, left ACA territory white matter 23.9+6.5 ml/100gm/min, right middle cererbal artery (MCA) territory gray matter 43.9+6.1 ml/100gm/min, right MCA white matter 28.9+ 6.6 ml/100gm/min, left MCA gray matter 48.2+7.1 ml/100gm/min, left MCA territory white matter 25.3+6.2 ml/100gm/min, right posterior cerebral artery (PCA) territory gray matter 44.3 + 5.9 ml/100gm/min, right PCA territory white matter 23.5+5.4

ml/100gm/min, left PCA territory gray matter 56.4+8.2 ml/100gm/min, left PCA territory white matter 34.5+4.9 ml/100gm/min, right basal ganglion 81.7+10.2 ml/100gm/min, left basal ganglion 86.5+9.4 ml/100gm/min, right thalamus 82.8+11.3 ml/100gm/min, left thalamus 87.9+8.7 ml/100gm/min. Mean of calculated CMRO2 was 2.9+1.1 ml/100gm/min on the right hemisphere and 2.7+1.3 ml/100gm/min on the left hemisphere. Mean of calculated OEF was 49.3+4.5 % on the right hemisphere and 46.5+5.1 % on the left hemisphere. Mean Glasgow outcome scale was 4.5+0.9 for this group of patients.

The analysis of H-MRS revealed a 78 % decrease of NAA and 54% decrease of creatine on the areas of brain contussion. These finding is correlated with the decrease of CBF in these areas. A 122% increase of lactate is also noticed in these areas. The correlation among individual ICP, CBF, NAA and creatine decrease and lactate increase was significant (p= 0.039). The correlation among H-MRS changes , Glasgow coma scale, and Glasgow outcome scale was not significant (p=0.063).

Discussion

The change of autoregulation at the initial stage of cerebral trauma consists of multiple phases. Both hyperemia anf hyporemia has been observed (16). In the study of Barclay et al., a generalized reduction of CBFwas found and a close correlation between the reduction of CBF and the degree of brain damage was noted (13). However, recent studies revealed a more frequently seen hyperperfusion and CBF increase in post-traumatic stage (14-16). This difference may attribute to the observation at different stage of head injury (17).

In the study of Uzzell, rapid elevation of ICP at the early stage of head injury

correlated with CBF increase (18). This change also affect the outcome of the patients, especially, the recovery of neuropsychological function (18-19). Thus, both hyperemia or hyporemia after head injury are detrimental to the outcome of the patients.

The development of cerebral ischemia and infarction is not only decided by the change of CBF but also decided by the change of cerebral metabolism. Recent advance of jugular bulb cathterization and oxygen saturation measurement (20) can provide us a direct method to determine oxygen difference in the cerebral circulation. Thus, SjvO2 measurement has been used as an indicator of cerebral metabolism (20). However, without counting the influencing factor of CBF, SjvO2 per se can not stand for the real condition of cerebral oxygen consumption. In the report of Muizelaar, uncoupling of CBF and CMRO2 exist in patients with severe head injury(21). Jaggi et al used Xe-133 to measure CBF and calculated CMRO2 from AVDO2. Their results revealed a 82% sensitivity for the prediction of patient outcome (22). The using of Xe-133 can only measure cortical CBF. Another drawback of Xe-133 method is the radioactivity of this isotope. In the present study, we used stable xenon/CT method to measure CBF in the cortex, the white matter, and the basal ganglion. Our result demonstrated decreased CMRO2 in patients with severe head injury. This change correlated well with the severeity of head injury and the outcome of the patient. Oxygen extraction fraction is also elevated in patients with severe head injury. Although it is not significantly correlated with the outcome of the patients, elevation of OEF to the range near 50% indicate the breakdown of cerebral aoturegulation and possible detrimental outcome of the patients.

In conclusion, cerebral circulation is compromized in patients with moderated to

severe head injury. The change of CBF is majorly determined by the change of intracranial pressure. However, cerebral oxygen consumption is more important then CBF in the prediction of patients outcome or the decision making of the patient treatment.