行政院國家科學委員會補助專題研究計劃成果報告

腦出血後血腫附近腦血流量變化及腦組織質子磁共振頻譜與病人預後之相關

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Correlation among changes of regional cerebral blood flow, brain tissue proton magnetic resonance spectroscopy, and clinical outcome in intracerebral hemorrhage

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Introduction

Spontaneous intracerebral hemorrhage or hypertensive intracerebral hemorrhage due to the rupture of small intracerebral perforating artery causes dissection and destruction of brain parenchyma. This primary insult can not be reversed and is not the target of clinical treatment. However, progressive expansion of the hematoma to cause local pressure effect and alteration of cerebral circulation will be the major cause of secondary insult and its severity will be the determinant factor to affect the clinical prognosis and therapeutic efficacy (1, 2). Intracerebral hemorrhage and the edema exists in the surrounding brain tissue will elevate intracranial pressure and causes a series of hemodynamic change in cerebral circulation. At the initial stage, depending on the size of hematoma and the degree of the edema, cerebral blood flow (CBF) will increase or decrease to cause hyperemia or hyporemia of the brain (3, 4). Thus, a single measurement of CBF will not provide any value on the prediction of clinical outcome.

Recent developed proton magnetic resonance spectroscopy (H-MRS) technique provide a possible approach to analyze the real time biochemical and metabolic changes of the brain tissue *in vivo* (5, 6). Studies on the changes of N-acetyl asparatate, cholin, and lactate after cerebral ischemia demonstrated that reciprocal changes of these cellular metabolite over a certain period of time after ischemia are well correlated with the clinical severity and the outcome of the patients (7, 8, 9). However, no similar study has been applied in spontaneous intracerebral hemorrhage yet. In this study, we evaluated both regional CBF and H-MRS on patients with intracerebral hemorrhage to elucidate the sequential hemodynamic and biochemical alterations on brain tissue surrounding the hematoma and correlated these changes with the clinical outcome of the patients.

Material and Methods

General Protocol

From 2000 to 2001, a total of 11 patients had spontaneous intracerebral hemorrhage entered this study. All the patients received computed tomographic (CT) scan to confirm the diagnosis and were admitted into the intensive care unit for at least 7 days. Current American Heart Association guidelines of management of intracerebral hemorrhage (10) including administration of hyperosmotic agents, anticonvulsants, and controlled ventilation were applied in these patients. Arterial and central venous catheterization were introduced to continuously monitor mean arterial blood pressure, arterial oxygen saturation, arterial oxygen contents, and central venous pressure.

The study includes three sets of measurements. The first set of measurements was performed in 24 hours after the onset of intracerebral hemorrhage. Blood pressure and Glasgow Coma Scale (GCS) of the patients were recorded. Blood flow velocities of the intracranial vessels were measured with transcranial Dopple (TCD). Regional cerebral blood flow was measured with xenon/CT method (11) and H-MRS was applied to analyze the brain tissue surrounding the hematoma. The second set of measurements was performed on day 3 to day 5 and the third sets on day 7 to day 10 after the bleeding.

Glasgow Coma Scale was recorded again on day 15 and day 30 and Glasgow Outcome Score (GOS) was recorded on day 30.

Inclusion Criteria

Patients enter this study has to meet these including criteria: 1) Age between 15-65. 2) The initial GSC between 10-15. 3) The volume of hematoma between 15-45 ml. The hematome should be located at the subcortical region, the capsule and the basal ganglion 4) The patients has no previous brain surgery or installation of metallic clip and pacemaker which will affect the MRS procedure. 5) Patient without the need of artificial ventilation. Patients with a possible necessity of operation to evacuate the hematoma will not be included in this study. Patients with an obvious history of trauma or young patients with the suspicion of harboring an arteriovenous malformation were also excluded form this study.

Measurement of cerebral blood flow

Xenon /CT method of the regional cerebral blood flow (rCBF) measurement was applied in this study. Patient receiving this measurement has to omit oral intake for at least 6 hours. Blood pressure and peripheral blood hematocrit (Ht) was measured

before the study. During the measurement, a gas mask was applied to allow the patient inhale air or a gas mixture of 30% xenon + 30% oxygen + 40% air. Two sets of baseline CT scan were obtained while the patient is inhaling air. These data were averaged to minimize the error and used as the standard for flow calculation. Three more sets of CT were obtained at 1, 3, and 5 minutes after the patient start to inhale the gas mixture.

By the using of a plastic head holder, the patient's head is fixed to a constant position on CT scanner as well as on MR scanner. The using of this device enables the comparison of different data from a certain brain region between different measurements. According to the markers on this head holder, four constant axial cuts of the xenon / CT study were selected for the choosing of regions of interest (ROIs) to analyze rCBF. In this study, ROIs were selected from the areas anterior, posterior, right, left, superior, and inferior to the hematoma. Symmetric anatomical areas of these regions on the other hemisphere were also selected as ROIs. Thus, every axial cut consists 12 ROIs.

The calculation of rCBF is according to Fick's principle and Kety-Schmidt equation that is described elsewhere (11).

Measurement of biochemical changes of the brain tissue by proton magnetic resonance spectroscopy

A 1.5T magnetic resonance system (General Eletrical Signa Unit) incooperated with spectroscopy software (Proton Brain Exam PROBE Spectroscopy) was used for H-MRS measurements. A low-pass birdcage resonator was also used for the transmission and receiving of proton frequency at 89MHz and a self-shield gradient coil was applied during the measurement. Before the measurement, a T2 weighted (TR: 2 Sec., TE 30 and 80 mSec.) magnetic resonance imaging (MRI) was obtained to analyze other visible pathology near the hematoma. By the using of the same machine localized H-MRS is than measured. Twelve areas of interest (AOIs), each has a volume of 2x2x2 cm^3 voxel, corresponding the ROIs of the rCBF study were chose. The ROIs were arraged to be at the center of each corresponding AOIs. Special attention was paid to avoid the inclusion of scalp and skull in thes voxel of AOIs to minimize lactate signal produced by lipid.

Two different TE acquisition technique were used for the localized H-MRS analysis: 1) Long TE acquisition (TR: 1 Sec., Te 135 or 270 mSec.) was used for the detection of cholin (Cho), creatine (Cr) and N-acetyl asparatate (NAA) peaks. 2) Short TE acquisition (TR: 1 Sec., TE: 30 mSec.) for the detection of glutamine and glutamate waves. The measured H-MRS waveform of each voxel is obtained by semi-automated line fitting software. The peak at 1.34 ppm, 2.02ppm, 3.03 ppm, 3.20

ppm, and 2.68 ppm are representing lactate, NAA, Cr, Cho, asparatate, glutamine, and glutamate waveforms, respectively (fig 1).

Data analysis and statistics

The rCBF of the 4 cut of axial slices of each ROIs are averaged to represent the rCBF of that ROI of a single study. Averaging of the H-MRS value of each AOI is obtained with the same method. Statistic significances between the difference of the first, the second, and the third set of measurements were tested with Scheffe-F-test. The correlation among rCBF, H-MRS value, GCS, and GOS were analyzed with ANOVA.

Results

Among the 11 patients, there were 7 males and 4 females. The mean of their age was 63.4 + 7.7 years. The average GCS at onset was 13.7 + 3.2, 13.1 + 2.9 on day 3-5, 13.5 + 3.4 on day 7-10, 14.5 + 2.2 on day 15 and 14.7 + 3.0 on day 30. The average GOS on day 30 was 4.1 + 0.6. The size of hematoma is 27.5 + 18.7 ml.

The average rCBF is 12.5 + 7.3 ml/100gm/min, 14.2 + 8.3 ml/100gm/min, 15.3 + 10.2 ml/100gm/min, 11.8 + 7.1 ml/100gm/min, 11.9 + 8.8 ml/100gm/min, and 13.3 +9.0 ml/100gm/min at the ROIs superior, anterior, right, posterior, left, and inferior to the hematoma, respectively. The rCBF values of the corresponding ROIs at the opposite hemisphere are 21.4 + 10.9 ml/100gm/min, 19.4 + 9.7 ml/100gm/min, 22.5 +10.2 ml/100gm/min, 17.9 + 12.7 ml/100gm/min, 24.1 + 10.2 ml/100gm/min, and 20.0 + 11.6 ml/100gm/min (fig 2, fig 3). All these paired rCBF values showed significant difference between data from two hemispheres.

The H-MRS study revealed increased lactate level from 2.5 + 2.6 to 7.5 + 7.7, 1.5 + 1.3 to 5.8 +2.4, 1.6 + 1.2 to 8.2 + 3.4, 2.4 + 1.9 to 9.6 + 4.9, 3.0 +1.3 to 8.9 + 5.5, and 2.1 + 2.0 to 7.1 +6.2 and decreased NAA level from 18.2 + 4.4 to 10.3 + 3.7, 13.2 +7.4 to 7.7 + 6.8, 20.0 +15.2 to 11.2 + 9.3, 18.9 +15.2 to 9.3 + 10.5, 17. 4 + 12.1 to 7.8 +7.1, and 16.5 + 10.3 to 8.9 + 6.4 in the AOIs of the lesion side hemisphere corresponding the ROIs of the above mentioned rCBF study (fig. 4, fig. 5, fig. 6) All these changes are statistically significant. The changes of the lactate and NAA level obtained from different AOIs on the other hemisphere are insignificant.

The correlation of rCBF values, lactate levels determined from H-MRS, and GCS and GOS revealed no significant correlation in this study ($r = 0.11$, $P > 0.05$).

Discussion

Intracerebral hemorrhage is generally recognized as a problem of bleeding, however, it may also create ischemia and edema on the surrounding tissue of

hematoma. Sinar et al. demonstrated an immediate edematous reaction around the hematoma after the experimental intracerebral hemorrhage in the animal (12). In several studies, ischemic zone surrounding the hematoma is also found on animals with intracerebral hemorrhage (13, 14, 15). In fact, the compression effect of the hemaotma and the biochemical reaction of this hematoma to the surrounding brain tissue will cause brain edema to increase intracranial pressure (ICP). The initial reaction after the increase of ICP will cause a transient increase of CBF to overcome the ICP increasing to maintain sufficient cerebral perfusion pressure (CPP). However, progressive development of local ischemia and metabolic discrepancy may future elevate ICP and produce subsequent herniation formation. This will result in reduction of rCBF and CPP to start a vicious cycle and create more neuronal damage.

The clinical therapeutic goal is to prevent and to reverse the development of this vicious cycle. Among various secondary physiological changes, ischemia has the most profound effect on triggering this vicious cycle (16) and should be the primary target of treatment after cerebral hemorrhage.

In the clinical observation, both hyperemia and hyporemia had been found after intracerebral hemorrhage. However, ischemia will occur after the long run (17). In the routine autopsy, more than 90% of the patients had the pathological finding of cerebral ischemia (16). A good correlation among the size of hematoma, the degree of focal edema, and the rCBF was demonstrated in the study of Muizelear et al (18). Uzzell reported that the increase of rCBF is related to the early elevation of ICP and may affect the prognosis, especially, the recovery of neuropsychological function of the patient (19).

Recent clinical studies of H-MRS on cerebral ischemia found that elevation of lactate occurs on a week after cerebral infarct and the degree of NAA reduction is correlated to the patient's prognosis (20). Elevation of lactate on the first week is associated with the reduction of NAA and creatine but not cholin, and slight reduction of lactate after its elevation at the first week is also noticed (21). In animal studies, 25% elevation of lactate associated with reduction of NAA is observed as early as 1.5 hours after the ligation of middle cerebral artery on rat. The peak of NAA on H-MRS almost disappeared at 24 hours after the ligation of the artery, however, the reduction of other cellular metabolite such as creatine, cholin, and glutamate is much later. If reperfusion is applied, lactate level will return to normal but elevated again with the reduction of NAA after 3 hours. The final infarction volume is well correlated with the degree of lactate elevation (22). In another study of gerbil ischemic model, change of lactate level after cerebral ischemia is correlated with the change of rCBF detected by oxygen clearance method (23). Thus, the level of lactate detected by H-MRS is considered to be the most indicator of clinical prognosis after cerebral ischemia (24,

25, 26).

In the present study, we used H-MRS to evaluate the focal metabolic change after cerebral hemorrhage with concurrent rCBF measurement. Significant rCBF reduction is noticed at the areas near to the hematoma. Marked elevation of lactate level with insignificant NAA change is also noticed, especially at the first set of measurement, i.e. 3-5 days after the onset of hemorrhage. However, we can not find any significant correlation among the reduction of rCBF, the level of lactate elevation and the clinical prognosis (GSC and GOC) of the patients. In our data analysis process, averaging of rCBF values from various sites may create error and blurred the significant change. The other problem we have in this study is that the size of hematoma and the degree of perifocal edema are very different form patient to patient. We will try to recruit more patients and exclude the data from patients with very small or very large hematoma and re-analyze our data with focus on the selection of ROIs and AOIs. We hope that a more precise data analysis will demonstrate the statistic significance of using the parameters of rCBF and H-MRS findings to predict the clinical outcome of intracerebral hemorrhage.

Figures and legends

Figure 1. Xenon/CT rCBF study on a case with left frontal small hematoma (arrow) demonstrating decreased rCBF at the left frontal area.

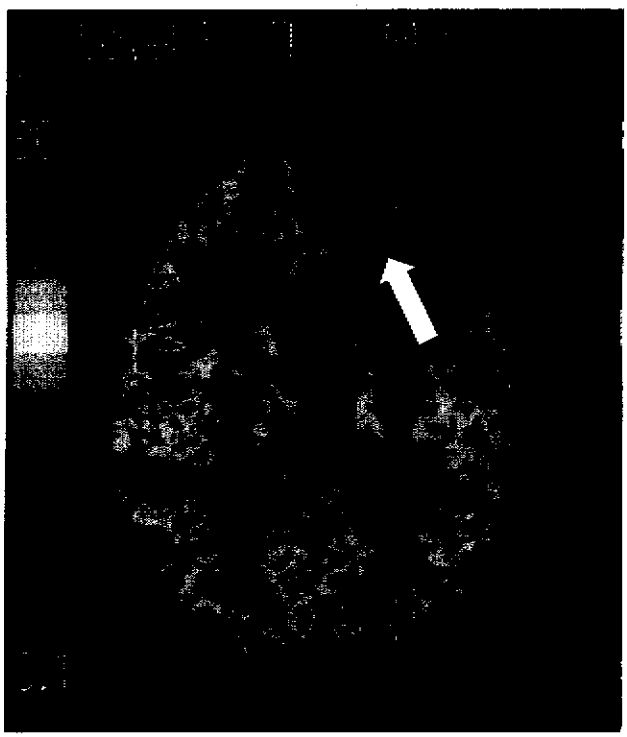


Figure 2. A case of left putaminal hemorrhage revealed a large hematoma (arrow) with marked perifocal edema. Xenon/CT rCBF study demonstrates reduced blood flow at the areas surrounding the hematoma.

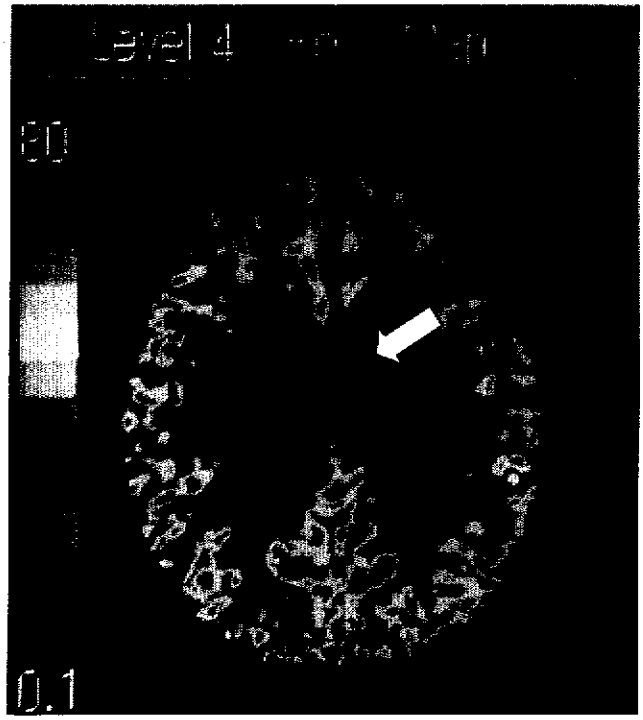


Figure 3. H-MRS study on day 5 of a patient with frontal hematoma. The double wave at 1.35 representing lactate level, the peak at 2.02 ppm representing the wave of NAA, the peak at 3.03 ppm representing creatine and the peak at 3.32 ppm representing cholin.

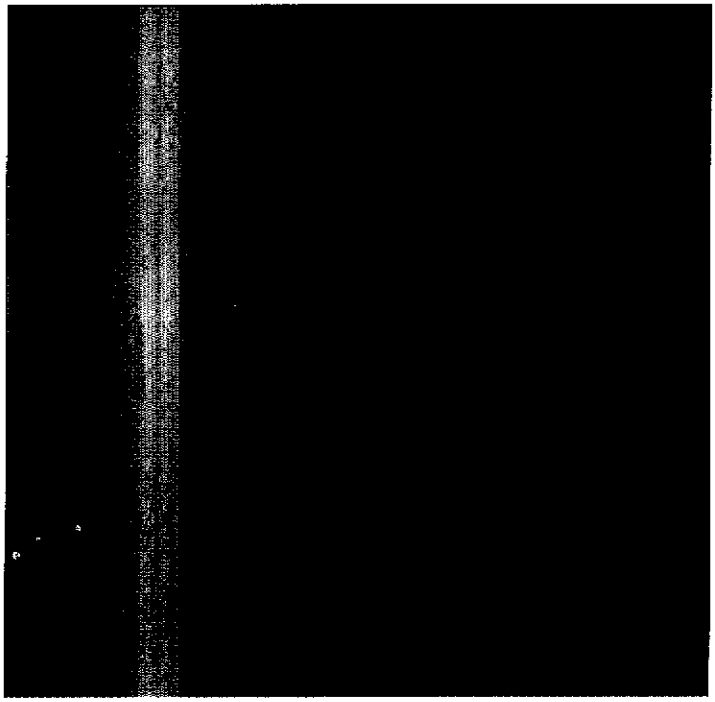


Figure 4. Same study of the same patient with the calculated value of NAA, creatine and cholin. The decreased ratio of NAA /Cho + Cr indicate the reduction of NAA level

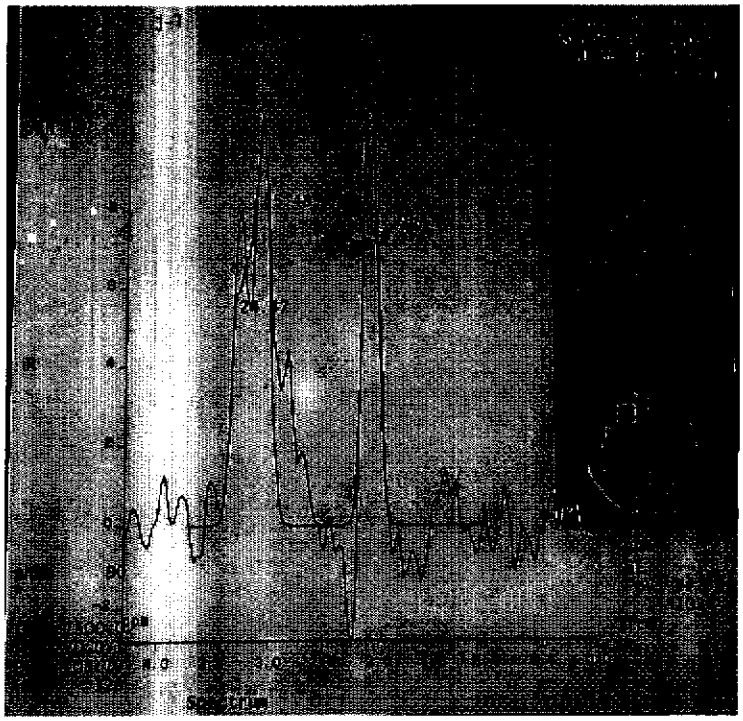


Figure 5. Baseline H-MRS study of a case with intracerebral hemorrhage on day 1.

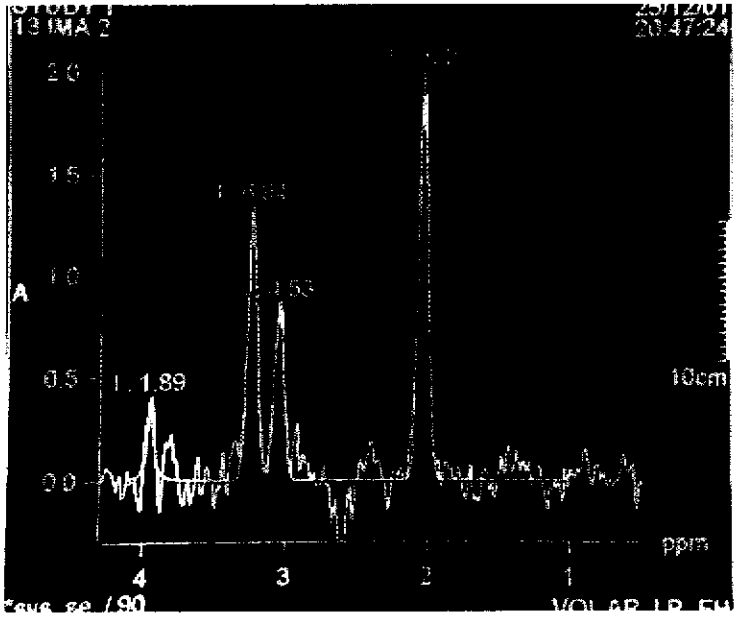
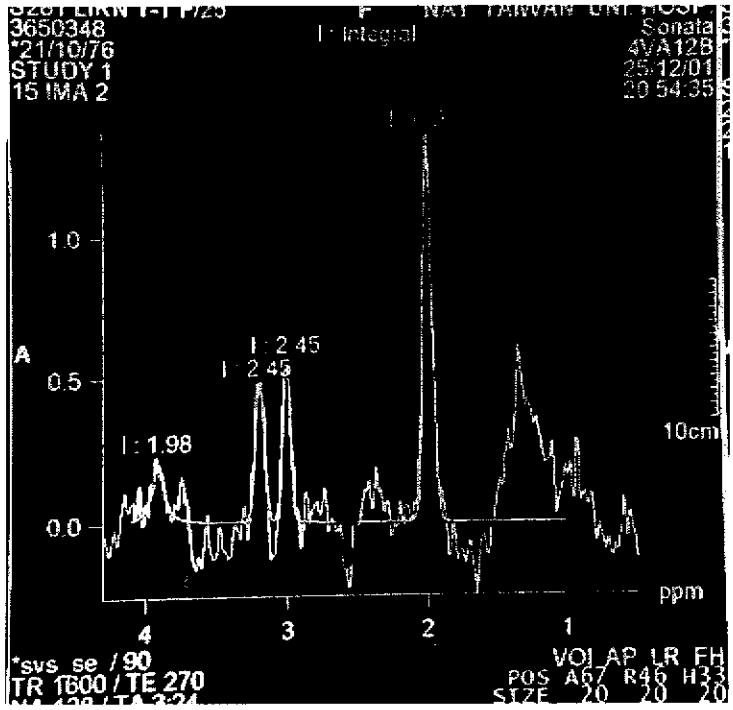


Figure 6. H-MRS study of the same patient on day 5. increase of lactate level, decrease of NAA level are noted.



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