Relationship of Cerebral Blood Flow, Cerebral Metabolism, and Electroencephalography to Outcome in Acute Experimental Compression Ischemia
—Barbiturate Effects on Delayed Brain Swelling—

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Abstract

Acute compression ischemia was induced in 30 cats by progressive inflation of an epidural balloon, followed by rapid decompression. Changes in intracranial pressure, mean arterial blood pressure, cerebral blood flow (CBF), arteriovenous oxygen difference (AVDO₂), cerebral metabolic rate of oxygen (CMRO₂), and electroencephalography (EEG) were studied in 13 untreated animals and in seven animals receiving barbiturate. Ten cats with cardiovascular or respiratory problems, or intracranial hematoma were excluded from the study. In untreated animals, six (46%) survived with no brain swelling and were classified as the "no swelling group," and seven (56%) died from fatal brain swelling and were classified as the "delayed swelling group." All animals with barbiturate therapy showed no brain swelling. Serial measurement of CBF, AVDO₂, and CMRO₂ indicated the existence of postischemic delayed hypoperfusion associated with relative hypermetabolism in untreated animals. Good recovery of CBF and CMRO₂ was observed in the "no swelling group," and poor recovery in the "delayed swelling group." The time course of the total fast-wave components on EEG was quite similar to that of CMRO₂, and the time course of the "CBF index," which is % fast-wave component of EEG divided by AVDO₂, was similar to that of CBF. Barbiturates reduced CMRO₂ and fast-wave component during administration, possibly improving the relatively hypermetabolic state, and reduced the mortality rate to 0%. The maximum effects of barbiturate could be expected by administering the drug at the stage of delayed hypoperfusion with relative hypermetabolism, indicated by rapid recovery of the % fast-wave component, high AVDO₂, and low CBF index.

Key words: compression ischemia, cerebral blood flow, cerebral metabolism, electroencephalography, barbiturate, arteriovenous oxygen difference

Introduction

Acute traumatic space-occupying lesions, such as acute subdural, epidural, and intracerebral hematomas, account for approximately half of all severe head injuries. Craniotomies for decompression and removal of hematoma do not always prevent a subsequent increase in intracranial pressure (ICP), resulting in fatal brain swelling. The pathophysiology of brain swelling (edema) following removal of the acute space-occupying lesion is not clearly understood, but factors such as duration and extent of cerebral compression, or intensity of the metabolic disturbance, are important in inducing brain swelling. Several studies have suggested that the magnitude of reduction in the cerebral metabolic rate of oxygen (CMRO₂) may be more closely related to the outcome than reduced cerebral blood flow (CBF). However, conventional methods for CBF measurement, such as the xenon method, nitrous oxide method, positron emission tomography, and single photon emission computed tomography, can-
not monitor the exact value of CMRO$_2$ and CBF continuously at the bedside. We previously reported that, in very severely head-injured patients who died from acute brain swelling, the arterio-jugular venous difference of oxygen content (AVDO$_2$) was significantly lower than in patients with less severe injury. This phenomenon suggests that a marked imbalance of CBF and cerebral metabolism may be detected by measuring AVDO$_2$.

In the present study using the cat compression ischemia model, we aimed to measure the exact value of CBF and cerebral metabolism by measuring the fast-wave component of the electroencephalography (EEG), and combining this with AVDO$_2$ as a substitute for CMRO$_2$. We simultaneously observed the early postischemic changes in CBF and cerebral metabolism, following global ischemia and reperfusion, to compare the conventional method and our new method. Also, the effect of barbiturates on secondary cerebral ischemia was evaluated by both methods.

Materials and Methods

Experiments were performed on 30 adult cats. Figure 1 shows the experimental arrangement. Anesthesia was induced by intramuscular injection of ketamine (150 mg), and surgical procedures were usually completed under ketamine and $\alpha$-chloralose. During recording of various parameters, intermittent intravenous administration of $\alpha$-chloralose (50 mg/kg) was given. Slit pupils were maintained, and no secretion of saliva was observed throughout the experiment. All cats were paralyzed with intermittent intravenous administration of pancuronium bromide and ventilated artificially. The PaCO$_2$ was continuously monitored by an endotidal CO$_2$ meter (Respina IH32; NEC San Ei, Tokyo) and maintained at 27-33 mmHg by the adjustment of the ventilator. The left femoral artery and bilateral femoral veins were cannulated for continuous measurement of the mean arterial blood pressure (ABP), obtaining blood for gas analysis (Pa$_O_2$, Pa$_CO_2$, HCO$_3^-$), and administration of fluid and drugs. The mean ABP and arterial HCO$_3^-$ were maintained at about 110 mmHg and 15 mg/dl by intravenous injection of trimethaphan or sodium bicarbonate, respectively. The rectal temperature was kept at 37-38°C by radiant heat. The ICP was monitored by a fiber optic transducer (Camino Lab., San Diego, Cal., U.S.A.) inserted into the subcortical region of the right occipital lobe. EEG was recorded made using a screw electrode located epidurally over the bilateral sensorimotor cortices and a data recorder (RD-111 PCM Data Recorder; Teac, Tokyo). The reference electrode was placed subcutaneously over the nasion. EEG was recorded for 5 minutes every hour until the end of the experiments. EEG data were transferred to an EEG trend monitor for fast Fourier transform spectrum band analysis (Nihon-Kohden, Tokyo). The bands were $\delta$ (2-4 Hz), $\theta$ (4-7 Hz), $\alpha_1$ (8-10 Hz), $\alpha_2$ (11-13 Hz), and $\beta$ (20-30 Hz). Regional CBF was measured by the hydrogen clearance method. Platinum needle electrodes (needle type, UHE-100; Unique Medical, Tokyo) were stereotactically inserted into the bilateral thalami and connected to an amplifier and personal computer (PC 9801 VM21; NEC, Tokyo). Clearance curves were recorded and input into the computer. The clearance curve was analyzed by the height-over-area method for the CBF values. AVDO$_2$ and CMRO$_2$ were measured in all cats. The superior sagittal sinus was cannulated anteroposteriorly towards the confluence. The AVDO$_2$ was calculated as the difference in O$_2$ content between arterial and superior sagittal sinus samples taken simultaneously, using:

$$AVDO_2 = \{Sat(a)O_2 - Sat(v)O_2\} \times 1.34 \times \frac{Hb}{100} + 0.0031$$

where Hb = hemoglobin and Sat O$_2$ = oxygen saturation. The CMRO$_2$ was estimated from the AVDO$_2$ and the mean CBF:

$$CMRO_2 = AVDO_2 \times CBF/100$$

Mean ABP, EEG, ICP, CBF, and AVDO$_2$ values were first measured as a control value for each animal. Then a 3- to 4-mm diameter rubber balloon located in the right frontal epidural space was
gradually inflated using physiological saline to increase the ICP by 10 mmHg per 10 minutes. The CBF was measured after every 20-mmHg ICP rise. Trimethaphan was occasionally administered to avoid excessive ABP increase due to Cushing's phenomenon. The ICP was raised until the EEG become completely isoelectric, and hydrogen clearance ceased. This was defined as "global ischemia." Global ischemia was maintained for 5 minutes in all cats because we previously found that 5-minute duration of global ischemia was the border zone for causing irreversible metabolic damage. The balloon was then deflated and removed. All parameters were recorded 10 minutes after balloon deflation, then hourly for either 24 hours or until brain death occurred due to increased ICP. Continuous venous injection of thiopental at 10-15 mg/hr was started after confirming EEG recovery following balloon deflation in seven cats. This was the minimum dose to maintain the burst and suppression EEG pattern without critical cardiovascular depression. No thiopental was administered after decompression in 13 cats. All animals developing cardiovascular or respiratory problems, or intracranial hemorrhage during the experiment were excluded from the study (10 cats). All brains were removed and fixed in formalin. Sections were prepared to identify the locations of the platinum electrode and intraparenchymal hemorrhage.

All values are given as mean ± SEM. Wilcoxon test was used for comparison of physiological variables within groups. A calculated difference of p < 0.01 was considered to be statistically significant.

**Results**

Figure 2 shows the changes in ICP after balloon deflation. These can be classified into two groups: no or only minimal increase in ICP (the no swelling group), and fatal brain swelling at 6-14 hours after deflation (the delayed swelling group). Of 13 cats undergoing 5-minute global ischemia, six cats were in the no swelling group and seven in the delayed swelling group. Thus, 54% of animals died of brain swelling caused by compression ischemia. In contrast, all seven cats receiving barbiturate at reappearance of EEG after 5-minute global ischemia demonstrated no rises in ICP. These cats were the barbiturate no swelling group.

Figure 3A shows the changes in thalamic CBF. CBF control values showed no statistical difference between the three groups. CBF increased markedly following balloon deflation in all three groups, with values significantly higher than the control within 10 minutes (p < 0.01). This was considered to be initial "postischemic reactive hyperemia" according to the criteria proposed by Obrist et al.351 One hour after balloon deflation, however, the CBF fell to approximately half to one-third of the control value in all three groups (p < 0.01). The CBF then gradually recovered in the no swelling group. In the delayed swelling group, the CBF was lower than in the no swelling group at 2 hours after deflation, remained the same for 7-8 hours, and then gradually fell. In the barbiturate no swelling group, the values obtained during administration of thiopental within 5 hours were similar to those of the delayed swelling group, but then recovered markedly after cessation of the barbiturate administration to about the values of the no swelling group.

Figure 3B shows the AVDO2 values at 1-hour intervals following global ischemia. The AVDO2 decreased markedly during 10-30 minutes after balloon deflation in all three groups. A rapid increase occurred after 1 hour, reaching more than 130% of the control value (p < 0.01) 2-3 hours after deflation, and remained high for 7-9 hours. The no swelling and the barbiturate no swelling groups demonstrated a clear and slight AVDO2 increase after 9 hours. In contrast, the delayed swelling group showed a rapid decrease of AVDO2 after 8 hours, with values significantly lower than in other groups (p < 0.01). The fall in AVDO2 was accompanied by brain swelling leading to brain death.

Figure 3C shows the changes in CMRO2. Rapid and sustained recovery of the CMRO2 was observed after deflation in the no swelling group, reaching the control value after 17 hours. On the other hand, CMRO2 failed to continuously increase after the initial rapid recovery in the delayed swelling group, and started to decrease after 8 hours to become
significantly lower than the other groups after 12 hours (p < 0.01). In the barbiturate no swelling group, rapid and progressive recovery of CMRO₂ as in the no swelling group was seen, after 5 hours of marked suppression by the drug administration.

Figure 4 shows the % power spectrum EEG band analysis before and after global ischemia in typical cases in the no swelling and the delayed swelling groups. In the no swelling group, all frequency bands, including the fast waves, recovered rapidly to the control level. The delayed swelling group demonstrated a predominance of the slow waves, especially after several hours.

Figure 5 shows the % fast-wave component (α + β) with time. The time course is similar to that of the CMRO₂ shown in Fig. 3C. The fast-wave component recovered quickly in the no swelling group and in the delayed swelling group initially, but was followed by a gradual, then in the delayed swelling group rapid fall to a significantly lower level after 11 hours (p < 0.01). The changes in fast-wave component in the barbiturate no swelling group also resembled those of the CMRO₂, remained low during drug administration, and quickly recovered afterwards, finally reaching a value close to that of the no swelling group.

The CBF index is defined as the % fast-wave component divided by the AVDO₂ values, and plotted against time (Fig. 6). Both CBF index and the
measured CBF values (Fig. 3A) showed a marked rise on balloon deflation and were followed by a quick fall. The rate of reduction in CBF index was least in the no swelling group, and stabilized thereafter. The CBF index quickly decreased after 8 hours, significantly after 12 hours (p < 0.01), in the delayed swelling group. In the barbiturate no swelling group, the value was low during thiopental administration, but was similar to that of the no swelling group after discontinuation of the drug.

**Discussion**

The arterial occlusion-reperfusion model demonstrates marked hyperemia, or reactive hyperemia, following recirculation probably caused by a large blood flow into maximally dilated vessels during reperfusion. This vessel dilatation probably occurs during temporary ischemia under several conditions, including lactic acidosis and excess extracellular Ca ions. Hyperemia is followed by secondary hypoperfusion, or delayed hypoperfusion. This condition may also develop from various causes such as abnormal cerebral vasoconstriction and increase of blood viscosity. Even during the stage of hypoperfusion, rapid recovery of high energy phosphate metabolism, the so-called posts ischemic hypermetabolism, may develop.

The combination of hypoperfusion and hypermetabolism aggravates the ischemia, causing conditions in the brain very likely leading to irreversible metabolic failure.

The compression ischemia model used in this study, unlike the arterial occlusion-reperfusion model, may induce many types of insult other than pure ischemia. However, all these events occur in actual severe head injury associated with intracranial hematoma, so this model is realistic for assessing the clinical problems.

Hyperemia followed by persisting lower CBF was observed after balloon deflation in all three groups (Fig. 3A). This suggests that the "postischemic hypoperfusion" following arterial occlusion and reperfusion reported by Levy et al. also occurs in the brain compression-decompression model. Postischemic hypoperfusion is of special importance because it may modify the extent of cell damage caused by the primary ischemia.

Our study found no increase in ICP during the first 6 hours after balloon deflation (Fig. 2). This would contraindicate the generally accepted treatment for intensive head injury, mainly reduction of the increased ICP. However, Levy et al. clearly indicated that the chain of ischemic insults, hyperemia, delayed hypoperfusion, and increased cerebral energy demand, lasts for several hours peaking 4 hours after reperfusion. Our findings support this view. Therefore, treatment aimed to increase CBF and decrease cerebral metabolism at this stage should minimize the secondary ischemic insult, and also minimize the extent of cellular deaths. It is extremely difficult to trace the rapid changes in cerebral ischemia using the time-consuming conventional CBF measurement methods, such as the xenon method, nitrous oxide method (Kety-Schmidt), positron emission tomography, or single photon emission computed tomography. Our study shows that serial measurement of AVDO₂ allows some
evaluation of the changes in CBF. However, being the quotient of CMRO₂ and CBF, AVDO₂ alone cannot be an exact indicator of cerebral ischemia. We therefore substituted EEG monitoring for CMRO₂.

Hockaday et al.⁹ reported that the EEG slow-wave component persisted longer with increased severity of ischemic damage following global ischemia and recirculation. The same phenomenon was seen in experimental¹⁰ as well as in clinical studies.¹¹ In contrast, others found a greater fast-wave component related to higher CMRO₂.²³ Our previous report showed that severity of primary ischemic insult can roughly be predicted by combining EEG and the time course of AVDO₂.⁴⁴,⁴⁵ In the present study, we quantitatively analyzed the fast-wave component using fast Fourier transform,²⁹ and the total of α + β wave components was defined as the % fast-wave component. The time course of the % fast-wave component was quite similar to that of CMRO₂ (Fig. 5). Also, the changes in the % fast-wave component divided by AVDO₂ (CBF index) closely resembled changes in the CBF. These results suggest the usefulness of the % fast-wave component and CBF index instead of CMRO₂ and CBF.

Without treatment after 5-minute global ischemia, 46% of cats achieved recovery of normal brain functions (the no swelling group), and 54% died from brain swelling after showing transient recovery of EEG. Animals which ultimately recovered brain function demonstrated parallel and steady recovery of both CMRO₂ and AVDO₂, while the cats which died showed recovery of CMRO₂, with persistent low CBF (Fig. 3). This relative ischemic state leads to irreversible metabolic change, finally causing the decline of CMRO₂ and fatal brain swelling. Barbiturate administration has demonstrated many beneficial effects of cerebral protection in experiments, by preventing the tissue damage and edema caused by cerebral ischemia or hypoxia, and by reducing intracranial hypertension.⁴,⁷,³⁰,³¹,³³,³⁸,⁴¹,⁴² However, some workers²⁴,³⁷,³⁸,⁴⁵ are pessimistic about the efficacy of barbiturates in the clinical field, especially in treating severe brain injury. Even in experiments, some authors²³,³⁵,⁴³ doubt whether barbiturates provide cerebral protection at all, since the maximum dose can only reduce CMRO₂ to 58% of the control,²⁶ while CBF can be compromised by far smaller doses.¹⁵

Although not well established, the beneficial effects of barbiturates are: 1) suppression of cerebral hypermetabolism due to catecholamine released by cerebral tissue damage;²² 2) inhibition of glucose metabolism and reduction of the CMRO₂, combined with reduced CBF;³¹,³⁴; 3) inhibition of cellular efflux of various metabolites and K⁺ with prevention of influx and accumulation of Na⁺;²; 4) protection of the endothelium of the blood vessels;²⁰; 5) prevention of intravascular thrombosis;²⁰; and 6) inhibition of the brainstem neurogenic mechanism for vasoparalysis.²² Effects such as sealing of membranes and scavenging of a few oxygen radicals have also been proposed.⁵,⁴⁶,⁴³ In summary, barbiturates minimize the ischemic damage by improving the metabolic process, stabilizing the cell membrane, and improving the microcirculation. Therefore, administration of barbiturate should be ideal for reversing the relative ischemia following brain compression. In fact, we achieved 100% survival with good recovery of both CBF and CMRO₂ in the group treated by the administration of barbiturates, as compared to only 46% survival rate in the untreated group.

Based on the experimental results, we conclude that: Five-minute duration of global ischemia is the borderline zone for causing irreversible metabolic damage to the brain, where a subtle alteration in cerebral metabolism and/or circulation can affect the prognosis markedly. By reducing the CMRO₂ before irreversible damage occurs, even with some reduction in CBF, barbiturates improved the relatively ischemic state of metabolism, that is poor CBF recovery combined with rapid recovery of CMRO₂, thus improving the final outcome. Administering the drug while the ICP was still low might have enhanced the protective effect, by ensuring maintenance of a relatively high cerebral perfusion pressure and minimizing compression to the cerebral vessels by cerebral edema which may cause further vascular resistance.

Therefore, we consider that the maximum effect of barbiturates in clinical cases can be expected by administration at the stage of ischemic metabolism. The stage of ischemic metabolism is characterized by: 1) rapid recovery of % fast-wave component following surgical decompression of intracranial traumatic hematoma, 2) high AVDO₂, and 3) low CBF index. We consider this a new mode of treatment, at least one step ahead of the conventional use of barbiturates only to reduce ICP.

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