AVDO₂ and EEG as Indicators for Treatment of Post-traumatic Brain Swelling

—Experimental Study—

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Abstract

A cat model of compression ischemia using epidural balloon inflation investigated: 1) the relationship between postischemic cerebral blood flow (CBF) and metabolism and brain swelling, 2) the use of arteriovenous oxygen difference (AVDO₂) and electroencephalographic (EEG) frequency band analysis for monitoring CBF and cerebral metabolism, and 3) indications for selecting the therapy. Global ischemia was induced by brain compression, followed by rapid decompression, and AVDO₂, CBF, cerebral metabolic rate for oxygen, and EEG were monitored. The animals were divided into delayed brain swelling and no swelling groups. The severity of compression ischemia influenced the recovery of CBF and cerebral metabolism. The AVDO₂ and EEG reflected the CBF and cerebral metabolism. These parameters are useful in selecting the therapy for focal brain injury.

Key words: focal brain injury, cerebral metabolism, electroencephalography, cerebral blood flow, brain swelling

Introduction

Focal brain injuries, such as acute subdural or epidural and intracerebral hematomas, account for approximately 50% of all severe head injuries. In most cases, decompressive craniotomy and hematoma removal fail to prevent a subsequent increase in intracranial pressure (ICP), sometimes leading to fatal brain swelling.

An important cause of such post-decompression brain swelling is primary ischemia due to brain compression.^{1,5,8)} Primary ischemia may cause various secondary changes, such as vasomotor paralysis,²⁾ vasogenic edema,³⁾ and cytotoxic edema.⁴⁾ Post-decompression brain swelling, usually observed as increased ICP, is probably caused by a combination of these intracranial mass effects.¹⁰⁾ The major factor apparently differs in each case, probably due to the duration and severity of ischemia modified by multi-

ple postischemic factors.

Management of post-decompression intracranial hypertension by simply reducing the ICP is probably not the optimum method. A logical mode of therapy should be based on the exact nature of the secondary ischemia in each case. Therefore, the cerebral blood flow (CBF), cerebral metabolic rate for oxygen (CMRO₂), and the relationship between these factors must be investigated in the post-decompression period. Most reported methods for measuring CBF and CMRO₂ in head injury are quite complicated. Repeated observations of CBF and/or CMRO₂ are not practical in the first 12 hours following surgical decompression, when secondary ischemic insult is most likely to evolve.

The arteriovenous oxygen difference (AVDO₂) can be calculated from blood sampled from the internal jugular vein and any artery. The method is simple, inexpensive, and can be repeated frequently. We

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previously investigated the clinical significance of $AVDO_2$. Cases of severe head injury could be classified into three groups: 1) ICP controllable by treatment; 2) noncritical increased ICP in the first 24 hours after craniotomy, but resulting in brain death from uncontrollable intracranial hypertension; and 3) continuously increased ICP after surgical decompression resulting in brain death within 24 hours. The $AVDO_2$ values were clearly lower in groups 2) and 3) than in group 1) during the first 12 hours following decompressive craniotomy.¹³⁾ The recovery rate of electroencephalography (EEG) correlates with the severity of the primary ischemic insult.^{11,12)} If the EEG recovery reflects the $CMRO_2$ recovery, $AVDO_2$ and EEG measurements can be used to estimate the CBF value.

This study therefore investigated the following points. 1) Does the recovery pattern of the cerebral energy metabolism (EEG, $CMRO_2$) or CBF reflect the degree of primary ischemic insult? 2) Does the $AVDO_2$ reflect any such difference? 3) Can $AVDO_2$ and EEG measurements be used to predict delayed post-decompression brain swelling, diagnose the nature of the secondary ischemic insult, and indicate the optimum treatment for individual cases?

Materials and Methods

Forty-six mongrel cats, weighing 3.63 ± 0.66 kg, were anesthetized by an intramuscular injection of 2 ml ketamine, followed by intermittent intravenous injections of 50 mg/kg alpha-chloralose to maintain the anesthesia. The bilateral femoral veins and unilateral femoral artery were cannulated to monitor the blood pressure, inject drugs, and sample blood (Fig. 1). A tracheostomy was performed, and the

cats were mechanically ventilated under full muscle relaxation induced by intermittent injections of pancuronium bromide.

The arterial carbon dioxide tension was monitored by endtidal CO_2 meter (Respina IH32; NEC-San-ei, Tokyo) and maintained at about 30 mmHg. The mean arterial blood pressure (ABP) and arterial HCO_3^- were maintained at about 140 mmHg and 16 mg/dl by intravenous injection of trimethaphan and sodium bicarbonate, respectively.

EEG recordings were made using active screw electrodes located epidurally over the bilateral sensorimotor cortices and a data recorder (RD111 PCM Data Recorder; TEAC, Tokyo). The reference electrode was located subcutaneously over the nasion. EEG recordings were made for 10 minutes every hour until the end of the experiment. The recorded EEG data were transferred into an EEG trend monitor (Nihon Kodan, Tokyo) for fast Fourier transform (FFT) percentage spectrum band analysis. The bands were δ (2–4 cps), θ (4–8 cps), α_1 (8–10 cps), α_2 (11–13 cps), and β (20–30 cps).

The CBF was measured by the hydrogen clearance method.⁹⁾ Platinum needle electrodes were inserted into the bilateral thalami stereotactically and connected to an amplifier (UH-meter PHG-201; Unique Medical, Tokyo) and personal computer (PC9801 VM21; NEC). The CBF values were calculated by the height-over-area method.

The ICP was monitored by a fiberoptic transducer (Camino Laboratories, San Diego, Cal., U.S.A.) inserted into the subcortical region of the right occipital lobe. The ABP was continuously recorded from the left femoral artery.

The superior sagittal sinus was cannulated anteroposteriorly towards the confluence. Blood samples were taken simultaneously from the artery to calculate the $AVDO_2$. Equation for calculating $AVDO_2$ was as follows:

$$AVDO_2 = (S_{aO_2} - S_{avO_2}) \times 1.34 \times Hb/100 + (PaO_2 - PvO_2) \times 0.0031$$

$CMRO_2$ was calculated as follows:

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

Mean ABP, ICP, CBF, EEG, somatosensory evoked potential, and $AVDO_2$ values were first measured for the control value for each animal. A rubber balloon, 3–4 mm in diameter located in the right frontal epidural space, was inflated gradually to increase the ICP at a rate of 10 mmHg in 10 minutes. The CBF was measured after every 20 mmHg ICP rise to check that no gradient developed. The ICP was raised until the EEG became completely iso-

Fig. 1 Schematic representation of the experimental model.

electric, and hydrogen clearance ceased. This was defined as "global ischemia." Global ischemia was maintained for 5 minutes in 20 cats and 15 minutes in 26 cats. The balloon was then quickly deflated and removed. All parameters were recorded 10 minutes after balloon deflation, then 1 hourly thereafter for either 24 hours or until brain death occurred due to increased ICP. The parameters were analyzed using the Wilcoxon test.

All brains were removed and fixed in formalin following the experiment. All brains were sectioned to investigate the location of the platinum electrode and intraparenchymal hemorrhage. Six animals demonstrating cardiovascular or respiratory problems or intracranial hemorrhage were excluded from the study.

Results

Figure 2 shows the changes in ICP after balloon deflation. Nine cats undergoing global ischemia for 15

Fig. 2 Changes in ICP for all animals.

minutes ultimately demonstrated brain death due to severe brain swelling. However, the delay was at least 9 hours. These cases were classified as the "15 minutes delayed swelling" group. Eight cats undergoing global ischemia for 5 minutes showed the same pattern of intracranial hypertension, and were

Fig. 3 Changes in CBF (A), AVDO₂ (B), and CMRO₂ (C) during and after balloon inflation and deflation in 15 minutes delayed swelling ($\square$, $n = 9$), 5 minutes no swelling ($\circ$, $n = 8$), and 5 minutes delayed swelling groups ($\bullet$, $n = 8$). Values are means $\pm$ SE.

Fig. 4 Changes in bilateral EEG and ICP before and after global ischemia. A: In the 15 minutes delayed swelling group, no EEG recovery is seen for the first 6 hours, and burst-type slow waves increase with increased ICP. B: In the 5 minutes no swelling group, rapid recovery of EEG accompanies stable ICP. C: In the 5 minutes delayed swelling group, recovery of EEG is rapid, but later accompanied by marked increase in ICP, leading to re-disappearance of EEG.

classified as the "5 minutes delayed swelling" group. Eight cats undergoing global ischemia for 5 minutes demonstrated no or mild, transient brain swelling during the 24-hour experimental period. These cases were classified as the "5 minutes no swelling" group.

Eight cats undergoing 15 minutes global ischemia and one undergoing 5 minutes global ischemia demonstrated rapid, continuous rises in ICP followed by brain death within 3 hours. These cats were the "acute swelling" group. Six cats undergoing 15 minutes global ischemia demonstrated no brain swelling for 24 hours, and were classified as the "15 minutes no swelling" group. These two groups were excluded from this study and will be discussed elsewhere.

Figure 3A shows the changes in the thalamic CBF measured by the hydrogen clearance method. There was no statistical difference between the control values and the CBF increased rapidly following balloon deflation in all three groups. Values were significantly higher than the control within 10 minutes. This was considered to be the initial postischemic hyperemia. After 1 hour, however, the CBF fell to approximately one-third of the control value. This low perfusion state was similar for 5 hours in all three groups. After 5 hours, the CBF in the 5 minutes no swelling group gradually increased, and was significantly higher than in the other groups

after 9 hours ($p < 0.025$).

The AVDO₂ was decreased markedly 10 minutes after balloon deflation (Fig. 3B). The 5 minutes no swelling and 5 minutes delayed swelling groups demonstrated rapid increases after 1 hour, reaching more than 130% of the control value 2 hours after deflation. The 15 minutes delayed swelling group demonstrated a clearly slower AVDO₂ recovery following the initial decrease, with values significantly lower than the other groups for the first 4 hours ($p < 0.05$). In the 5 minutes no swelling group, the AVDO₂ gradually decreased after 5 hours. However, the 5 minutes delayed swelling group maintained high values for 10 hours.

The CMRO₂ recovery was also poor in the 15 minutes delayed swelling group (Fig. 3C). Values were significantly lower than in the 5 minutes no swelling group 2 hours after deflation ($p < 0.1$), and the difference became greater with time ($p < 0.05$ at 8–10 hrs). The CMRO₂ recovery in the 5 minutes delayed swelling group was also poor, being slightly higher than in the 15 minutes delayed swelling group in the early stage, but becoming significantly lower than in the 5 minutes no swelling group 8 hours after deflation ($p < 0.1$).

Figure 4 shows the EEG and ICP changes during the experiments. Figure 4A shows a typical case in the 15 minutes delayed swelling group. The EEG did

Fig. 5 Percentage spectrum EEG analysis before and after global ischemia. Rapid recovery of all spectrum bands is seen in the 5 minutes no swelling group (*left*), but in the 5 minutes delayed swelling group (*right*) recovery is predominantly slow waves, especially in the compressed side. *arrow*: deflation.

not recover for the first 6 hours. Recovery began with high amplitude burst-type waves. Further recovery with increased frequency and amplitude was accompanied by a gradual increase in ICP ending in brain death. Figure 4B shows a typical case in the 5 minutes no swelling group. There was a very quick EEG recovery with no ICP increase. Figure 4C is a case in the 5 minutes delayed swelling group. Although the EEG recovery was quick, the gradual increase in ICP finally resulted in fatal brain swelling. These typical EEG patterns were seen in 87.5% of the 5 minutes no swelling group, 77.8% of the 15 minutes delayed swelling group, and 87.5% of the 5 minutes delayed swelling group.

The percentage spectrum EEG band analysis for cases in the 5 minutes no swelling and 5 minutes delayed swelling groups are shown in Fig. 5. In the 5 minutes no swelling group, all frequency bands, including the fast waves, recovered rapidly to the control level. No asymmetry was observed in the bilateral recordings. The 5 minutes delayed swelling group demonstrated a predominance of slow waves (especially δ waves) with considerable asymmetry, affecting the compressed side more.

Discussion

The compression ischemia model used in this study,

unlike the arterial occlusion model, may induce many types of insults other than pure ischemia. For example, brain shift causing considerable CBF heterogeneity, brainstem displacement and damage, and an uncertain extent of ischemia before global ischemia may occur. However, all these events occur in actual focal brain injury so this model is realistic for assessing the clinical problems.

Increased ICP after balloon deflation manifested as either acute or delayed swelling. This study investigated the delayed swelling and no swelling groups, and rejected all acute swelling cases. The reasons for this selection were: 1) There was a time delay of at least 9 hours between balloon deflation and fatal brain swelling, enabling precise and sequential measurements of each parameter; and 2) some EEG recovery occurred in all cases in the delayed swelling group, implying that the primary ischemic insult had not caused brain death so therapy could possibly modify the outcome.

Hyperemia followed by persistently decreased CBF was observed after balloon deflation in all three groups, regardless of the ischemia duration. This suggests that the "postischemic hypoperfusion" following arterial occlusion and reperfusion reported by Levy *et al.*^{6,7)} also occurs in the brain compression-decompression model. Postischemic hypoperfusion is very important because changes in the brain in-

duced by primary ischemia are not always irreversible. Secondary ischemia and associated metabolic changes are major factors in completing the process. Further, major changes probably occur during postischemic hypoperfusion following cerebral compression while the ICP is still low. Therefore, present treatment methods for severe head injury mainly aimed at reducing increased ICP should be changed. Treatment must begin earlier, and should be based on the CBF and cerebral metabolic conditions at each stage.

Levy *et al.*^{6,7)} reported that the cerebral energy demand ($\sim p$ = high energy use rate) was higher than the control value during significantly low CBF following unilateral carotid occlusion and reperfusion. This lasted several hours, peaking at 4 hours. Thus, the increased energy consumption greatly surpassed energy supply. The CBF recovery started 5 hours after reperfusion and reached the preischemic value within 24 hours. Thus, the marked uncoupling between CBF and cerebral metabolism only lasted for a few hours. However, this was considered enough to cause extensive cell death or large cerebral infarction in the affected hemisphere.

In our 5 minutes ischemia group, the EEG recovered rapidly and the AVDO₂ (oxygen extraction) also increased to 130% of the control value after 2 hours. This phenomenon is not necessarily equivalent to the increased energy consumption in delayed postischemic hypoperfusion of Levy *et al.* but could be called "relative hypermetabolism." In the 5 minutes no swelling group, the CBF increased and the AVDO₂ decreased after 5 hours. Thus, the relative hypermetabolism lasted for a few hours only. In contrast, the 5 minutes delayed swelling group demonstrated no CBF recovery for more than 9 hours and the AVDO₂ value remained high. Therefore, relative hypermetabolism lasted much longer than in the no swelling group, and a greater insult occurred in the 5 minutes delayed swelling group.

Levy's and this work demonstrated slow wave

EEG appearing soon after balloon deflation. This might reflect abnormal cerebral energy consumption not necessarily associated with energy supply. The calculated CMRO₂ was as low as 50% of the control value from 1 to 5 hours in both the 5 minutes no swelling and delayed swelling groups. The EEG recovered much sooner in both groups, suggesting a delay between EEG recovery or the proposed energy consumption and the actual CMRO₂. The CMRO₂ increased after 5 hours in the 5 minutes no swelling group, but not in the 5 minutes delayed swelling group.

Hockaday *et al.*²⁾ reported EEG recovery after global ischemia began with slow waves, then fast components appeared and finally returned to the preischemic state. The rate of recovery depended on the severity of the primary ischemic insult. We used percentage frequency band analysis by FFT to investigate the EEG recovery pattern. In the 5 minutes no swelling group, all frequency bands including the fast components recovered within 1 hour without asymmetry. In contrast, the 5 minutes delayed swelling group demonstrated mainly slow components, especially on the compressed side.

The 15 minutes delayed swelling group demonstrated very poor recovery of CBF, EEG, CMRO₂, and AVDO₂. The EEG took over 6 hours to reappear, and contained only slow waves. Increased ICP was often associated with the EEG recovery. This might indicate abnormal energy consumption without adequate energy supply because of hypoperfusion. Presumably, progressive anaerobic glycolysis resulting in lactic acidosis and accumulated cell membrane breakdown products, such as free fatty acids, may lead to secondary metabolic failure. Therefore, the early recovery of the EEG mainly composed of slow waves does not necessarily mean early recovery of normal cerebral metabolism. It may indicate the postischemic hypermetabolic state. The appearance of fast EEG waves is associated with normal metabolism.

Based on our findings, we propose three classifica-

Table 1 AVDO₂ in early (1-2 hrs) and late phases (5-6 hrs) before EEG recovery, and dominant frequency band of recovered EEG

Group	AVDO ₂		EEG recovery	EEG frequency band	Suitable treatment
	Early phase	Late phase			
15 minutes delayed swelling	→ or ↓	→ or ↓	≥ 6 hrs	none	none
5 minutes no swelling	↑	→	1-2 hrs	normal and symmetrical	hyperosmotic diuretics
5 minutes delayed swelling	↑	↑	1-2 hrs	slow and asymmetrical	hyperosmotic diuretics + barbiturates <i>etc.</i>

tions of primary ischemic insult and early stage secondary ischemia after brain compression. Suitable modes of treatment can also be suggested for each classification (Table 1).

1) Where a severe primary ischemic insult has caused widespread irreversible brain damage, only very little recovery of cerebral metabolism is expected. The $AVDO_2$ will remain in the low or normal range, and EEG contain almost exclusively slow waves. No treatment will be helpful in modifying the outcome.

2) When the primary ischemic insult was relatively slight and subsequent brain swelling is unlikely, the $AVDO_2$ will rise to an abnormally high value 1–2 hours after decompression, then fall to the normal level in 5–6 hours. The EEG will recover within 1 hour and demonstrate normally distributed frequency bands without asymmetry. In such cases, increasing or maintaining the CBF is quite important. Thus, hyperosmolar diuretics, such as mannitol or glycerol, should be given, even in the absence of increased ICP, and the cerebral perfusion pressure should be maintained by correcting hypotension. Hyperventilation must be avoided in the early postoperative stage.

3) In cases with greater primary ischemic insult but recovery of cerebral metabolism still occurs, the $AVDO_2$ increases and the high value persists after 6 hours. The EEG also recovers within 1 hour of decompression, but mainly consists of slow waves, with the compressed side more affected. The most vigorous treatment is required in these cases. The CBF must be maintained as in 1), but cerebral metabolic depressants, such as barbiturates or gamma-hydroxybutyrate, are also required. Hyperventilation must be strictly avoided, and the greatest care taken to avoid hypotension due to barbiturates.

References

- 1) Fujimoto T, Walker JT, Spatz M, Klatzo I: Pathophysiologic aspects of ischemic edema, in Pappius HM, Feindel W (eds): *Dynamics of Brain Edema*. Berlin, Springer, 1976, pp 171–180
- 2) Hockaday JM, Potts F, Epstein E, Bonazzi A, Schwab R: Electroencephalographic changes in acute cerebral anoxia from cardiac or respiratory arrest. *Electroenceph Clin Neurophysiol* 18: 575–586, 1965
- 3) Hossmann KA: Development and resolution of ischemic brain swelling, in Pappius HM, Feindel W (eds): *Dynamics of Brain Edema*. Berlin, Springer, 1976, pp 219–227
- 4) Jakobsson KE, Lofgren J, Zwetnow NN: Critical thresholds of rebound ICP after cerebral compression, in Hoff JT, Betz AL (eds): *Intracranial Pressure VII*. Berlin, Springer, 1988, pp 853–857
- 5) Kojima T, Iwata K, Yuasa H, Sugiyama T: Influences of intracranial pressure on regional cerebral blood flow, in Hoff JT, Betz AL (eds): *Intracranial Pressure VII*. Berlin, Springer, 1988, pp 867–869
- 6) Levy D, Brierley JB, Plum F: Ischaemic brain damage in the gerbil in the absence of “no-reflow.” *J Neurol Neurosurg Psychiatry* 38: 1197–1205, 1975
- 7) Levy DE, Uiter RVU, Pike CL: Delayed postischemic hypoperfusion: A potentially damaging consequence of stroke. *Neurology (Minneapolis)* 29: 1245–1253, 1979
- 8) Miller JD: Head injury and brain ischemia: Implications for therapy. *Br J Anaesth* 57: 120–129, 1985
- 9) Paszor E, Symon L, Dorsch NWC, Branston NM: The hydrogen clearance method in assessment of blood flow in cortex, white matter, and deep nuclei of baboons. *Stroke* 4: 556–567, 1973
- 10) Plum F, Posner JB, Alvord EC Jr: Development and resolution of ischemic brain swelling. *Arch Neurol (Chicago)* 9: 563–570, 1963
- 11) Robertson CS, Narayan RK, Gokaslan ZL, Pahwa R, Grossman RG, Caram P Jr, Allen E: Cerebral arteriovenous oxygen difference as an estimate of cerebral blood flow in comatose patients. *J Neurosurg* 70: 222–230, 1989
- 12) Sakurada O, Takagi S, Sato K, Ishii S: Electroencephalography of experimental brain anoxia: Attempt of rating by quantitative analysis of electroencephalography. *Saigai Igaku* 18: 631–636, 1975 (in Japanese)
- 13) Yabuki A, Maeda M, Ishii S: The use of narcotics and hyperventilation for the treatment of post-traumatic brain swelling: Theoretical basis and clinical experience, in Hoff JT, Betz AL (eds): *Intracranial Pressure VII*. Berlin, Springer, 1988, pp 706–708

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