Sudden Death in a Rat Subarachnoid Hemorrhage Model

Weiguo ZHAO, Hiroshi UJIIE*, Yoshinori TAMANO*, Keiko AKIMOTO*, Tomokatsu HORI*, and Kintomo TAKAKURA*

Department of Neurosurgery, Rui-jin Hospital, Shanghai 2nd Medical University, Shanghai, People’s Republic of China; *Department of Neurosurgery, Neurological Institute, Tokyo Women’s Medical University, Tokyo

Abstract

The pathogenesis of sudden death during subarachnoid hemorrhage (SAH) still remains to be elucidated. A new rat common carotid artery-prechiasmal extracorporeal shunt model was designed to study the effect of different severities of SAH on intracranial pressure (ICP), regional cerebral blood flow (rCBF), and mortality. Different severities of SAH were induced by controlling the bleeding period (from 30 to 90 sec) and number of bleedings (one or three times). SAH caused a dramatic increase in ICP and immediate depression of rCBF, which recovered slowly to a certain extent. ICP increased sharply within the first 30 seconds and reached a plateau concomitant with nearly zero rCBF, which suggested the occurrence of cerebral circulation arrest. Bleeding of more than 60 seconds and increased ICP over 80 mmHg were directly correlated with the mortality. Respiratory arrest was the first sign of death, immediately followed by cardiac depression resulting in sudden death. This model combines arterial bleeding with systemic blood pressure and controlled bleeding time to simulate the acute period of SAH.

Key words: subarachnoid hemorrhage, rat model, regional cerebral blood flow, intracranial pressure

Introduction

Aneurysmal subarachnoid hemorrhage (SAH) manifests as a wide spectrum of clinical symptoms from mild headache to sudden death. A recent study on the outcome of patients showed that mortality from initial bleeding was unacceptably high.16,21,24 Investigation of the cause of death and disability from SAH in a population-based study found that initial bleeding rather than vasospasm contributed most to the cause of death and disability after SAH.6 Nearly two-thirds of patients died of ruptured aneurysmal SAH before or at admission. The rapidity of death of these patients indicates that present medical strategies are unlikely to improve the grim outcome of the disease.11,15 However, advances in neurosurgical care and vasospasm management have improved the prognosis for survivors of the first SAH attack, so the importance of initial bleeding on the outcome now draws much attention.16,24

Investigation of the pathogenesis of sudden death under severe SAH requires a suitable animal model to mimic the real clinical conditions in the acute phase. Injection of autologous blood into the subarachnoid space cannot reflect the real conditions when a sudden rise of intracranial pressure (ICP) occurs. The endovascular puncture model4,27 allows this condition but the severity of the SAH cannot be controlled. A sudden and sharp rise of ICP and controllable bleeding time are two important factors needed in a suitable animal model for the pathophysiology of SAH leading to sudden death.

This study describes the common carotid artery (CCA)-prechiasmal cistern extracorporeal shunt model in the rat which was designed to meet these requirements. Experimental SAH was implemented for 30 to 90 seconds to mimic the varying clinical severity, and to induce ICP elevation, allowing investigation of the relation to sudden death, the effect on cerebral microcirculation, and the difference between single and multiple hemorrhages.

Materials and Methods

The research protocol was approved by the Ethical Committee for Animal Experiments at Tokyo Women’s Medical University. Fifty-eight male Wistar Kyoto rats (weighing 300 to 400 g) were used in this study. After initial anesthesia by in-
traperitoneal injection of pentobarbital sodium (40 mg/kg), a tracheal tube was inserted surgically to ensure an unobstructed airway and the animal allowed to breathe spontaneously through the tracheostomy with room air during the experiment. Then the left femoral vein was exposed and cannulated for infusion of physiological saline at 3 ml/hr to prevent volume depletion and allow infusion of additional barbiturate. Infusion of pentobarbital was titrated to eliminate paw withdrawal reflexes to pain stimuli.

Blood pressure and heart rate were monitored through a polyethylene catheter (SP-31) inserted into the left femoral artery and connected to a transducer (TP-400T; Nihon Kohden, Tokyo). The left CCA was cannulated with a polyethylene catheter (SP-45) to allow shunting of blood to the prechiasmatic cistern under systemic blood pressure.

After these preparations, the rats were moved from the supine to the prone position, and the head was fixed on a stereotactic head frame (Natsume, Tokyo). A midline scalp incision of about 2.5 cm in length was made and the cranial vault was exposed. A 2-mm trepanation was carried out on the right parietal bone, 5 mm behind the coronal suture and 4 mm lateral to the midline. The underlying dura was pierced just enough for insertion of an ICP microsensor (Codman, Raynham, Mass., U.S.A.), which was connected to a polygraph.

Laser Doppler flowmetry (BPM model 403; TSI Inc., St. Paul, Minn., U.S.A.) was used to monitor the regional cerebral blood flow (rCBF) in the left parietal region through a 5-mm cranial window. Care was taken not to injure the cortical surface. The mechanical stability of the probe was maintained by using a micromanipulator to place the probe (2 mm diameter) lightly onto the dura away from the large dural and pial vessels, according to the published method.

SAH was induced through a shunt tube as follows. A burr hole of about 3 mm diameter was made in the frontal bone near the midline just before the tip of the frontal lobe. Particular care was taken not to damage the superior sagittal sinus. After cutting the dura, a clamped shunt tube from the CCA was stereotactically inserted into the prechiasmatic cistern by passing through the olfactory bulb and interhemispheric fissure and then opening as desired. The insertion place of the shunt tube was chosen deliberately to minimize the penetrative damage to the brain and the tubing fit snugly in the hole. The experimental set-up is shown in Fig. 1.

Physiological parameters such as mean arterial blood pressure (MABP), heart rate, ICP, and rCBF were recorded simultaneously for at least 2 hours after the implementation of SAH using a Macintosh Powerbook 5300cs through the connection to the polygraph with MacLab software and a four-channel data-acquisition board.

In the pilot study, 10 rats were used for test measurement of ICP and rCBF and confirmation of the successful establishment of the SAH model by postmortem histological examination. Forty-four rats were randomly divided into four groups of 11 rats each, and exposed to SAH for 30, 60, and 90 seconds, and three 30-second bleedings at one-minute intervals (referred to as 3-SAH), respectively.

Four rats were used to observe the cortical microcirculation after the onset of SAH. A 6- to 8-mm cranial window was made in the left frontoparietal area and covered with a slide cover glass (0.15 mm in thickness) in watertight fashion with Biobond® (EDH adhesive; Yoshitomi Pharmaceuticals, Osaka). A videomicroscope with a charge-coupled device camera was applied to the cranial glass window and the cerebral cortical microcirculation change due to SAH was recorded in real time.

All values are given as mean and SE. Serial changes of ICP, cerebral perfusion pressure (CPP = MABP − mean ICP), and rCBF were compared between the four groups. The values obtained before, during, 1 minute after SAH, and every 10 minutes thereafter were averaged. The effect of SAH on the parameters before and 2 hours after SAH were analyzed by analysis of variance. The Bonferroni/Duncan correction for post hoc analysis was used. The level of significance was p < 0.05.

Results

Postmortem examination verified extensive bleeding in the subarachnoid spaces such as the basal

Neurol Med Chir (Tokyo) 39, October, 1999
cistern, convexity, interhemispheric fissure, quadrigeminal cistern, and cisterna magna. No hematoma was found in the cerebral parenchyma. Coronal slices with HE staining showed extensive SAH mainly around the optic nerve, chiasma, and anterior cerebral arteries (Fig. 2).

Fig. 2 *left:* Photograph showing diffuse subarachnoid hemorrhage and clot in the basal cistern. *right:* Photomicrograph of a coronal section of rat brain obtained 2 hours after subarachnoid hemorrhage showing thick layered blood in the subarachnoid space. HE stain, ×40.

I. Effect of SAH on cardiopulmonary function and mortality

All rats in the 30-second SAH group survived with no obvious respiratory disturbance. These rats recovered well at the end of the 2-hour observation period. Temporary suspension of respiration was seen during SAH in 6/11, 7/11, and 6/11 rats in the 60-second SAH, 90-second SAH, and 3-SAH groups, respectively (Table 1). Most rats developed respiratory arrest concomitant with serious cardiac suppression, which resulted in sudden death in 4/11, 5/11, and 5/11 rats, respectively. Typical Cushing response such as a considerable increase in systemic blood pressure and bradycardia was rarely observed. The heart rate response was variable, and bradycardia and tachycardia occurred irregularly despite the increased ICP.

Respiratory arrest was the first sign that the rat was moribund. If the rat survived the bleeding

<table>
<thead>
<tr>
<th>Table 1 Apnea and sudden death after subarachnoid hemorrhage (SAH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-second SAH (n = 11)</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>60-second SAH (n = 11)</td>
</tr>
<tr>
<td>90-second SAH (n = 11)</td>
</tr>
<tr>
<td>three 30-second SAH (n = 11)</td>
</tr>
</tbody>
</table>

Fig. 3 Polygraph recordings (blood pressure [BP], heart rate [HR], intracranial pressure [ICP], and regional cerebral blood flow [rCBF]) from a 60-second subarachnoid hemorrhage (SAH) rat (left) which survived respiratory distress, and a 90-second SAH rat (right) showing respiratory arrest followed by immediate death. BT: body temperature.

Neurol Med Chir (Tokyo) 39, October, 1999
period with no sign of respiratory disturbance, then there was no risk of death during the observation period (Fig. 3). The duration from the initial respiratory disturbance to total circulatory arrest varies from 186 to 384 seconds (mean 269 ± 23 sec).

II. ICP and rCBF monitoring

The ICP under barbiturate anesthesia was 4.26 ± 0.21 mmHg (n = 44). Maximum ICP reached 72.92 ± 4.41, 92.46 ± 3.66, and 106.48 ± 5.13 mmHg in the 30-, 60-, and 90-second SAH groups, respectively. In the 3-SAHI group, progressive increase of ICP to 89.58 ± 4.19 mmHg was observed. Ten minutes after SAH, the ICP returned to only slightly above the baseline and changed little throughout the subsequent 2 hours. There was a significant difference in ICP increase between the 30- and 60-second SAH groups (p = 0.0026), but not between the 60- and 90-second SAH groups (p = 0.0722).

The rate of increase of ICP after SAH in all rats showed that the most rapid increase (2.19 ± 0.066 mmHg/sec) occurred in the initial 30 seconds of ICP elevation (n = 44), compared with 0.63 ± 0.18 mmHg/sec in the second 30-second period of the 60-second SAH group, and 2.09 ± 0.21, 0.75 ± 0.18, and 0.20 ± 0.31 mmHg/sec in 90-second SAH group in the initial, middle, and late 30-second periods, respectively, of the 90-second SAH group. The rate of increase of ICP in the 3-SAHI group was 2.18 ± 0.10, 2.06 ± 0.22, and 1.89 ± 0.16 mmHg/sec at each bleeding. Statistical analysis showed no significant difference between the first 30-second period between the four groups (p = 0.535). As ICP increased over 80 mmHg, mortality began to rise in an ICP-dependent pattern (Fig. 4). No rats with ICP below 80 mmHg during the 2-hour observation period developed respiratory complication and died.

rCBF decreased dramatically after the onset of SAH to about 10% of the original value. Despite the quick normalization of CPP along with the recovery of ICP, rCBF remained low, and gradually recovered in a SAH severity-dependent pattern. At the end of 2-hour observation, rCBF recovered to 66%, 37%, 15%, and 38% of the pre-SAH level in the four groups (Fig. 5).

Monitoring of small cortical vessels using the videomicroscope clearly demonstrated that the no-reflow phenomenon took place soon after the onset of SAH, and gradually turned into a to-and-fro pattern even after the recovery of ICP.

Discussion

I. Evaluation of the model and clinical implications

Various SAH models have been established for dogs, cats, rats, and even primates. These animal models can be classified into two types. The first is based on injection of autologous arterial blood in a preselected volume into the subarachnoid spaces, the cisterna magna, and suprasellar cistern. As the blood is injected under an arbitrary pressure, this neglects the importance of exposure of the brain to the systemic arterial pressure, which might be as much as 20 to 40 times higher than the normal ICP. Thus these models cannot reflect the real situation in SAH, but are only useful for research of vasospasm which develops in the late phase after SAH. The second type is a vessel puncture model achieved either intracranially or endovascularly. The Sheffield model has a closer analogy to spontaneous SAH in that extensive intracranial manipulation is not needed, but still has the disadvantage of instability and difficulty in controlling the severity of bleeding. The present artery-cisternal shunt model, adapted from Steiner et al. and McCormick et al., implements the bleeding under the physiological systemic arterial blood pressure, and the changing CPP which acts as a driving force for bleeding is similar to the situation when an aneurysm ruptures. In this model bleeding definitely depends on pressure difference between in the cranium and in the CCA during release of the artery-cisternal shunt. The main modifications of this model are controlling the bleeding time and leaving rats without mechanical

![Fig. 4 Bar graph showing the mortality (shaded column: death, open column: alive) and maximum intracranial pressure (ICP) value during subarachnoid hemorrhage. Deaths occurred at more than 80 mmHg rise in ICP in an ICP-dependent manner.](image-url)
ventilation throughout the experiment. This allows study of the effect of the bleeding time on ICP elevation during the natural process of aneurysmal SAH.

This study found that the ICP sharply rose within the first 30 seconds during bleeding and reached a plateau almost the same as the diastolic arterial blood pressure, which implies that in the clinical setting, bleeding may not continue for much longer than one minute. The controlled bleeding of 30 seconds resembled mild SAH, whereas the 60- and 90-second bleeding resembled very severe SAH. This model can easily simulate stable SAH with different severities. Relatively delicate manipulation and technical requirements are the limits of the model. Another shortcoming of this model is to suddenly stop the bleeding, so that total amount of SAH may be insufficient and ICP decreases steeply as a result reflecting this condition.

II. ICP and sudden death

Sudden death after SAH is thought to be caused by neurogenic pulmonary edema and cardiac complications. However, whether cardiopulmonary disturbance is the primary cause of death or only an epiphenomenon reflecting rapidly increased ICP remains controversial. Respiratory disturbance appeared within minutes after aneurysm rupture in fatal SAH. We found that apnea was the first sign of impending death in this SAH model. Respiratory arrest may lead instantaneously to cardiac suppression and cause death within a few minutes. However, some direct suppressive effect on cardiac rhythm might occur simultaneously at SAH.

Respiratory disturbance appeared in rats in this...
model, subjected to bleeding of more than 60 seconds, which is always associated with acute elevation of ICP over 80 mmHg. Rats which survived the initial respiratory arrest during the peak ICP and recovered did not die during the subsequent 2 hours. This observation implies that initial respiratory disturbance in the progress of SAH may result from sudden cessation or global depression of the respiratory center in the medulla oblongata or pons. The respiratory center located in the medullary area and the brainstem provides respiratory rhythogenesis, but sectioning between the medulla and spinal cord causes spontaneous respiration to cease. Similarly, a dramatic elevation of ICP occurred within seconds after the onset of SAH and a significant pressure difference between the cranium and spinal cavity may cause a sectioning effect at the level of medulla oblongata followed by respiratory arrest. However, if apnea results from neurogenic pulmonary edema, the respiratory condition of the rat should worsen progressively with time, because the rat was left without mechanical ventilation. This was obviously not the case in our study.

ICP elevation is proportional to the bleeding period and the respiratory center is very sensitive to sudden ischemia due to the sharp ICP gradient. This study suggests that in clinical SAH, bleeding that continues for much longer than one minute or an ICP rise of more than 80 mmHg will probably result in death due to apnea.

III. Cerebral ischemia after SAH

Rats surviving the initial respiratory distress suffer neurological deficits caused by ischemia due to suppressed cortical blood flow. Our study showed that rCBF decreased immediately after the onset of SAH and remained low during the 2-hour observation period in rats with severe SAH even after the restoration of normal CPP. rCBF is not simply governed by CPP after SAH. The so-called no-reflow phenomenon after ischemia may explain this difference, which is not inconsistent with clinical evaluations. Autopsy has shown multi-infarction areas in the brains of patients who died of aneurysmal SAH. The combination of dysautoregulation and destruction of the blood-brain barrier due to SAH, which increases brain edema, may disturb the microcirculation and result in a vicious cycle. Further anoxia due to respiratory distress aggravates the post-SAH ischemia.

Interestingly, only the 3-SAH model showed a higher ICP level after SAH, in contrast to the single SAH model. The first 30-second bleeding contributed most to the ICP rise throughout the period of SAH. Thus the 3-SAH model may have the greatest volume of bleeding among the four groups. The high ICP may reflect this intracranial mass effect and/or acute hydrocephalic change, so that repeated SAH may cause gradual deterioration of brain function.

The present CCA-prechiasmal cistern shunt model of SAH can simulate clinical SAH from mild to severe, and allows study of the effects of aneurysmal SAH in the acute phase.

Acknowledgments

This work was supported in part by the Japan-China Sasakawa Medical Fellowship.

References


Neurol Med Chir (Tokyo) 39, October, 1999
Commentary

The authors have tried to elucidate the pathogenesis of sudden death during subarachnoid hemorrhage (SAH) by using a new experimental model, first described by Zhao et al. in this paper. The rat's common carotid artery-prechiasmal extracorporeal shunt model was designed to study the effect of different severities of SAH by controlling the bleeding period (from 30 to 90 seconds) and number of bleedings (one or three times). As a result, the SAH caused a dramatic increase in ICP with immediate depression of rCBF within the first 30 seconds. The ICP increased sharply and reached a plateau concomitant with nearly zero rCBF bleeding of more than 60 seconds and increased ICP over 80 mmHg were directly correlated with the mortality. This model, compared with the endovascular puncture model, is more accurate as it can reflect the effects of blood pressure in the SAH and its consequences in the ICP and rCBF. The paper is clear and objective. The statistic methods were correctly applied and the results confirmed the prime goals of the authors. Despite this, it is difficult to determine central nervous system causes for sudden deaths in SAH. As is known, SAH is associated with heart arrhythmias in human beings and this is an important point that must be highlighted and studied. A more careful record of heart rhythm, using electrophysiologic methods, may be applied to this model to fulfill this pitfall. Congratulations to the authors for this innovative paper.

Evandro de OLIVEIRA, M.D.
and Jorge MARTINEZ, M.D.
Instituto de Ciências Neurologicas
Sao Paulo, Brazil

The acute stages of SAH have received comparatively little attention over the years, with only a handful of experimental studies as discussed in this paper, and even fewer clinical reports. This article is an important addition, as the authors present a technique which is both controllable and more similar to the...
situation of aneurysm rupture in humans, where cessation of bleeding often depends mainly on the difference between ICP and BP. It is presumed that in most fatal cases the CPP is at or close to zero too long for recovery to be possible. The likelihood in this rat model that death is due primarily to respiratory suppression is interesting.

There is potential here for further study — it would be interesting to know, with flow measurement in the external shunt, what volume of blood is necessary to be fatal, with the possibility of extrapolating to the human condition. Other investigations could include electrocardiography to clarify the question of a possible primarily cardiac death. Also, in those surviving longer, evidence of secondary biochemical damage, well recognized in head injury and in other no-reflow situations, would be interesting.

I should point out that the primate technique mentioned in references 9 and 19 of this article was in fact one of vessel avulsion, rather than the injection of a fixed volume of blood as stated in the Discussion section. However, because of variations in vessel size and possibly local vasospasm, the hemorrhage was often not as large and certainly not as well controlled as in the present model, which lends itself better to study of the early effects of SAH.

References

1) Jakobsen M, Haase J: Proceedings of Sixth International Conference on Cerebral Vasospasm. (in press)

Nicholas W. C. DORSCH, M.D.
Division of Surgery
Westmead Hospital
Sydney, Australia

The details of the pathogenesis of sudden death during subarachnoid hemorrhage (SAH) have not been completely understood, which is the reason why the present study is of general interest. In this study, the authors designed the common carotid artery prechiasmal cistern extracorporeal shunt model in the rat to induce pathological conditions with sudden and sharp rise of intracranial pressure (ICP) and controllable bleeding time, and analyzed the effect of severities of SAH on ICP, cerebral blood flow and mortality. The authors found that bleeding of more than 60 seconds and increased ICP over 80 mmHg were directly correlated with the mortality. They also speculated that respiratory arrest was the first sign of death, and initial respiratory disturbance in the progress of SAH may result from sudden cessation or global depression of the respiratory center in the medulla oblongata or pons. This hypothesis may be comprehensive in a few patients with sudden death due to severe SAH, yet for clinical practice, other complicated factors must be also considered. For instance, we have noticed effects of rapid and severe changes of sympathetic nerve activity to respiratory and cardiac disorders in this clinical category. I expect further studies using this convenient experimental model with more detailed monitoring in order to evaluate the general conditions.

Reference


Shunro ENDO, M.D.
Department of Neurosurgery
Toyama Medical and Pharmaceutical University
Toyama, Japan

Subarachnoid hemorrhage (SAH), hemorrhage into the subarachnoid space, is just a simple event due to vessel (arterial) rupture. However, the consequences are variable from mild meningeal irritation to death. Recently, a remarkable improvement has been achieved in the management of aneurysmal patients. However, it is still disappointing to manage the poor-grade patients, of whom some patients cannot receive medical attention, leading to sudden death with cardiopulmonary disturbance. In other words, the initial injury of hemorrhage will mostly determine the fate of patients. Nowadays, I think it is one of the important roles of neurosurgeons to find a way to treat patients in these poor clinical conditions. In order to improve the outcome in these conditions, it may need a new approach, focusing on understanding of the initial injury and its related management strategy. Unfortunately, studies with emphasis on this point are relatively rare. From this aspect, this experimental paper provides a valuable information and emphasizes respiratory disturbance as a serious consideration in the cause of sudden death in severe SAH.

The rat SAH model used in this study, arterial shunt to prechiasmal cistern, seems to be similar to the clinical setting as in the clinical situation: bleeding under the influence of systemic blood pressure, ICP, and CPP. The graded severity of SAH could be obtained by the control of bleeding time at the constant flow rate, and was correlated with the changes of ICP and rCBF as well. As mentioned in this paper, the amount of hemorrhage may be short of what would
reach SAH arrest, which McCormick et al. (ref. 20 of this article) suggested was primarily influenced by the flow rate. Actually the volume of hemorrhage with that flow rate can be expected to be much more in a clinical SAH situation. Concerning sudden death in this fatal SAH, it may be conceivable that the cardiopulmonary complications can cause a sudden death simultaneously and furthermore respiratory arrest or cardiac suppression, which one comes first, cannot be clinically separated. Now that severity is graded ideally with the control of bleeding time in this model, respiratory arrest brought by brain distortion and ischemia due to the sharp elevation of ICP should be considered to be the first sign of sudden death. Shapiro1) reported the outcome of management of 26 SAH patients who presented with respiratory arrest and required cardiopulmonary resuscitation (CPR), and concluded CPR with ICP control, surgery and active therapy could lead to 20% functional survival in what used to be sudden death from aneurysmal SAH. Therefore, this experimental study provides some supporting clues for getting good outcome, when it comes to the management of fatal SAH with respiratory arrest. Additionally, the data contribute to the understanding of brain injury at the acute stage of SAH, and provide the clinical rationale for acute management of SAH when patients are in poor grade or dead, even in respiratory arrest.

Reference


Dae Hee HAN, M.D.
Department of Neurosurgery
Seoul National University Hospital
Seoul, Korea, R.O.K.

The authors offer extremely interesting observations that support the contention that immediately after SAH, there is a dramatic increase in ICP and immediate depression of rCBF which can result in sudden death. They used the common carotid artery prechiasmal cistern extracorporeal shunt model in the rat which was designed to mimic the real clinical conditions in the acute stage of SAH. The two main factors will be 1) bleeding under the physiological systemic arterial blood pressure and 2) changing cerebral perfusion pressure similar to the situation when an aneurysm ruptures. In addition, the bleeding time can be controlled and rats can be left without mechanical ventilation throughout the experiment.

The important observations are that ICP increased sharply within the first 30 seconds and reached a plateau concomitant with nearly zero rCBF, which suggested the occurrence of cerebral circulation arrest. They also logically speculate that the bleeding of more than 60 seconds and increased ICP over 80 mmHg were directly correlated with the mortality. This theory is, of course, not new, but is reasonable and stimulates neurosurgeons to understand pathophysiological states of the patient immediately after SAH. This speculation may be interesting and strengthened by adding simultaneous and more detailed observations of the cerebral microcirculation using a videomicroscope, when recorded in real time.

Lately, it has been well recognized that most deaths after SAH occur very rapidly and are due to the initial hemorrhage. Undoubtedly, the clinical and pathophysiological condition of the patients is multifactorial. The authors go on to suggest that respiratory arrest was the first sign of death, immediately followed by cardiac depression resulting in sudden death. If so, is it possible that the resuscitation during acute stage can improve the grim outcome of these rats? Further investigation will be required.

Ryoji ISHII, M.D.
Department of Neurosurgery
Kawasaki Medical School
Okayama, Japan

Neurol Med Chir (Tokyo) 39, October, 1999