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Experimental Study of Venous Circulatory Disturbance by Dural Sinus Occlusion

M. Gotoh[1], **T. Ohmoto**[1], and **H. Kuyama**[2]

[1]Department of Neurological Surgery, Okayama University Medical School, Okayama and [2]Department of Neurological Surgery, Kagawa Medical School, Kagawa, Japan

Summary

Using a newly devised model of dural sinus occlusion, we investigated the pathophysiology of venous haemorrhage as well as venous circulatory disturbance. The superior sagittal sinus (SSS) and diploic veins (DV) were occluded in 16 cats. Intracranial pressure (ICP), cerebral blood volume (CBV) and regional cerebral blood flow (rCBF) were measured for 12 hours after the occlusion. At the end of the experiment, cerebral water content was estimated. In another 8 cats additional occlusions of cortical veins were carried out. In both groups, the blood-brain barrier permeability was evaluated with Evans blue or horseradish peroxidase.

The SSS and DV occlusion produced a significant increase in ICP and CBV concomitant with a significant decrease in rCBF. Cerebral water content also increased significantly. However, there was no transition of Evans blue and horseradish peroxidase through the cerebral vessels, and no haemorrhages could be observed. In contrast, the additional occlusion of cortical veins produced haemorrhagic infarctions with Evans blue extravasation in 6 out of the 8 cats.

These data suggest that dural sinus occlusion may lead to an increase in CBV and cerebral water content resulting in intracranial hypertension and decreased rCBF. The brain oedema in this model seemed to be mainly hydrostatic oedema, and might also be contributed by cytotoxic oedema. The additional occlusion of cortical veins might be essential in the development of haemorrhage in this model, and the blood-brain barrier was also disrupted in these areas.

Keywords: Dural sinus occlusion; cortical venous occlusion; venous haemorrhage; hydrostatic oedema.

Introduction

The cerebral venous system plays an important role in cerebral circulation. Cerebral sinus thrombosis or resection of the large cerebral veins during surgery may cause venous hypertension, often leading to brain oedema and intracerebral haemorrhage which result in neurological deficit. The pathophysiology of venous circulatory disturbance, however, is poorly understood.

Various experimental models have been utilized for cerebral venous occlusion[2, 4, 5, 8, 10, 16, 20]. The results of these studies, however, widely vary, suggesting the difficulty in developing a standardized and reproducible experimental model.

We devised a new experimental model of venous circulatory disturbance on the basis of anatomical study of the cerebral venous system in cats. The purpose of the present study is to clarify the pathophysiology of venous haemorrhage as well as venous circulatory disturbance using this model.

Materials and Methods

Animal Preparation

Twenty-nine adult cats of either sex, weighing 2.5 to 4.0 kg, were anaesthetized with ketamine hydrochloride (25 mg/kg) for induction. After tracheotomy, anaesthesia was maintained with 1% halothane and pancronium bromide (0.5 mg/kg/h) throughout the experiment. The right femoral artery and vein were cannulated for blood gas analysis, mean arterial blood pressure (MABP) monitoring, and Ringer's lactate infusion (10 ml/kg/h) respectively. Body temperature and arterial blood gases were maintained within the physiological ranges.

Experiment 1: Pathophysiology of Dural Sinus Occlusion

Twenty-one cats were used to study the pathophysiology of dural sinus occlusion. The procedure of dural sinus occlusion has been previously reported in detail[15]. Each cat was placed in a stereotaxic frame in the sphinx position. A midline scalp incision was made to expose the calvarium. After reflecting the temporalis muscles and opening the frontal sinus, two burr holes were made over the anterior end of the superior sagittal sinus (SSS) and the posterior end near the confluence of the sinuses. Outer table was also drilled away to make a groove 3–5 mm in width around the calvarium to expose diploic veins (DV). An intracranial pressure (ICP) transducer and a cerebral blood volume (CBV) sensor were inserted through a burr-

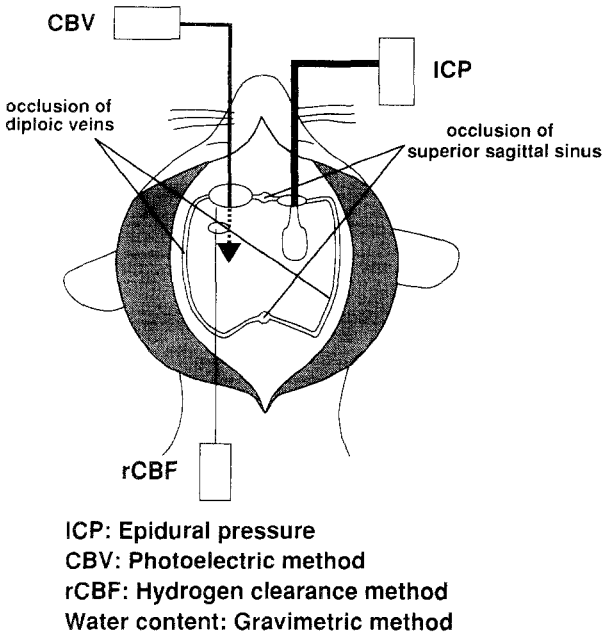

Fig. 1. Schematic drawing demonstrating the relative locations of venous system occlusion, rCBF probe, ICP and CBV sensors

hole into the epidural space and the subdural space respectively. CBV was measured by the photo-electric method[9]. A platinum electrode was also inserted into the cerebral cortex via a burr-hole for the measurement of regional cerebral blood flow (rCBF) by the hydrogen clearance technique[1]. After baseline measurements were completed, the SSS was occluded by coagulating at the above-mentioned two points, and DV by sealing with bone wax (Fig.1). MABP, ICP, and CBV were continuously recorded and rCBF was measured every hour for 12 hours after occlusion.

Five animals were sacrificed by the intravenous administration of potassium chloride solution 6 hours after occlusion, and small tissue samples were taken from the gray matter and the white matter for water content measurements using the specific gravimetric technique[11]. The residual 16 animals received an injection of 2.0% Evans blue solution (1 ml/kg) or horseradish peroxidase (HRP) Type II (100 mg/kg) dissolved in saline 11 hours after the occlusion, and were sacrificed 12 hours after the occlusion in the same manner as above. After the brain was removed evaluated macroscopically for Evans blue extravasation, the cerebral water content was estimated as well. The HRP-treated animals were perfused via the bilateral common carotid arteries first with 500 ml of saline, and then with 500 ml of fixative (2.0% paraformaldehyde, 2.0% glutaraldehyde in 0.1 M phosphate buffer). Half of the perfused brains were processed for enzyme histochemical reactions according to the method of Reese and Karnovsky[14]. Tissue slices were post-fixed in 1% osmium tetroxide, dehydrated, embedded in epoxy resin, and stained with saturated uranyl acetate in distilled water and lead citrate until electron microscopic examination. The remaining parts of the brains were processed for staining with haematoxylin-eosin and examined by light microscopy.

Experiment 2: Pathophysiology of Venous Haemorrhage

Eight cats were used to investigate the pathophysiology of venous haemorrhage. After fixing the animal's head in a stereotaxic frame, a burr-hole was made over the anterior end of the SSS. DV were occluded by the same method as in experiment 1. The SSS was occluded by injecting 0.3–0.5 ml α-cyanoacrylate monomer through a 27 G catheter introduced into the sinus.

The animals received an injection of 2.0% Evans blue solution (1 ml/kg) dissolved in saline 11 hours after the occlusion. The brain, removed 12 hours after the occlusion, was processed for histological examination in the same manner as described in experiment 1.

Data Analysis

All data in experiment 1 are given as average ± standard deviation of the mean. Results were compared by nonpaired or paired Students' t-test as appropriate, and considered significantly different at values of $p < 0.05$.

Results

Experiment 1

Body temperature, arterial blood gas, and MABP remained stable during the experiment.

Data on ICP, CBV, rCBF, and cerebral water content are shown in Fig. 2. The dural sinus occlusion gradually raised the ICP, which became significant 2 hours after the occlusion ($p < 0.05$). The ICP reached 18.8 ± 6.9 and 36.3 ± 12.2 mmHg at 6 and 12 hours after the occlusion, respectively.

CBV values in this study represent the percentage changes of optical absorption by haemoglobin in the brain tissue[9]. The animals exhibited rapidly increased CBV after the occlusion. The CBV continued to increase until 9 hours after the occlusion, and then remained at a constant level.

The rCBF was 50.1 ± 5.8 ml/100 gm/min at baseline. The dural sinus occlusion led to the sequential and significant reduction in rCBF during the experiment ($p < 0.01$ vs. baseline). The rCBF decreased to 23.0 ± 4.8 and 19.8 ± 4.6 ml/100 gm/min at 6 and 12 hours after the occlusion, respectively; The degree of reduction was not uniform, but more prominent within 6 hours after the occlusion.

The cerebral water content in the control cats ($n = 5$) was 79.2 ± 0.4% and 67.6 ± 0.6% in the gray and the white matter respectively. The animals subjected to the 6 hours dural sinus occlusion had a significantly greater amount of water: the gray and white matter contained 81.9 ± 0.5% and 73.3 ± 1.5% of water, respectively. The dural sinus occlusion for 12 hours led to a greater water content increase than that for 6 hours: the cerebral water content was 83.4 ± 1.2% and 76.8 ± 1.6% in the gray and the white matter, respectively ($p < 0.01$).

Macroscopically, Evans blue extravasation was visualized only in the injured areas probably due to the

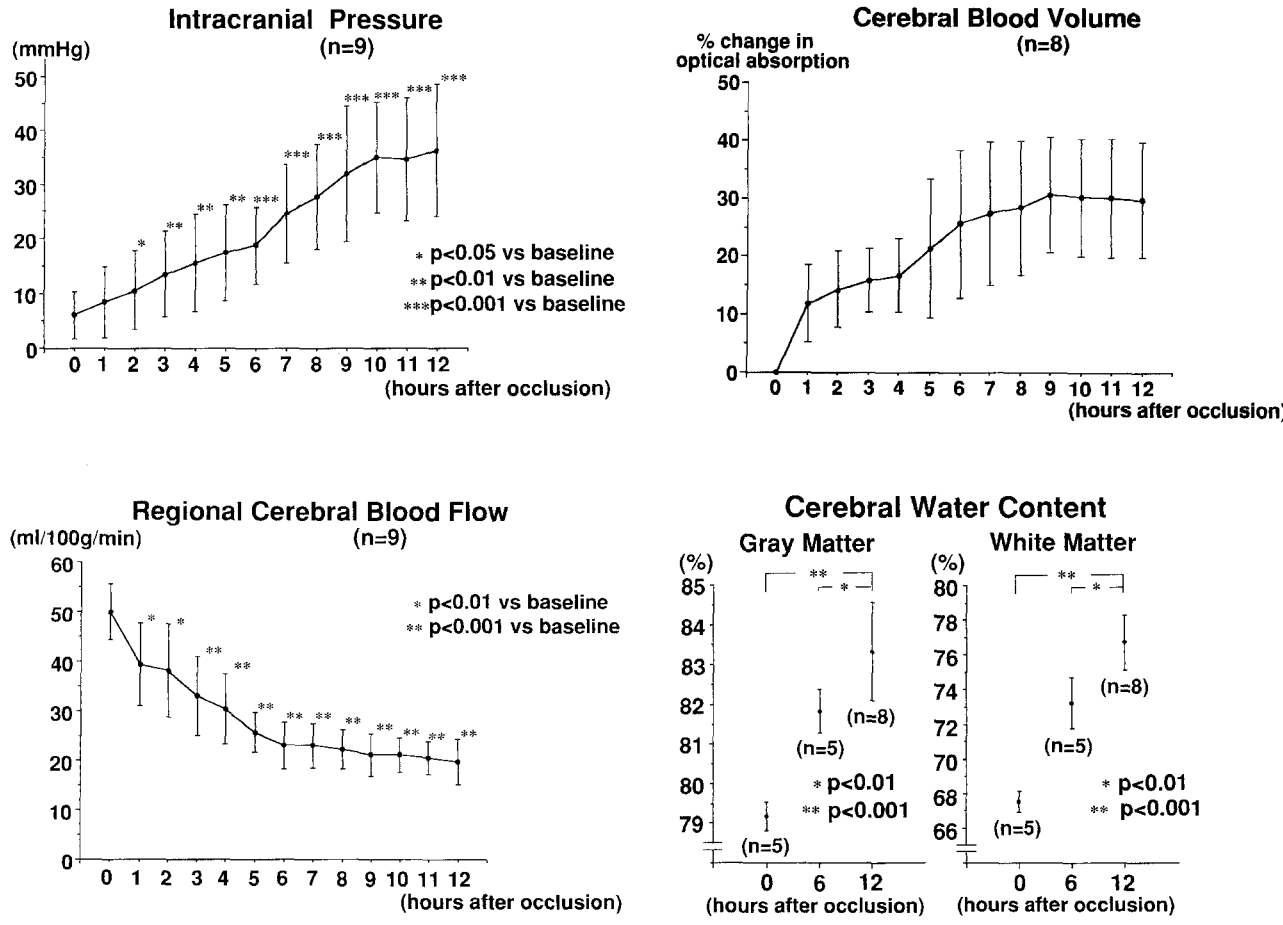

Fig. 2. Sequential changes in ICP (upper left), CBV (upper right), rCBF (lower left) after the dural sinus occlusion. The dural sinus occlusion produced an increase in ICP and CBV, and a decrease in rCBF. However, the changes of CBV and rCBF were less prominent than those of ICP later than 6 hours after the occlusion. Cerebral water content 12 hours after occlusion (gray matter 83.4 ± 1.2%, white matter 76.8 ± 1.6%) increased significantly compared with the baseline (gray matter 79.2 ± 0.4%, white matter 67.6 ± 0.6%) and 6 hours after the occlusion (gray matter 81.9 ± 0.5%, white matter 73.3 ± 1.5%) (lower right)

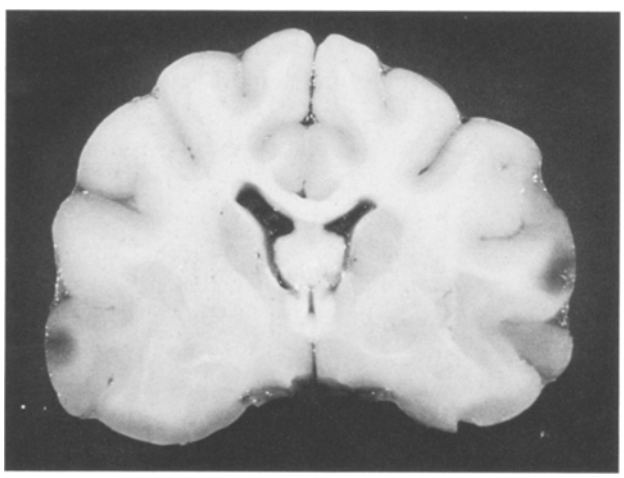

Fig. 3. Coronal section of the brain in experiment 1 shows that Evans blue extravasation was visualized only in the injured area probably due to the surgical procedure

surgical procedure (Fig. 3). Light microscopic examination showed oedematous changes including enlarged extracellular space and rarefaction both in the gray and the white matter (Fig. 4). However, no haemorrhages could be observed, when thrombi were defined within the SSS. On electron microscopy, no HRP extravasation was observed, although an uptake of HRP was seen into the endothelial cytoplasm. The endothelial cells were morphologically preserved (Fig. 5).

Experiment 2

Macroscopic examination showed haemorrhagic infarctions in the parasagittal cortex in 6 cats out of 8 studied (Fig. 6). The haemorrhages were restricted to the territory of occluded cortical veins. Evans blue dye was extravasated mainly around the gray matter ac-

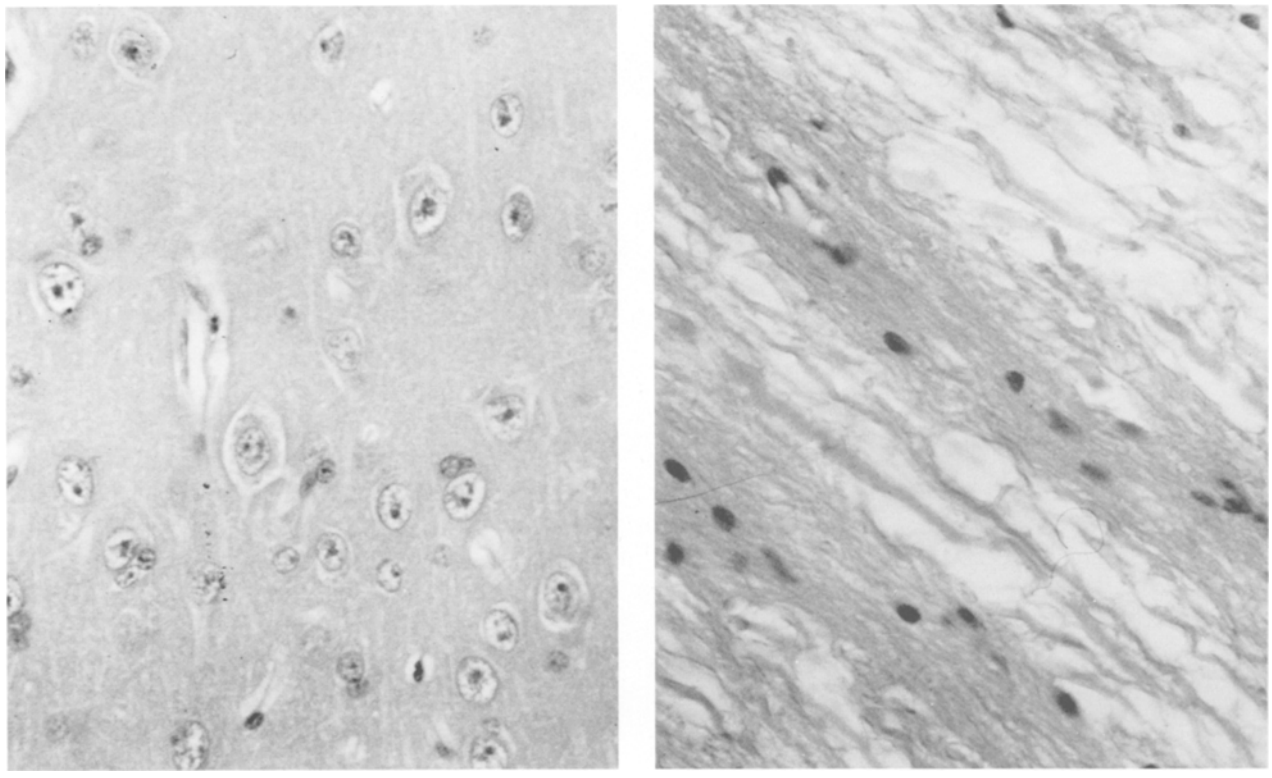

Fig. 4. Light photomicrogram in experiment 1 showing oedematous changes both in the gray (left) and in the white matter (right). Note no haemorrhage can be seen. H.E. Stain, × 200

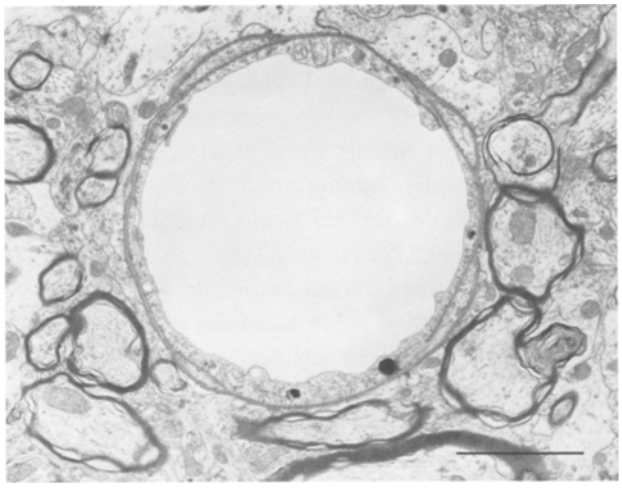

Fig. 5. Electronmicrograph in experiment 1. No HRP was extravasated although an uptake of HRP was seen in the capillary endothelium. × 6000, bar = 5 μm

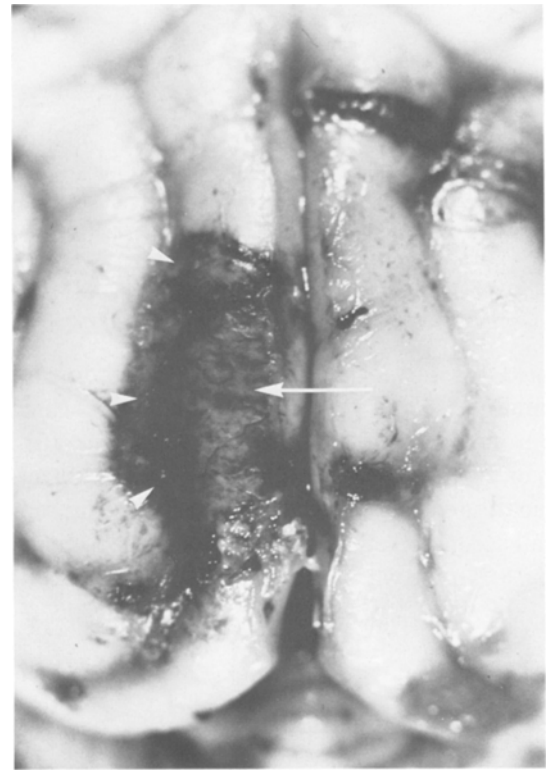

Fig. 6. Postmortem photograph of the brain in experiment 2 showing haemorrhagic infarction (arrow) in the parasagittal cortex where a cortical vein was occluded. Note the area stained with Evans blue dye around the haemorrhagic infarction (arrowheads)

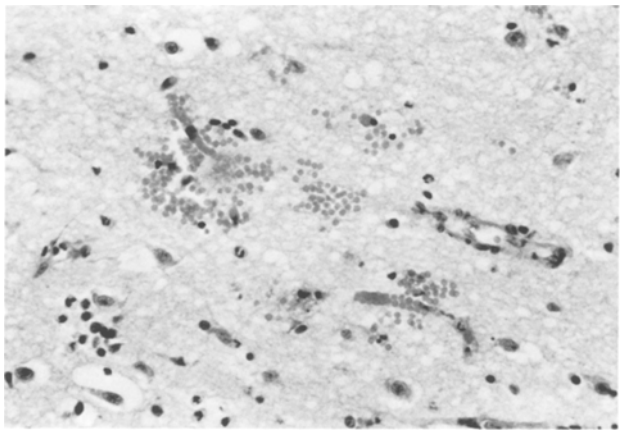

Fig. 7. Microscopic pictures of the cerebral cortex in experiment 2 showing petechial haemorrhages surrounding the dilated capillaries. H.E. Stain, × 200

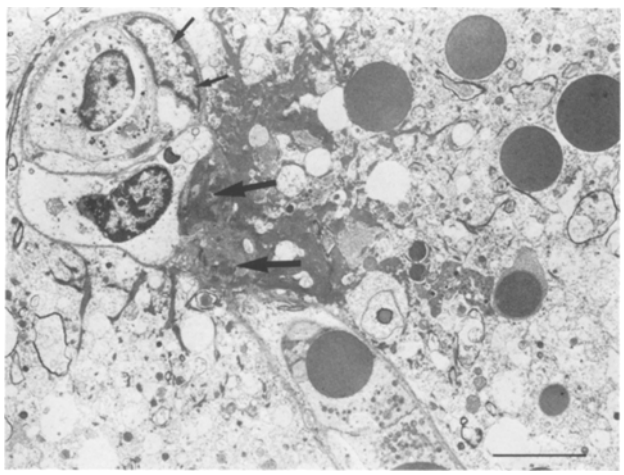

Fig. 8. Electronmicrograph in experiment 2. In the gray matter, erythrocytes were extravasated with disruption of the capillary wall (large arrows) accompanied by degeneration of the endothelial cells (small arrows). Massive degeneration of the brain parenchyma was also seen. × 2400, bar = 10μm

companied by haemorrhages. Light microscopy revealed multiple foci of petechial haemorrhages, which spread around dilated capillaries, with degenerative changes of the brain parenchyma (Fig. 7). Electron microscopic observation provided disruption of the capillary wall accompanied by degeneration of endothelial cells (Fig. 8). In the white matter, myelinolysis was observed.

Discussion

Several experimental studies[2, 4, 5, 8, 10, 16, 20] have reported the pathophysiology of cerebral venous occlusion, showing different results. The possible reasons for these differences include the different species and various methods of venous occlusion as well as individual variations of cerebral venous system. Prior to this experiment, we studied the anatomy of the cerebral venous system in cats and confirmed that it consisted of the superficial and the deep venous system[15]. The former, which is the major channel conveying venous blood from the cerebrum to the jugular veins, has two main draining pathways. Originating at the SSS, one drains into the internal jugular veins through the transverse sinuses and the other into the external jugular veins through DV. Therefore, SSS occlusion alone seems to be inadequate to produce venous circulatory disturbance. The external jugular system is able to be occluded by packing bone wax into the groove, which can be made around the extensively exposed skull. This method facilitates the obstruction of the widely distributed DV in the skull and makes an adequate congestion of cerebral venous channels without the danger of brain damage.

The present study suggested that the intracranial hypertension resulted from an increase in CBV and cerebral water content during dural sinus occlusion. Especially in the early period, the CBV raised the ICP, since the increase in ICP for the first 6 hours correlated with the changes in CBV. There are very few reports relating to the sequential changes in ICP under the condition of venous circulatory disturbance. Fries *et al.*[4], in their experimental study using pigs, reported that the occlusion of the SSS alone did not affect ICP. Occlusion of the middle third of the SSS would not raise ICP naturally. Angiograms showed collateral circulation via the cortical veins into the SSS posterior to the occlusion site. We occluded the total SSS whereas they only performed partial occlusion. Tychmanowicz *et al.*[20] also examined the intracranial volume-pressure relations during the SSS occlusion in cats. They found that ICP increased significantly immediately after the occlusion, followed by small changes for 5 hours. However, they performed no additional occlusion of DV, which might have influenced the difference in ICP changes between their experiment and the present study. The dural sinus occlusion in our study raised the ICP to 18.8 ± 6.9 mmHg within 6 hours. These findings correspond to those reported by Fujita and co-workers[5]; they demonstrated that the rapid occlusion of the SSS elevated ICP to 20 ± 5.5 mmHg in dogs.

The CBV measured in this study mainly reflects venous blood volume in brain tissue[9], because it

amounted to about 70% of the total CBV in cats[19]. Therefore it seems that the increase in CBV resulted from intracerebral venous congestion. The increase was less prominent later than 6 hours after occlusion. The deep venous system preserved in this model may be a collateral pathway.

In our study, cortical rCBF gradually decreased in spite of mild intracranial hypertension. This finding has previously been reported in the literature[10, 16], but does not agree with the observations of Shulman and Verdier[17]; They studied cerebral vascular resistance changes to rapidly induced intracranial hypertension and concluded that elevation of cerebrospinal fluid pressure less than 400 mmH_2O did not decrease CBF. Kety *et al.*[6] also reported the same observation in a clinical study. However, in the venous circulatory disturbance, an elevation of venous pressure rather than an increase in ICP may decrease rCBF. Wagner and Traystman examined rCBF responses to elevated jugular venous pressure and found that rCBF decreased significantly when cerebral perfusion pressure (CPP) decreased to values below 60 mmHg[21]. Kurokawa *et al.*, using a model of cerebral venous hypertension in rats, measured NADH fluorescence in the brain and reported that the extent of the metabolic disturbance was proportional to a decrease in CPP[8]. We supposed that decreased rCBF resulted from lowered CPP. The fact that rCBF reduced less prominently later than 6 hours after the occlusion may also suggest that a collateral circulation may relieve the further decrease in CPP.

Miller classified cerebral oedema into following five types; vasogenic, cytotoxic, hydrostatic, interstitial, and hypo-osmotic[13]. The present macroscopic and microscopic examinations indicated that the blood-brain barrier (BBB) was not disrupted. Under venous circulatory disturbances, it is likely that intravascular pressure would become high enough upset the Starling equilibrium. Hydrostatic force would play an important role in oedema formation under these conditions. Sato *et al.*[16], in contrast to the present finding, showed that diapedesis of fluorescein dye was observed 5 minutes after sinus occlusion. This result suggests that the BBB might be disrupted transiently in the early period of the dural sinus occlusion. Cytotoxic oedema may also be responsible for the cerebral oedema in this model, because rCBF reduced to the flow threshold to leading to cytotoxic oedema[18]. Further examination is required to clarify the mechanism and types of brain oedema under these conditions.

Concerning haemorrhage following sinus occlusion, several clinical and experimental studies have indicated the importance of extended occlusion of the cortical veins[3–5, 7]. The present results support this conception. Previous reports hardly discussed the pathophysiology of venous haemorrhage; only Fujita *et al.* reported that venous hypertension caused disruption of cortical and subcortical veins which led to subarachnoid haemorrhage and haemorrhagic infarction[5]. In the present study, we observed no haemorrhages in areas where cortical venous occlusion was restricted only to the aperture into the SSS. Light microscopy revealed that haemorrhages mainly occurred around dilated capillaries. These findings suggest that haemorrhage may occur at capillaries or venules when the occlusion involves the confluent portions of collecting venules and veins. In addition electron microscopic findings revealed disruption of the capillary wall accompanied by degeneration of the endothelial cells as well as the brain parenchyma. Cortical venous occlusion beyond the confluent portion may produce severe regional ischaemia, which leads to the necrosis of the capillary wall resulting in haemorrhages. The fact that Evans blue dye was extravasated around haemorrhage in the gray matter may confirm the concept, although Evans blue dye hardly reaches the haemorrhagic areas when rCBF is lowered considerably.

Mayhan and Heistad, in their experiment, reported that all stimuli that may disrupt the BBB do not involve increases in venous pressure[12]. The venous hypertension, however, undoubtedly plays an important role in the pathophysiology of venous haemorrhage as well as various types of oedema. It produces intracerebral venous congestion, raises intravascular pressure, and lowers CPP. These factors lead to the complicated pathological events under these conditions. Venous haemorrhage is considered to be the final consequence in the consecutive pathological processes and may develop depending upon the degree of venous pressure distal to the occlusion site and the time interval from venous occlusion.

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Correspondence: Masaki Gotoh, M.D., Gough-Cooper Department of Neurological Surgery, Institute of Neurology, The National Hospital, Queen Square, London, WC1N 3BG, U.K.