Acute intracranial hypertension and brain-stem blood flow

An experimental study

Seigo Nagao, M.D., Norio Sunami, M.D., Takumi Tsutsui, M.D., Yutaka Honma, M.D., Fumiyuki Momma, M.D., Tsukasa Nishihara, M.D., and Akira Nishimoto, M.D.

Department of Neurological Surgery, Okayama University Medical School, Okayama, Japan

This study has been carried out to evaluate the effect of supratentorial mass lesions on the local cerebral blood flow (CBF) of the brain stem. Local CBF of the thalamus, inferior colliculus, and medulla oblongata, and supra- and infratentorial pressure were serially measured in 52 cats with intracranial hypertension produced by supratentorial balloon expansion. The mean control local CBF's in the thalamus, inferior colliculus, and medulla oblongata were 37.5, 42.1, and 30.7 ml/100 gm/min, respectively. At 20 to 30 mm Hg of supratentorial pressure, the local CBF of the thalamus started to decrease, and at 20 mm Hg of infratentorial pressure, the local CBF of the inferior colliculus began to decrease. Finally, at 40 to 60 mm Hg of infratentorial pressure, the local CBF of the medulla oblongata was affected. The Cushing response was evoked at a mean supratentorial pressure of 93.4 mm Hg and infratentorial pressure of 49.9 mm Hg in 16 cats. When the systemic arterial pressure was increased to the highest level in 13 cats, the mean local CBF of the medulla oblongata did not show significant change (a decrease from 22.8 to 20.9 ml/100 gm/min). The results suggest that at the beginning of uncal herniation, the local CBF of the upper brain stem markedly decreased. During the Cushing response, the local CBF of the medulla oblongata did not change significantly.

Key Words: brain stem • cerebral blood flow • intracranial pressure • uncal herniation • medulla oblongata

Materials and Methods

Experiments were conducted with 52 unselected mongrel cats, weighing between 3 to 4.5 kg each. Anesthesia was induced with 30 mg ketamine hydrochloride, and the trachea was cannulated. The animals were paralyzed with 10 mg gallamine triethiodide (Flaxedil) administered intravenously, and maintained on a respirator* while the arterial pCO2 was kept between 30 and 35 mm Hg. Arterial pO2 was reviewed intermittently,† and maintained at between 80 and 110 mm Hg. The animal's temperature was maintained by a

* ACOMA respirator, Model AR-300, manufactured by ACOMA, Inc., Tokyo, Japan.
† pH/blood gas analyzer, Model 165/2, manufactured by Corning Medical, Corning Glass Works, Medfield, Massachusetts.
Intracranial hypertension and brain-stem blood flow

Intracranial hypertension and brain-stem blood flow

heating lamp at approximately 38°C. The femoral artery and vein were cannulated for measurement of arterial pressure, and for the administration of drugs and physiological saline solution.

The ICP was increased by intermittent inflation with 0.2 ml saline of a small balloon placed in the epidural space of the right middle fossa to simulate an epidural hematoma. The supra- and infratentorial pressure were continuously measured by plate-type pressure transducers§ (6.5 mm) placed at the left middle fossa and posterior fossa in the midsagittal epidural space. The systemic arterial pressure and ICP were continuously recorded. The local CBF was measured at three sites in each animal by the hydrogen clearance technique each time the balloon was inflated, at approximately 15-minute intervals.

A dental drill was used to create three small holes in the left parietal and posterior fossa convexity, through which platinum electrodes with a bared conical tip, 1 mm in length and 0.3 mm in diameter, were stereotaxically placed through the intact dura mater into the thalamus (at A11, L5, H4 on the contralateral side of the mass), the inferior colliculus (at P2.5, L5, H4), and the reticular formation of the medulla oblongata (at P0, L2, H2.5) according to the atlas of Snider and Niemer. The electrodes for the latter two targets were inserted via the small holes in the posterior fossa.

After insertion of the electrodes to the targets, the stereotaxic electrode holders were removed in order to permit mobility of the electrodes following brain-stem displacement secondary to supratentorial mass expansion. The value of local CBF was determined from the initial-slope method of the clearance curve following 3 minutes of inhalation of 4% to 7% hydrogen gas. After stabilization of each electrode and of the animals' blood gases, baseline local CBF was determined twice at each site. At the termination of the experiments, the brain tissue at the tip of the electrode was coagulated in order to confirm the exact site of the electrode while the balloon was left expanded. The cat brain was removed and fixed in 10% formalin solution for 2 weeks, then sectioned in the coronal plane. In macro- and microscopic examination, all three electrodes were placed correctly in the thalamus, inferior colliculus, and medulla oblongata in 30 animals.

Results

The control values of local CBF's of the thalamus, inferior colliculus, and medulla oblongata were 37.5 ± 9.9, 42.1 ± 8.6, and 30.7 ± 4.9 ml/100 gm/min, respectively (mean ± standard deviation in 60 measurements from 30 cats). In this experimental model, free movement of the local CBF electrodes is essential since there is caudal displacement of the brain stem secondary to an expanding supratentorial lesion.

Figure 1 presents serial x-ray documentation of the gradual movement of the local CBF electrodes concomitant with brain-stem displacement due to supratentorial balloon expansion. In the normal cat (Fig. 1 upper), the electrode placed in the inferior colliculus is just beneath the bony tentorium (arrow). At a supratentorial balloon volume of 1 ml (Fig. 1 center), some caudal

---

† Statham P50 pressure transducer manufactured by Statham Instruments Division, Gould Inc., Oxnard, California.
§ Epidural transducer, Model P-16S, manufactured by Telemex, Inc., Tokyo, Japan.
FIG. 2. Relationship between the local cerebral blood flow (CBF) of the thalamus (Th) and supratentorial pressure (STP). At 20 to 30 mm Hg of supratentorial pressure, the local CBF of the thalamus started to decrease in the majority of the animals.

FIG. 3. Correlation between the local cerebral blood flow (CBF) of the inferior colliculus (IC) and infratentorial pressure (ITP). At 20 to 30 mm Hg of infratentorial pressure, a decrease in the local CBF of the inferior colliculus was observed.

FIG. 4. Correlation between the local cerebral blood flow (CBF) of the medulla oblongata (MO) and infratentorial pressure (ITP). The local CBF of the medulla oblongata did not show significant change until infratentorial pressure reached 40 to 60 mm Hg.

Movement of the electrode in the inferior colliculus was observed adjacent to the tentorial hiatus, while that in the medulla oblongata seemed to be less affected. At a balloon volume of 2 ml (Fig. 1 lower), the electrodes in both the inferior colliculus and medulla oblongata were markedly displaced caudally due to brain-stem movement caused by direct compression by the herniated brain.

Local CBF's of the thalamus, inferior colliculus, and medulla oblongata were measured serially during brain-stem movement caused by the supratentorial balloon expansion. The stepwise decreases of local CBF of the thalamus during increases in supratentorial pressure in 30 animals are presented in Fig. 2. The local CBF of the thalamus started to decrease at 20 to 30 mm Hg of supratentorial pressure in 22 of 30 animals, decreased to less than 20 ml/100 gm/min in 16 animals at 40 mm Hg of supratentorial pressure, and fell to zero in 10 cats (one-third of the animals) when the supratentorial pressure increased to 60 mm Hg.

Concomitant with supratentorial balloon expansion, infratentorial pressure also gradually increased, and local CBF of the brain stem decreased. The local CBF of the inferior colliculus was reduced at 20 mm Hg of infratentorial pressure in 23 of the 30 animals. When infratentorial pressure increased to 40 to 50 mm Hg, local CBF was less than 10 ml/100 gm/min in 27 cats, and only three animals exhibited local CBF of more than 20 ml/100 gm/min (Fig. 3).

On the other hand, local CBF of the medulla oblongata did not decrease significantly from the control value at 40 mm Hg of infratentorial pressure in 14 of 30 animals (Fig. 4). In our experimental model with middle fossa compression, a pupillary change was shown to be one of the earliest clinical signs of uncal herniation. Pupillary dilatation ipsilateral to the expanding middle fossa balloon was clearly observed in 16 of 30 animals. At this stage, supratentorial balloon volume was 1.3 ± 0.42 ml in these 16 animals (approximately 6.5% of the supratentorial brain volume of the cat), supratentorial pressure was 48.3 ± 17.6 mm Hg, infratentorial pressure was 23.5 ± 9.7 mm Hg, and the difference between supratentorial pressure and infratentorial pressure was 24.6 ± 11.4 mm Hg. In 12 of the 16 animals (75%), local CBF of the inferior colliculus decreased to zero when the supratentorial pressure-infratentorial pressure difference approached 40 mm Hg.

In order to study the changes in local CBF of the upper brain stem at the beginning of uncal herniation, the changes in local CBF of the inferior colliculus immediately before and after pupillary change were closely correlated (Fig. 5). In the 16 animals that exhibited pupillary change, the local CBF of the inferior colliculus varied from 14.8 to 53.3 ml/100 gm/min immediately before pupillary change. In 13 animals, local CBF of the inferior colliculus decreased abruptly at this stage. After pupillary dilatation, the mean local CBF of the inferior colliculus was significantly sup-
Intracranial hypertension and brain-stem blood flow

pressed from 33.7 ± 12.2 to 19.6 ± 12.6 ml/100 gm/min. In three animals, local CBF of the inferior colliculus fell to zero, indicating that severe compression ischemia in the inferior colliculus had occurred at the beginning of uncal herniation.

During supratentorial balloon expansion, 16 of 30 cats demonstrated a progressive increase in the mean arterial blood pressure (MABP) of 15 to 60 mm Hg associated with bradycardia and increased pulse pressure (Cushing response). The blood pressure response (beginning of the rise of MABP) was evoked when supratentorial pressure and infratentorial pressure were 93.4 ± 14.6 and 49.9 ± 6.8 mm Hg, respectively, in 16 animals. Table 1 summarizes the alterations in the MABP, the cerebral perfusion pressure (CPP, defined as the MABP minus the mean ICP) of the supratentorial (CPP-ST) and infratentorial cavity (CPP-IT), and the local CBF of the thalamus, the inferior colliculus and the medulla oblongata in 13 animals in which local CBF was measured before and during the Cushing response. The MABP increased significantly from 121.5 ± 17.1 to 140.0 ± 14.4 mm Hg, whereas the CPP-ST and CPP-IT changed from 60.9 ± 23.8 to 46.3 ± 17.2 and 89.0 ± 16.4 to 89.6 ± 15.1 mm Hg, neither of which were significant. The mean value of local CBF of the thalamus and inferior colliculus slightly decreased and that of the medulla oblongata changed from 22.8 ± 7.6 to 20.9 ± 5.3 ml/100 gm/min, which was not statistically significant. Figure 6 illustrates the changes in the MABP and local CBF of the medulla oblongata before and during the Cushing response for the 13 animals. In spite of the rise of MABP, the local CBF of the medulla oblongata did not increase, as shown in the mean value.

![Fig. 5. Changes in the local cerebral blood flow (CBF) of the inferior colliculus (IC) immediately before and after anisocoria. At the beginning of uncal herniation, indicated by anisocoria, the local CBF of the inferior colliculus abruptly decreased from 33.7 to 19.6 ml/100 gm/min (mean value of 16 animals).](image)

**Discussion**

In a supratentorial experimental mass lesion, displacement and distortion of the midbrain due to uncal herniation could account for the suppression of the electroencephalogram, and axial brain-stem distortion can also cause alterations in cardiorespiratory activity. It has previously been reported that gradual

### TABLE 1

**Pressure and flow changes before and during the Cushing response**

<table>
<thead>
<tr>
<th>Cat No.</th>
<th>Before Cushing Response</th>
<th>During Cushing Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BP ST</td>
<td>IT</td>
</tr>
<tr>
<td>1</td>
<td>130</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>94</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>136</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>118</td>
<td>56</td>
</tr>
<tr>
<td>10</td>
<td>106</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td>136</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>126</td>
<td>104</td>
</tr>
<tr>
<td>13</td>
<td>126</td>
<td>62</td>
</tr>
<tr>
<td>14</td>
<td>104</td>
<td>54</td>
</tr>
<tr>
<td>17</td>
<td>146</td>
<td>92</td>
</tr>
<tr>
<td>18</td>
<td>146</td>
<td>92</td>
</tr>
<tr>
<td>22</td>
<td>106</td>
<td>40</td>
</tr>
<tr>
<td>27</td>
<td>110</td>
<td>44</td>
</tr>
<tr>
<td>mean</td>
<td>121.5</td>
<td>60.9</td>
</tr>
<tr>
<td>SD</td>
<td>17.1</td>
<td>23.8</td>
</tr>
</tbody>
</table>

*Changes in the arterial blood pressure (BP), cerebral perfusion pressure (CPP), and the local cerebral blood flow (CBF) of the thalamus (Th), inferior colliculus (IC) and medulla oblongata (MO) immediately before and during the Cushing response in 13 animals. Measurements are in mm Hg (pressure) and ml/100 gm/min (flow). ST = supratentorial; IT = infratentorial; SD = standard deviation.
and local cerebral blood flow (ICBF) of the medulla oblongata
ported that the baseline local CBF of the brain stem in
experimental intracranial hypertension produced by
cisterna magna infusion, Rowan and Teasdale 
recently reviewed the changes in local CBF in response to experimental
hypertension with cisterna magna infusion, the blood
pressure response produced no significant increase in
the brain-stem blood flow in four out of six baboons.
Zierski, et al., reported that control local CBF of the thalamus, midbrain, and lower medulla oblongata in cats is 41.4, 42.4, and 25.6 ml/100 gm/min, respectively, as measured by the radioactive microsphere method. They noted two patterns of change in local CBF in response to experimental supratentorial balloon expansion: 1) a uniform and equal decrease of CBF in the cerebral hemispheres, midbrain, pons, and medulla oblongata; and 2) dissociated behavior of the CBF decrease in the cerebral hemispheric and midbrain flow, with a small reduction in the pons and medulla oblongata. Our data showed that local CBF of the thalamus first started to decrease at 20 to 30 mm Hg of supratentorial pressure, then local CBF of the inferior colliculus was affected at 20 mm Hg of infratentorial pressure. In half our animals, local CBF of the medulla oblongata was preserved until infratentorial pressure became 40 mm Hg. These results strongly suggest that supratentorial mass lesions induce rostrocaudal reduction of local CBF of the deep cerebral structures, because of different degrees of transmission of the pressure. A possible anatomical explanation may be that the thalamus (the deep supratentorial structure) is easily displaced and squeezed by balloon expansion; next, the inferior colliculus adjacent to the tentorial hiatus can be directly compressed by the herniated brain; local CBF of the medulla oblongata, however, appears to be preserved, as the pressure on it was reduced by the displacement and shortening of the upper brain stem.

In a clinical study, Kaufmann and Clark recorded intraventricular and cervical subarachnoid cerebrospinal fluid pressure, and all their patients with a pressure gradient greater than 10 mm Hg revealed severe trans-tentorial and/or tonsillar herniation. In our results, uncal herniation, as presumed by the appearance of anisocoria, occurred at a supra- and infratentorial pressure difference of 24.6 ± 11.4 mm Hg, which correlated with a marked reduction of local CBF of the inferior colliculus. A supra- and infratentorial pressure difference of 40 mm Hg was enough to result in complete ischemia of the inferior colliculus. Although the difficulty of translating these results to humans is recognized, it would be reasonable to assume that, in humans, local CBF of the upper brain stem is also severely impaired when anisocoria is observed (that is, at the beginning of uncal herniation).

The increase in blood pressure occurring with intracranial hypertension (Cushing response) has been thought of as a compensatory mechanism to preserve CBF by maintaining CPP in the face of rising ICP. Previous experiments have demonstrated that the Cushing response is evoked when the ventricular pressure reaches a mean value of 92.0 ± 5.8 mm Hg in a cold lesion of the cerebral cortex, and when the infratentorial pressure exceeds 45 mm Hg in a supratentorial mass in cats. Our data correspond with these results. For many years, it has been a matter of controversy whether the blood pressure response results in a significant increase in blood flow, especially in the brain stem. In experimental studies of brain swelling, Shalit and Cotev observed that elevated MABP was followed by a marked increase in ICP and a decrease in cortical CBF. They concluded that the Cushing response could not be regarded as a beneficial, compensatory mechanism, but rather as a deleterious phenomenon. In Rowan and Teasdale’s study of acute intracranial hypertension with cisterna magna infusion, the blood pressure response produced no significant increase in the brain-stem blood flow in four out of six baboons. Zierski, et al., reported that, in supratentorial mass lesions, reactive systemic hypertension at the state of complete midbrain herniation resulted in only a small increase or further decrease of CPP, with no noticeable improvement of local CBF of the cats’ brain stem. Our

FIG. 6. Changes in the mean arterial blood pressure (BP) and local cerebral blood flow (ICBF) of the medulla oblongata before (open circles) and during (closed circles) the Cushing response in 13 cats. The solid line shows the mean value.

caudal movement of the brain stem secondary to a supratentorial mass lesion suppressed the neural activity of the auditory pathways of the brain stem. These data imply that brain-stem movement and compression due to supratentorial mass lesions may affect the brain-stem functions by mechanical stresses on the nuclei and neuronal pathways lying in the affected portion of the brain stem. Impairment of brain-stem circulation due to decreased CPP and stretching and compression of the basal vascular architecture by supratentorial mass lesions has also been thought to be responsible for brain-stem dysfunction. However, very few studies have been carried out concerning the changes in blood flow of the brain stem in acute intracranial hypertension. In experimental intracranial hypertension produced by cisterna magna infusion, Rowan and Teasdale reported that the baseline local CBF of the brain stem in the baboon was 34 ± 8 ml/100 gm/min, and brain-stem blood flow did not fall until ICP was greater than 90 mm Hg and CPP less than 40 mm Hg.

Recently, Zierski, et al., showed that control local CBF of the thalamus, midbrain, and lower medulla oblongata in cats is 41.4, 42.4, and 25.6 ml/100 gm/min, respectively, as measured by the radioactive microsphere method. They noted two patterns of change in local CBF in response to experimental supratentorial balloon expansion: 1) a uniform and equal decrease of CBF in the cerebral hemispheres, midbrain, and lower medulla oblongata before (open circles) and during (closed circles) the Cushing response in 13 cats. The solid line shows the mean value.

Recently, Zierski, et al., showed that control local CBF of the thalamus, midbrain, and lower medulla oblongata in cats is 41.4, 42.4, and 25.6 ml/100 gm/min, respectively, as measured by the radioactive microsphere method. They noted two patterns of change in local CBF in response to experimental supratentorial balloon expansion: 1) a uniform and equal decrease of CBF in the cerebral hemispheres, midbrain, and lower medulla oblongata; and 2) dissociated behavior of the CBF decrease in the cerebral and midbrain flow, with a small reduction in the pons and medulla oblongata. Our data showed that local CBF of the thalamus first started to decrease at 20 to 30 mm Hg of supratentorial pressure, then local CBF of the inferior colliculus was affected at 20 mm Hg of infratentorial pressure. In half our animals, local CBF of the medulla oblongata was preserved until infratentorial pressure became 40 mm Hg. These results strongly suggest that supratentorial mass lesions induce rostrocaudal reduction of local CBF of the deep cerebral structures, because of different degrees of transmission of the pressure. A possible anatomical explanation may be that the thalamus (the deep supratentorial structure) is easily displaced and squeezed by balloon expansion; next, the inferior colliculus adjacent to the tentorial hiatus can be directly compressed by the herniated brain; local CBF of the medulla oblongata, however, appears to be preserved, as the pressure on it was reduced by the displacement and shortening of the upper brain stem.

In a clinical study, Kaufmann and Clark recorded intraventricular and cervical subarachnoid cerebrospinal fluid pressure, and all their patients with a pressure gradient greater than 10 mm Hg revealed severe trans-tentorial and/or tonsillar herniation. In our results, uncal herniation, as presumed by the appearance of anisocoria, occurred at a supra- and infratentorial pressure difference of 24.6 ± 11.4 mm Hg, which correlated with a marked reduction of local CBF of the inferior colliculus. A supra- and infratentorial pressure difference of 40 mm Hg was enough to result in complete ischemia of the inferior colliculus. Although the difficulty of translating these results to humans is recognized, it would be reasonable to assume that, in humans, local CBF of the upper brain stem is also severely impaired when anisocoria is observed (that is, at the beginning of uncal herniation).

The increase in blood pressure occurring with intracranial hypertension (Cushing response) has been thought of as a compensatory mechanism to preserve CBF by maintaining CPP in the face of rising ICP. Previous experiments have demonstrated that the Cushing response is evoked when the ventricular pressure reaches a mean value of 92.0 ± 5.8 mm Hg in a cold lesion of the cerebral cortex, and when the infratentorial pressure exceeds 45 mm Hg in a supratentorial mass in cats. Our data correspond with these results. For many years, it has been a matter of controversy whether the blood pressure response results in a significant increase in blood flow, especially in the brain stem. In experimental studies of brain swelling, Shalit and Cotev observed that elevated MABP was followed by a marked increase in ICP and a decrease in cortical CBF. They concluded that the Cushing response could not be regarded as a beneficial, compensatory mechanism, but rather as a deleterious phenomenon. In Rowan and Teasdale’s study of acute intracranial hypertension with cisterna magna infusion, the blood pressure response produced no significant increase in the brain-stem blood flow in four out of six baboons. Zierski, et al., reported that, in supratentorial mass lesions, reactive systemic hypertension at the state of complete midbrain herniation resulted in only a small increase or further decrease of CPP, with no noticeable improvement of local CBF of the cats’ brain stem. Our

J. Neurosurg. / Volume 60 / March, 1984

S. Nagao, et al.
Intracranial hypertension and brain-stem blood flow

results showed that the Cushing response was evoked when the mean local CBF of the medulla oblongata was 22.8 ml/100 gm/min (70.4% of the control value) and was associated with no significant increase in either CPP or local CBF of the medulla oblongata. This experimental model does not clarify whether medullary ischemia or mechanical stress on the medulla oblongata are predominantly responsible for the cause of the Cushing response. However, our experience in this series suggests that an increase in MABP in intracranial hypertension is not a beneficial compensatory mechanism to increase brain-stem blood flow.

Acknowledgment

The authors gratefully acknowledge the suggestions and revisions of Dr. Robert A. Moody, Chairman of Neurosurgery, Guthrie Clinic, Sayre, Pennsylvania.

References


Manuscript received April 7, 1983. Accepted in final form August 30, 1983.

Address reprint requests to: Seigo Nagao, M.D., Department of Neurological Surgery, Okayama University Medical School, 2-5-1 Shikata-cho, Okayama, Japan.