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Intracranial pressure changes following middle cerebral artery occlusion in rats

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Summary. Prolonged recording of intracranial pressure (ICP) was performed on rats subjected to middle cerebral artery (MCA) occlusion. ICP was repeatedly recorded before and after occlusion of the vessel via a narrow catheter placed in the cisterna magna. MCA occlusion was followed by an increase in ICP, and a pressure peak occurred after 12–24 h in all animals. Subsequently, essentially two patterns of ICP changes were observed. These seemed to be related to the severity of neurological deficits and extension of the infarct area. In the most severely affected animals, raised ICP was noted throughout the 1st week after MCA occlusion; in rats with reversible neurological deficits, ICP returned to normal values after the first peak at 12–24 h. The present investigation shows that prolonged ICP recording is feasible in MCA-occluded rats. The MCA occusion model in rats is well characterized. Thus, ICP registration can be used in conjunction with other methods for evaluating treatment against increased ICP.

Key words: Intracranial pressure – Rats – Middle cerebral artery – Arterial occlusion – Neurological deficit

Introduction

Ischemic stroke remains the third largest cause of death in the industrial world [3]. In the acute phase of the disease, death is most commonly due to increased intracranial pressure (ICP) causing transtentorial herniation [14, 18, 19, 23]. Increased ICP may also aggravate patient's neurological deficit and probably also the size of the cerebral infarct [15, 18, 29, 23]. These circumstances motivate studies on intracranial pressure in focal cerebral ischemia.

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Cerebral edema appears to be a predominant cause of increased ICP in ischemic stroke [6, 7, 12, 14–16, 19]. In the patients, affected it is difficult to study the relation between ICP changes, edema formation and resolution, and cerebral tissue injury owing to the complexity of the disease and to variations between individual patients. An animal model is preferable for detailed studies of the pathophysiological events that lead to increased ICP in focal ischemia. We used the middle cerebral artery (MCA) occlusion model in rats [1, 24] for investigation of various aspects of focal brain ischemia. In this model, cerebral infarcts of rather uniform size and location – resembling those seen in man – can be produced [17]. The aim of the present study was to develop a method for prolonged recording of ICP in MCA-occluded rats in order to obtain basic information about ICP changes in this model. We have previously demonstrated that our model is effective for measurements lasting 8–12 h [11, 12].

Materials and methods

The sample consisted of 30 male Sprague-Dawley rats (320–420 g). They were allowed free access to food and water. During all surgical procedures the animals were anesthetized by i.p. injection of 1.3–1.5 ml of a mixture containing 4.25% chloral hydrate and 0.97% pentobarbital. They were breathing spontaneously.

ICP was measured via a narrow catheter (Portex pp 50) placed in the cisterna magna [5, 11, 21] and fixed to the skull with tissue glue (Histoacryl B: Braun, Melsungen, FRG) and dental cement (Zinc Cement; De Trey, UK). Figure 1 shows the method of catheter implantation. Out of 30 rats only 13, in which the catheters were patent for longer than 3 days, were included in the evaluation. The other 17 rats were excluded from this study.

MCA occlusion was performed in 10 rats as described by Tamura et al. [24]. MCA was coagulated from a point proximal to the olfactory tract to the inferior cerbral vein [1]. In 2 sham-operated rats, the same procedure was performed, but the MCA was not coagulated. In 1 rat a catheter was implanted only into the cisterna magna. The neurological status was assessed 6 h after MCA occlusion and then daily, using a grading system described elsewhere [1, 4] (grade 0, normal; grade I, forelimb flexion; grade II, forelimb flexion and decreased resistance to lateral push).

ICP (cerebrospinal fluid pressure in cisterna magna) was registered on a Grass polygraph model 70. Before each recording, the patency of the catheter was checked by confirming the

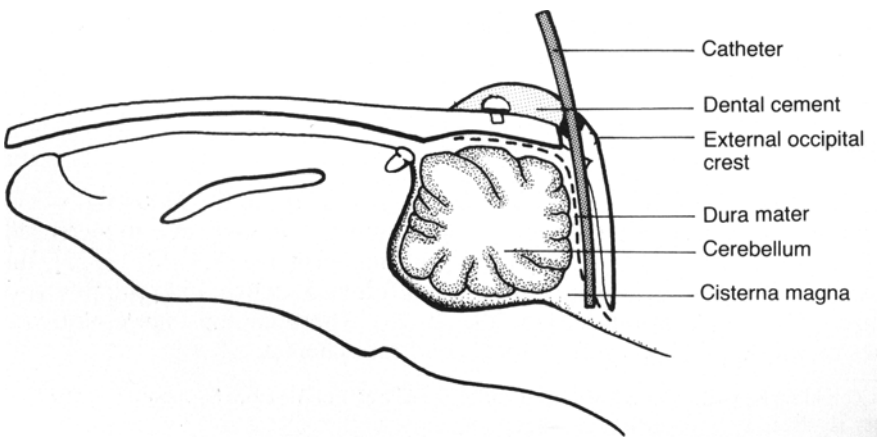

Fig. 1. Schematic showing the technique of implantation of the catheter into the cisterna magna

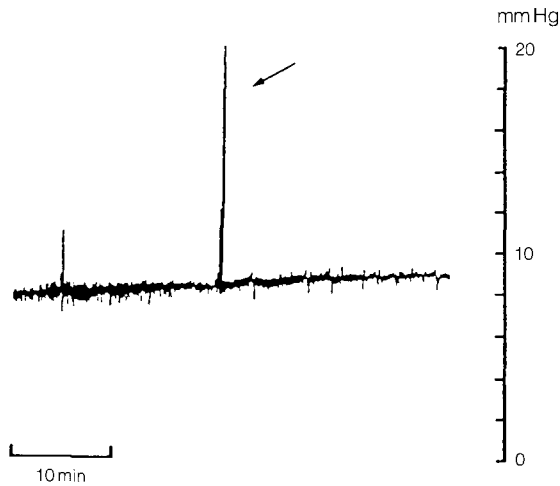

Fig. 2. ICP registration. *Arrow* indicates Valsalva maneuver

presence of cerebrospinal fluid pulsations. The catheter was connected via an air-free fluid system to a pressure transducer (model p 23 Id; Gould Statham Instrument, Puerto Rico). The patency of the system was further confirmed by a Valsalva maneuver, in which the thorax was gently compressed, resulting in a sudden increase in ICP (Fig. 2). Before starting this study, we performed continuous ICP reocrdings at different times, i.e. 2, 3, 5, and 7 days, after MCA occlusion , for 6–10 h in each case. We found that ICP levels were rather stable. Thus, in the experimental measurement, ICP was registered during MCA occlusion and for 3 h postoperatively. Subsequently measurements were made 4, 5, 6, and 12 h after surgery on unanesthetized rats, and then twice daily until the animals were killed. ICP recordings were performed for 5–10 min at each measurement.

After the end of the study, the rats were anesthetized and perfused through the heart with 200 ml of 4% buffered formaldehyde. Coronal sections of the brain were cut, embedded in paraffin, and stained with hematoxyline and eosin. The size of each infarct was estimated from camera lucida drawings of coronal sections at the level of the bregma. The area of each infarct was expressed as a percent age of the area of the contralateral hemisphere (relative size of the infarct) [17].

Results

Four MCA-occluded rats were studied for 7 days, one for 8 days, four for 9 days, and one for 15 days after MCA occlusion. All were neurologically assessed as grade II 24 h after surgery. Stable neurological deficits were recorded during the course of the experiment in seven animals. Three rats improved to grade I: one after 2 days, and two after 8 days. The control rats (one with catheter only and two sham-operated) showed no neurological deficits (grade 0) and no infarcts in histological studies.

After implantation of the catheter, ICP was approximately 5 mmHg (4–8 mmHg) in all rats. ICP decreased slightly during craniotomy after opening of the dura [8]. In the three control animals, ICP measured for 6–9 days varied between 5 and 8 mmHg (Fig. 3a).

Coagulation of the MCA did not immediately affect ICP, but within the first 2 h after surgery ICP rose to 10–15 mmHg. Subsequently, ICP changes appeared to follow different patterns. In three rats, the ICP curve showed the peak 12–24 h after occlusion; ICP values then dropped, reaching normal levels within 3–4

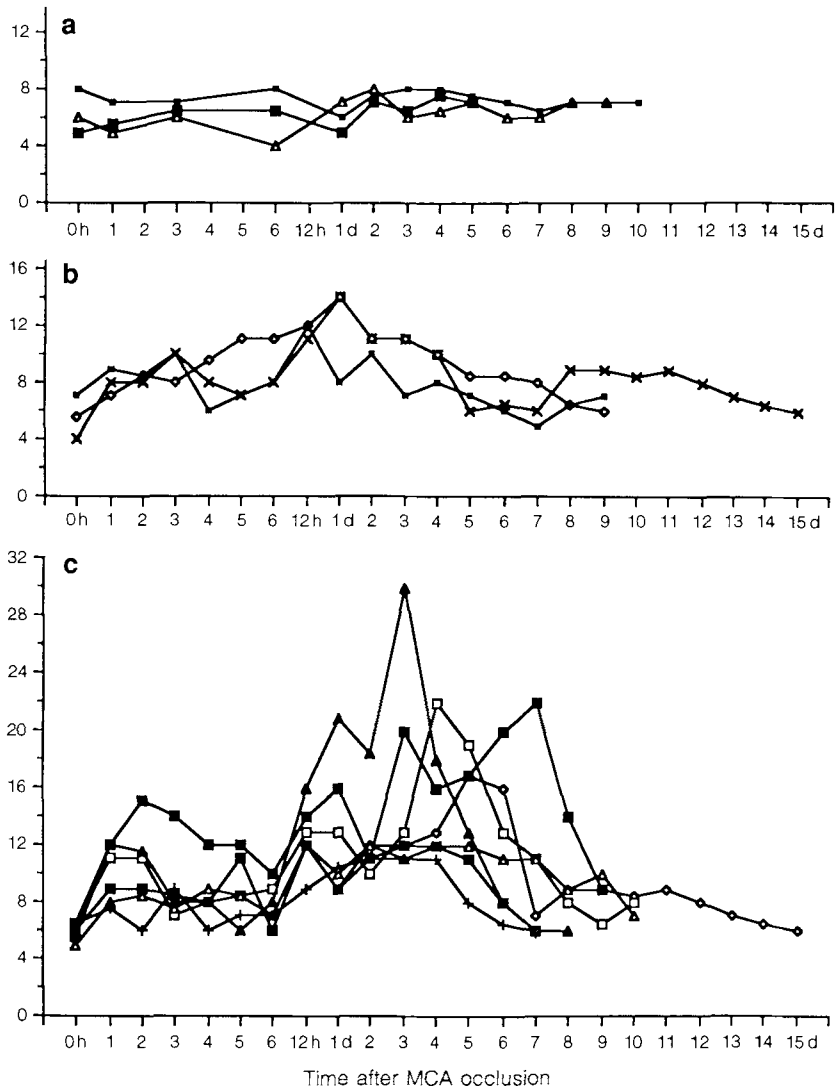

Fig. 3a. ICP in two sham-operated rats and one control rat. No differences are found. **b** ICP in three rats that showed neurological improvement and small infarcts. ICP is highest during the first two days after MCA occlusion. **c** ICP in seven non-improving rats with large infarcts. Note the second ICP peaks 3–4 days after MCA occlusion; h hours; d days

days (Fig. 3b). These rats improved neurologically from grade II to I and had relative infarct sizes of 9–15%.

Seven rats had stable neurological deficits and the relative sizes of their infarcts were 25–36%. In four animals, the ICP curves showed two peaks, one at 12–24 h and a second, higher peak at about 3 days (three rats) or 7 days (one rat) after occlusion. The remaining three rats in this group showed no clear second peak, but ICP remained at a level much higher than in the control group for up to 4 days before starting to decrease towards control values (Fig. 3c).

Discussion

The present study has shown that prolonged ICP registration is feasible in MCA-occluded rats. By implanting the catheter into the cisterna magna and fixing it to the skull, we were able to take repeated measurements of ICP in unanesthetized rats. However, in more than 50% of the animals ICP recordings could not be continued for more than 3 days because of obstruction of the catheter or dislocation of its tip from the cisterna magna.

ICP was measured in the cisterna magna, i.e., in the infratentorial compartment, and the cerebral lesion was supratentorial. In physiological conditions, ICP from the supratentorial compartment is easily transmitted into the posterior fossa [13]. With supratentorial lesions that do not produce transtentorial herniation and block basal cisterns there is full communication of pressure throughout the craniospinal axis [25]. MCA occlusion only rarely produces such large infarcts that herniation can take place [12, 17]. Thus, we believe that ICP recorded in the cisterna magna reflects real intracranial values.

MCA occlusion is always followed by an increase in ICP [9]. A pressure peak occurred after 12–24 h. Subsequently, essentially two patterns of ICP changes were observed and these seemed to be related to the severity of neurological deficits and the infarct's area. In rats with grade II deficits and large infarcts, increased ICP was noted throughout the 1st week after surgery. In improving rats with small infarcts, ICP returned to normal values after the first peak at 12–24 h. We found that ICP levels correlated with both the neurological grading system and the extent of the lesion. The second ICP peak coincided with the time of maximal enlargement of the affected hemisphere [17]. The ischemic lesion of the more affected rats apparently expanded to a critical size, which resulted in ICP increase. However, in less severely affected animals, the lesion did not reach such a critical size. The enlargement of the affected hemisphere appears to be due to cerbral edema [2, 7, 12, 22].

Some of our rats showed two distinct ICP peaks. It is tempting to assume that the first peak is related to time of maximal cytotoxic edema and the second one, to vasogenic edema [10, 26, 27].

The possibility of long-term recording of ICP in MCA-occluded rats in combination with other experimental methods makes it possible to perform detailed studies on the pathophysiology of focal cerebral ischemia. The course of ICP changes is important, because in clinical practice anti-edema treatment is based on ICP monitoring.

References

1. Bederson JB, Pitts LH, Tsuji M, Nishimura MC, Davis RL, Bartkowski H (1986) Rat middle cerebral artery occlusion: evaluation of the model and development of a neurological examination. Stroke 17:472–476
2. Bose B, Jones SC, Lorig R, Friel HT, Weinstein M, Little JR (1988) Evolving focal cerebral ischemia in cats: spatial correlation of nuclear magnetic resonance imaging, cerebral blood flow and histopathology. Stroke 19:28–37
3. Culicchia F, Mohr JP (1987) Morbidity and mortality of stroke. In: Moore WS (ed) Surgery for cerebrovascular disease. Churchill Livingstone, New York Edinburgh London Melbourne, pp 35–39
4. Germano IM, Bartkowski HM, Cassel ME, Pitts E (1987) The therapeutic value of nimodipine in experimental focal ischemia. J Neurosurg 67:81–87

5. Hårdemark HG, Persson L, Bolander HG, Hillered L, Olsson Y, Påhlman S (1988) Neuron-specific enolase is a marker of infarction development and size in a focal ischemia model. Stroke 19:1140–1144
6. Hatashita S, Hoff JT (1986) Cortical tissue pressure gradients in early ischemic brain edema. J Cereb Blood Flow Metab 6:1–7
7. Hatashita S, Hoff JT (1986) Role of hydrostatic pressure gradient in the formation of early ischemic brain edema. J Cereb Blood Flow Metab 6:546–552
8. Hatashita S, Hoff JT (1987) The effect of craniectomy on the biomechanics of normal brain. J Neurosurg 67:573–578
9. Hayakawa T, Waltz AG, Hansen T (1977) Relationships among intracranial pressure, blood pressure, and superficial cerebral vasculature after experimental occlusion of one middle cerebral artery. Stroke 8:426–432
10. Klatzo I (1967) Neuropathological aspects of brain edema. J Neuropathol Exp Neurol 26:1–14
11. Kotwica Z, Persson L (1989) The influence of nimodipine on intracranial pressure: experimental study in a rat model. Neurol Neurochir Pol 23:227–230
12. Kotwica Z, Persson L, Thuomas KA (1989) The effects of brain edema on intracranial pressure in focal cerebral ischemia: an experimental study in a rat using magnetic resonance imaging. Zentralbl Neurochir 50:68–71
13. Langfitt TW, Weinstein JD, Kassell NF, Simeone FA (1964) Transmission of increased intracranial pressure: I. Within the craniospinal axis. J Neurosurg 21:989–997
14. Ng LKY, Nimmannitya J (1970) Massive cerebral infarction with severe brain swelling: a clinicopathological study. Stroke 1:158–163
15. O'Brien MD (1979) Ischemic cerebral edema, a review. Stroke 10:623–628
16. O'Brien MD, Waltz AG, Jordan MM (1974) Ischemic cerebral edema. Arch Neurol 30:456–460
17. Persson L, Hårdemark HG, Bolander H, Olsson Y, Hillered L (1989) Neurologic and neuropathologic outcome after middle cerebral artery occlusion in rats. Stroke 20:641–645
18. Plum F (1961) Brain swelling and edema in cerebrovascular disease. Res Publ Assoc Res Nerv Dis 41:318–348
19. Ropper AH, Shafran B (1984) Brain edema after stroke: clinical syndrome and intracranial pressure. Arch Neurol 41:26–29
20. Sacquegna T, de Carolis P, Andreoli A (1984) Long-term prognosis after occlusion of middle cerebral artery. Br Med J 288:1490–1491
21. Sarna GS, Hutson PH, Tricklebank MD, Curzon G (1983) Determination of brain 5-hydroxytryptamine turnover in freely moving rats using repeated sampling of cerebrospinal fluid. J Neurochem 40:383–390
22. Schuier FJ, Hossmann KA (1980) Experimental brain infarcts in cats: Ischemic brain edema. Stroke 11:593–601
23. Silver FL, Norris JW, Lewis AJ, Hachinski VC (1984) Early mortality following stroke: a prospective review. Stroke 15:492–496
24. Tamura A, Graham DI, McCulloch J, Teasdale GM (1981) Focal cerebral ischemia in the rat: 1. Description of technique and early neuropathological consequences following middle cerebral artery occlusion. J Cereb Blood Flow Metab 1:53–60
25. Weinstein JD, Langfitt TW, Bruno LA, Zaren HA, Jackson JLF (1968) Experimental study of patterns of brain distortion and ischemia produced by an intracranial mass. J Neurosurg 28:513–521
26. Yamaguchi M, Shirakata S, Yamasaki S, Matsumoto S (1976) Ischemic brain edema and compression brain edema: water content, blood-brain barrier and circulation. Stroke 7:77–83
27. Young W, Rappaport ZH, Chalif DJ, Flamm E (1987) Regional brain sodium, potassium, and water changes in the rat middle cerebral artery occlusion model of ischemia. Stroke 18:751–759