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VARIATIONS IN BRAIN CAPSULE PRESSURE WITH THE ADMINISTRATION OF HYPERTONIC SOLUTIONS*

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Indexing Words

brain capsule pressure;
cerebrospinal fluid pressure;
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brain interstitial fluid pressure

Osamu MATSUO. *Variations in Brain Capsule Pressure with the Administration of Hypertonic Solutions.* Kobe J. Med. Sci. 19, 39-49, March 1973——In order to investigate the physiological significance of the fluid in the perforated capsule (BC) implanted in the brain parenchyma of dogs, hypertonic solutions of mannitol, urea and saline were intravenously administered, and the variations of the fluid pressure in BC and in cerebrospinal fluid (CSF) were both recorded and compared. Results obtained indicated the mode of pressure change in BC was different from those of CSF. The initial peak was small and flat in BC, but sharp and transient in CSF. The remarkable decrease of the pressure then followed in CSF as well as in BC. However, the rebound phenomenon was observed in CSF, but not in BC. These results indicated that the space in BC is independent from that of CSF, and is in nature an definitive extravascular space in the brain parenchyma. The relationship of the fluid space in BC to the brain interstitial fluid space was discussed.

INTRODUCTION

This study was done to investigate the effect of the intravenously administered hypertonic solutions on the fluid pressure in the capsule implanted in the brain of dogs. As reported previously by Adachi et al.,[1] a perforated capsule (BC) was implanted in the brain parenchyma of dog and the fluid pressure in the capsule was measured; this was essentially the same as Guyton's method.[3] The positive fluid pressure in the BC was apparently different from the negative fluid pressure in the capsule implanted in the subcutaneous or muscular tissue. The intracapsular fluid space in the subcutaneous or muscular tissue was reported by Guyton[3] to have free communication to the surrounding interstitial fluid space. So that the intracapsular fluid pressure was equal to the interstitial fluid pressure in the connective tissue surrounding the capsule. On the other hand, in the case of the capsule implanted

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in the brain parenchyma, the intracapsular fluid pressure could not be proved to be the brain interstitial fluid pressure, but the space in the BC was a definitive extravascular space in the brain parenchyma, independent of the cerebrospinal fluid (CSF) space.[2] However, the physiological significance of the fluid space in BC remained to be studied.

It is commonly known that the intravenously administered hypertonic solution can remove brain edema. This is possibly due to decreasing of the brain interstitial fluid. In the present study, the pressure change in BC was investigated by intravenously administering the hypertonic solutions which have the effect above mentioned, and the physiological response of the pressure in BC was inquired into. As a close relation of CSF to the brain interstitial fluid has been known, the CSF pressure measured was compared with the BC pressure.

MATERIALS AND METHODS

The materials and methods for the capsule implantation were essentially the same as those described previously.[1] The capsule used was a cylindrical acrylate capsule, 15 mm in length, 10 mm in diameter, having a projecting rim at the top, a rubber stopper, and rounded bottom with perforations (approximately 30 holes of 1 mm diameter) in the lower third.

Adult mongrel dogs weighing 8.7 to 12.8 Kg were anesthetized with pentobarbital sodium (Nembutal), and the capsule was then implanted aseptically as follows. A hole just suitable for the capsule size was trepanned in the right parietal region of the skull. The dura was incised and the free end pulled up through the open hole. The cerebral parenchyma in the hole was crossways scissored after the ligature of blood vessels running over the cortex and removed in part, and the capsule was then inserted into the brain parenchyma through the hole. The animals were postoperatively given penicillin and were kept in comfortable conditions.

The experiment was performed on the dog in which the capsule had been implanted more than four weeks before, under Pentobarbital podium anesthesia. The zero point and the reference pressure were set according to the procedure described previously.[1] An indwelling catheter was applied for the excretion of residual urine in the bladder, and then urine was collected. A 25 gauge syringe needle was inserted into the fluid space of BC through the skin and rubber stopper. A 22 gauge syringe needle was also inserted into the cisterna magna. These sterile needles were ocnnected to a strain-gauge transducer for the lower pressure range (P23BB, Statham Inst. and LPU-0.1, Tokyo Meas. Ins.) through a short hard polyethylen tube, and filled with sterile Ringer's solution. The pressure in BC and CSF was recorded on a multi-channel recorder (RM-150, Nihonkohden).

The pressure measurement was continued for a half to one hour until the pressure in steady state was recorded, and then hypertonic solutions were intravenously administered. The pressure recording was continued for 5 to 6 hours after the infusion of hypertonic solution.

Blood and urine were sampled before, immediately after, 30 min, one hour, and then every one hour after the administration of hypertonic solutions. Blood

samples were analyzed for hematocrit, sodium and potassium concentrations and osmotic pressure, and urine for volume and specific gravity. Sodium and potassium concentrations were determined by flame photometer (Model 205, Hitachi*), osmotic pressure by Knauel Halb-Mikro osmometer, and urine specific gravity by Uricon (Atago).

The 20% mannitol solution used was commercially obtained from Daiichi Kagaku Yakuhin (Tokyo). Hypertonic urea and saline solutions were freshly prepared before the experiments. With the hypertonic urea solution, 20% urea in distilled water was used in 3 cases, 20% urea in 5% invert sugar in 6 cases and 30% urea in 5% invert sugar in one case. Saline solution was of 10%. 90 ml to 150 ml (average 111.6 ml) of each solution was intravenously infused within one to 4 min with air-compressor. The average rate of infusion per Kg body weight was 5.8 ml/min/Kg in mannitol, 5.9 ml/min/Kg in urea and 4.3 ml/min/Kg in saline.

RESULTS

Effects of Hypertonic Mannitol Administration

The experiments of 20% mannitol administration were performed 13 times in 7 dogs.

1. BC

The continuous pressure recording was obtained in 6 cases without interruption (Fig. 1A). The BC pressure decreased when the infusion was started, followed by the increase on finishing the infusion, exceeded the initial level in about half cases, and reached to the maximum level at 4 to 58 min. Then the BC pressure decreased again gradually for the following 2 to 3 hours, and stayed lower than the initial pressure until the experiments were finished.

The initial pressure decrease had a significant correlation with the increase of serum osmotic pressure ($r = +0.6712$, $p < 0.05$).

2. CSF

The continuous pressure recording was obtained in 8 cases without interruption (Fig. 1B). The CSF pressure increased abruptly on starting the infusion, and decreased below the initial pressure. The maximum decrease in the CSF pressure appeared at about one hour after the administration, with the variation from 20 to 138 mmH_2O below the initial pressure. The rate of this pressure decrease did not have significant correlation with the increase in serum osmotic pressure. Thereafter, the CSF pressure increased gradually, reached the initial level about 2 to 4.5 hours after the infusion and still continued to increase. The rebound phenomenon was noticed in most cases.

* The flame photometer is kindly offered from the Department of Anesthesiology.

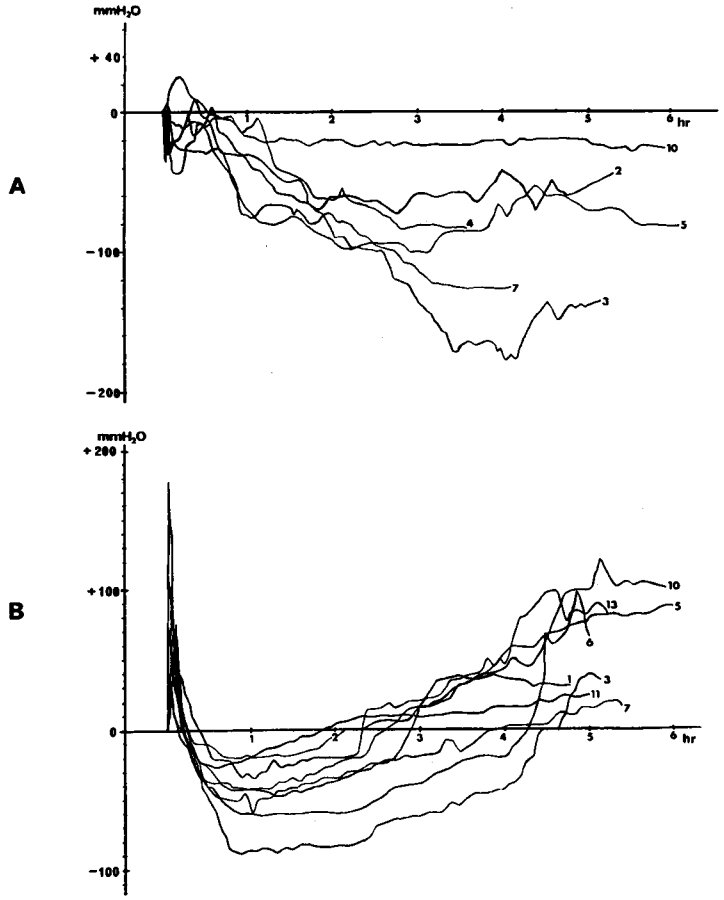

Fig. 1 Changes in pressure from the pre-infused level at zero time when 20% mannitol solution was infused.
Ordinate indicates pressure increase (+) or decrease (−) in mmH_2O after the infusion of 20% mannitol solution. Abscissa indicates the time (hour) elapsed after the infusion of 20% mannitol solution. The numbers attached on the trace indicate the number in the experimental series. A : BC pressure, B : CSF pressure.

The correlation between the pressure increase during the infusion and the rate of infusion per Kg body weight was significant ($r = +0.8793$, $p < 0.01$). Such pressure increase during the infusion as in the CSF was not observed in the BC.

Effects of Hypertonic Urea Administration

Hypertonic urea solution was administered 10 times in 6 dogs. In the case No. 5, 30% urea in 5% invert sugar was administered.

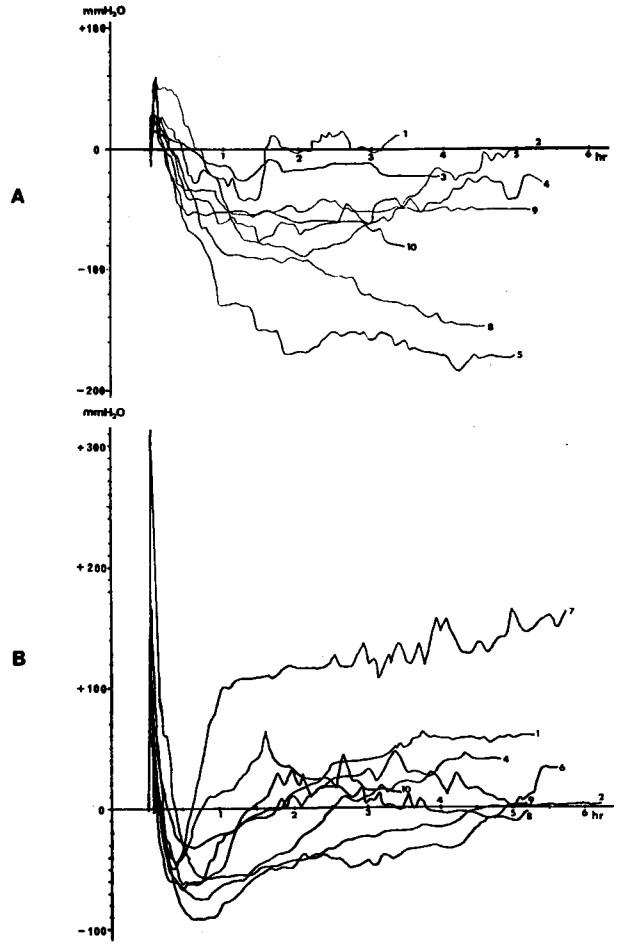

Fig. 2 Changes in pressure from the pre-infused level at zero time when the hypertonic urea solution was infused.
Ordinate indicates the pressure increase (+) or decrease (−) in mmH_2O after infusion of the hypertonic urea solution. Abscissa indicates the time (hour) elapsed after the infusion of the hypertonic urea solution. The numbers attached on the trace indicate the number in the experimental series. A: BC pressure, B: CSF pressure. In case No. 5, 30% urea in invert sugar was infused.

1. BC

The continuous pressure recording was obtained in 8 cases without interruption (Fig. 2A). In two cases that the infusion rate was low (4.89 ml/min/Kg), the BC pressure decreased transiently on starting the infusion, reached the minimum level at 1.1 min and then increased abruptly. In other cases that the infusion rate was high (6.55 ml/min/Kg), the BC pressure increased from the beginning of the

infusion, and reached the maximum level at 3 to 5 min. The rate of the pressure increase in the both had significant correlation with the infusion rate per Kg body weight ($r=+0.6618$, $p<0.05$).

The BC pressure in the both began to decrease and showed the maximum pressure decrease at 6 to 126 min. The BC pressure, thereafter, was kept low and then tended to increase gradually at 3 to 4 hours, but did not return to the initial level in most cases. In the case No. 5 in which 30% urea in 5% invert sugar was administered, the maximum pressure decrease was the greatest.

2. CSF

The continuous pressure recording was obtained in 8 cases without interruption (Fig. 2B). The CSF pressure increased remarkably on starting the infusion, fell down at the end of infusion or 1 to 2 min after the end of infusion, and showed the maximum pressure decrease at 30 to 40 min after the infusion. The CSF pressure then increased and reached the initial pressure at about 1.5 to 2.5 hours in most cases. In the cases that the CSF pressure returned quickly to the inital level, the rebound phenomenon was strongly manifested.

Effects of Hypertonic Saline Administration

10% saline solution was administered 9 times in 3 dogs.

1. BC

The continuous pressure recording was obtained in 7 cases without interruption (Fig. 3A). In four cases that the infusion rate was low, the BC pressure showed initial a slight decrease and then a large increase. In other cases that the infusion rate was high, the BC pressure increased from the beginning of the infusion. The BC pressure in the both reached the maximum level at 1 to 13 min, and stayed there in some cases for 5 to 25 min but in the other decreased soon. The BC pressure reached 40 to 60 mmH_2O below the initial level at 2 to 3 hours and remained low for long during the experiments, and did not return to the initial level within 5 to 6 hours.

2. CSF

The continuous pressure recording was obtained in 9 cases without interruption (Fig. 3B). The CSF pressure showed the rapid increase on starting the infusion and reached the maximum level at 1 to 6 min after starting of the infusion. The correlation between the rate of pressure increase and the infusion rate per Kg body weight was significant ($r=+0.7602$, $p<0.05$). The pressure then fell down remarkably and showed the minimum of 73 to 200 mmH_2O below the initial level at 30 to 100 min. Thereafter, the CSF pressure tended to increase and returned to the intial level at 3.5 to 5 hours. The rebound phenomenon was noticed in most cases.

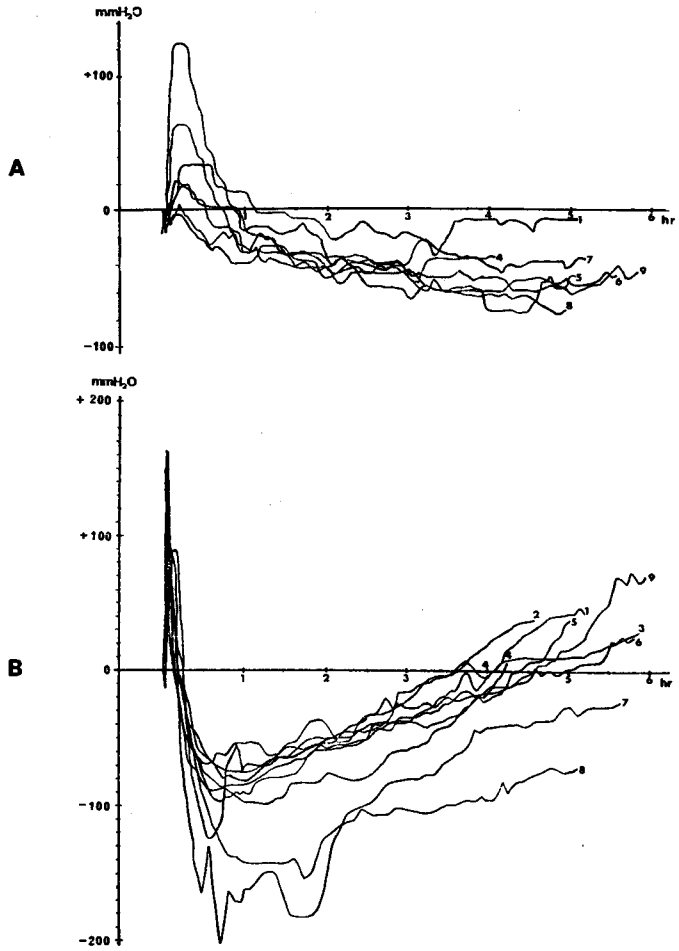

Fig. 3 Changes in pressure from the pre-infused level at zero time when 10% saline solution was infused.
Ordinate indicates the pressure increase (+) or decrease (−) in mmH_2O after the infusion of 10% saline solution. Abscissa indicates the time (hour) after the infusion of 10% saline solution. The numbers attached on the trace indicate the number in the experimental series. A: BC pressure, B: CSF pressure.

Effects of Hypertonic Solutions on Blood and Urine

Serum osmotic pressure increased greatly after the infusion of hypertonic urea and saline, and moderately after the infusion of mannitol (Fig. 4A). The decline in hematocrit was remarkable with mannitol, urea and saline in that order (Fig. 4B). Hematocrit returned to the control level about three hours after the infusion.

Serum sodium concentration increased remarkably with saline, but decreased with mannitol and urea (Fig. 4C). Serum potassium concentration decreased with saline and mannitol, but with urea it increased in the early stage (Fig. 4D).

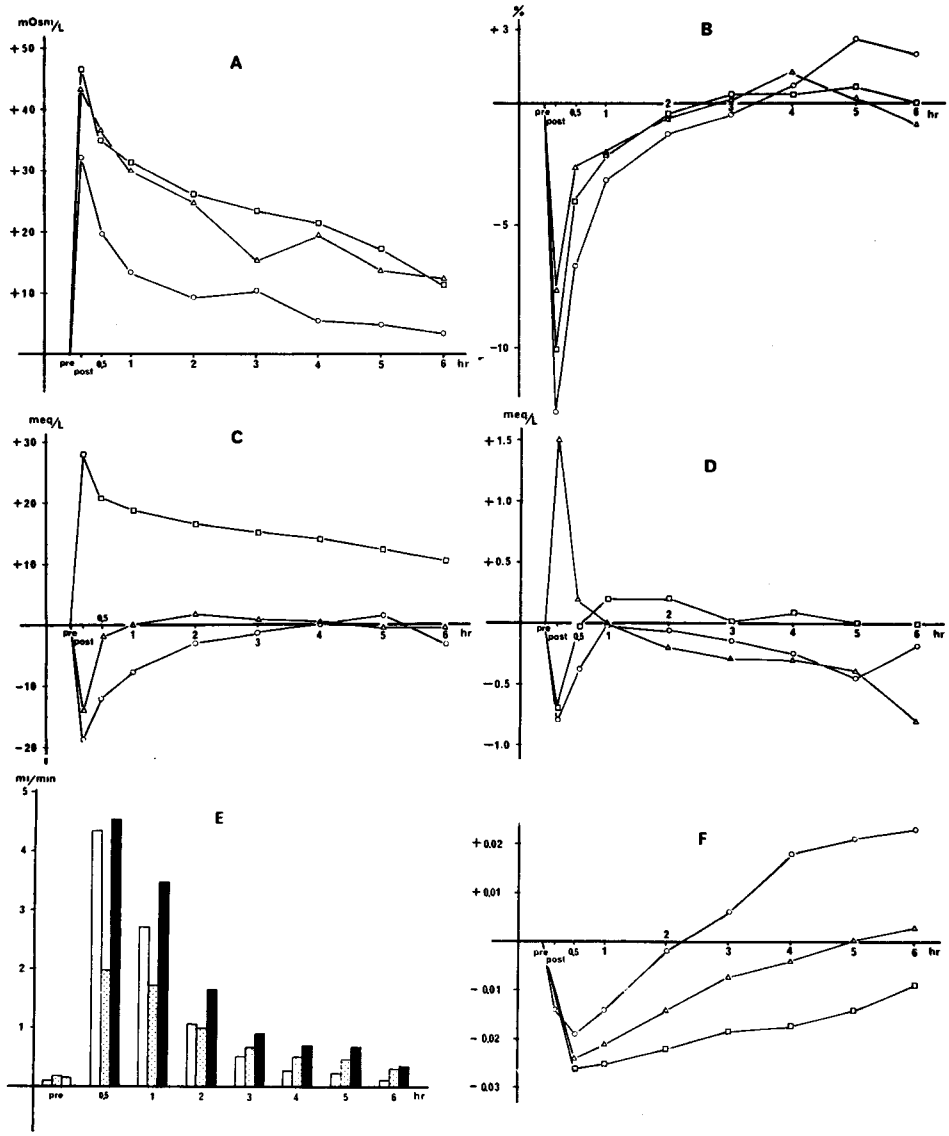

Fig. 4 Changes in serum osmotic pressure (A), hematocrit (B), serum Na (C) and K (D) concentrations, urine excretion rate (E) and urine specific gravity (F) after the administration of the hypertonic solutions.
Each point in A, B, C, D and F represents the mean of the deviated value at each time from the preinfused value. (+) means increase and (−) decrease. (○; mannitol, △; urea, □; saline) Each bar in (E) represents the mean rate of the urine volume at each time. (white bar; mannitol, dotted bar; urea, dark bar; saline) Abscissa indicates the time (hour) after the infusion of hypertonic solutions. Pre and post represent the time before and just after the infusion, respectively.

Urine excretion rate increased remarkably after the administration of hypertonic solutions (Fig. 4E). Total urine volume during the experiment was 3 to 5 times as much as the administered volume. Urine specific gravity decreased greatly on the maximum increase of urine volume (Fig. 4F).

DISCUSSION

It was previously reported by the author et al.[1] that the implantation of a perforated capsule into the brain parencyma of dogs caused tissue growth in the capsule and retention of fluid in the remaining space of the capsule. The fluid pressure in the capsule (BC) was positive, in contrast to the negative fluid pressure in the capsule implanted into the subcutaneous or muscular tissue. The negative fluid pressure in the capsule of the subcutaneous or muscular tissue was regarded by Guyton[3] to be equal to the interstitial fluid pressure in the tissue space surrounding the capsule. In the case of BC, the electrolyte concentrations in the intracapsular fluid was not similar to those of cerebrospinal fluid (CSF), but of plasma, and the histological examination indicated neither nerve cell nor glia cell in the tissue of BC was obserevd. Besides, the blood vessels in the tissue of BC were from those of the brain parenchyma. Therefore, the space in BC was concluded to be definitive and extravascular space, which may originate from the narrow space existed physiologically between the brain capillary and the glial membrane.[2] Actually the fluid pressure in BC was not equal to the pressure in the cerebral interstitial fluid. However, a question still remains ; what is physiological nature of the definitive extravascular space in BC. In approaching this problem the author investigated the mode of pressure change in the BC administering intravenously the hypertonic solutions the brain edema reducing effect of which has been known.

Since a large volume of hypertonic solutions was intravenously administered within several minutes in the present study, the pressure in BC and CSF might increase through the increase of intravascular volume and capillary pressure, and might decrease through the increase of serum osmotic pressure. This means that the effects of hypertonic solutions on the pressure in BC and CSF depend upon the net effect of two opposite directions of the pressure changes, and therefore may be somewhat complicated. However, the results obtained by the author indicated clearly that the pressure changes in the BC after the administration of hypertonic solutions are different from those of the CSF (Fig. 1, 2 and 3). That is: (A) In the initial phase, the BC pressure showed slow and rather flat pressure changes. On the other hand, the CSF pressure showed sharp and transient pressure changes. (B) In the latter phase, the BC pressure did not return to the initial level within 5 to 6 hours, in contrast with the CSF pressure which showed the rebound phenomenon in most cases.

It was shown that clear differences exist between the BC pressure change and the CSF pressure change after the administration of the hypertonic solutions even though the results were roughly analyzed. So, the author observed the differences in detail with the hope of discussing the cause for the differences. In the initial phase, with the hypertonic urea and saline solutions, the BC pressure increased slightly

and then decreased, and with the hypertonic mannitol solution, the BC pressure decreased during the infusion, then increased more or less on finishing the infusion, and slowly decreased again. On the other hand, with the hypertonic solutions the CSF pressure increased remarkably but transiently in the initial phase. Though the difference in the initial phase between the BC pressure change and the CSF pressure change was clear, any result to be able to explain directly the cause for the difference was not obtained. Only the abrupt increase in the CSF pressure can possibly be explained that the CSF pressure was increased due to the abrupt increase of the intracranial vascular volume and capillary pressure. As to the BC, the fluid space in BC hardly undergoes the pressure change in comparison with the CSF space.

In the latter phase, the BC pressures with the hypertonic solutions showed slow and lasting pressure change, and did not return to the initial level, whereas the CSF pressures showed fast pressure change and the rebound phenomenon was observed in most cases. This difference in the latter phase seems to imply rather important meanings from the point of brain water content and equilibration of the administered solutes. By Reed and Woodbury[4] variation of brain water content with the administration of hypertonic urea solution was studied; after the administration of hypertonic urea solution, the CSF pressure promptly fell to a minimum level in 15 min and returned to the initial level in 2 hours, whereas brain water content decreased in one hour and returned to the initial level in 8 hours. Thus the author would notice that the time course of the change in brain water content was similar to that in the BC pressure obtained in the present studies. Then the equilibration of administered solutes between the blood and brain parenchym would be discussed. As to urea, the fact that urea enters the brain relatively slowly is known. Schoolar et al.[5] investigated the penetration and regional deposition of ^{14}C-labeled urea, and reported that the equilibration between white matter and plasma was not achieved until 12 hours after injection. According to Reed and Woodbury,[4] brain radioactivity increased slowly for 8 hours, and after that the brain-plasma ratio remained constant. As to mannitol, Wise et al.[6] investigated the penetration of ^{14}C-labeled mannitol from serum into CSF and brain, and demonstrated that the equilibrium with serum mannitol was not reached within 6 hours. These findings would offer good explanation on the evidence that the BC pressure did not show the rebound phenomenon within 5 to 6 hours, and that the CSF pressure returned to the initial level and then showed the rebound phenomenon within 5 to 6 hours. Based upon the difference in the pressure changes considering the discussion on the equilibrium of the administered solutes and on the brain water content, it is possible to assume that the pressure change in BC reflects water balance in the brain better than that in the CSF. However, the author does not insist that the BC pressure represents directly the brain interstitial fluid pressure. Nevertheless, the author suggests that the BC implantation method can be used as an experimental material in a sense though the BC pressure is the third pressure in the brain which is different from blood pressure and CSF pressure.

SUMMARY

A perforated capsule (BC) was implanted into the brain parenchyma of dogs, and the effects of the intravenously administered hypertonic mannitol, urea and saline solutions on the fluid pressure in BC were investigated. The cerebrospinal fluid (CSF) pressure was simultaneously measured for the reference of the BC pressure.

1) The degree and time course of the pressure change in BC after the administration of the hypertonic solutions were not the same as those in CSF.

a. The initial phase: With the hypertonic urea and saline solutions, the BC pressure increased slightly and then decreased. With the hypertonic mannitol solution, the BC pressure decreased during the infusion, increased on finishing the infusion, and slowly decreased again. On the other hand, the CSF pressures with the hypertonic solutions increased remarkably but transiently.

b. The latter phase: The BC pressures with the hypertonic solutions showed slow and lasting pressure change and did not return to the initial level. While the CSF pressure showed fast pressure change and the rebound phenomenon was observed in most cases.

2) The physiological significance of the fluid space in BC was discussed.

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