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Intracranial volume–pressure relationships during experimental brain compression in primates

3. Effect of mannitol and hyperventilation

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SYNOPSIS In 10 anaesthetized and ventilated baboons a steady level of raised intracranial pressure was achieved by graduated inflation of an extradural balloon. Measurements were made of the ventricular fluid pressure, and of the change in this pressure after injection of 0·05 ml into the ventricle, the volume–pressure response. This response was studied at normocapnia and at hypocapnia (induced by hyperventilation), and before and after the intravenous administration of mannitol under normocapnic and hypercapnic conditions. During hypocapnia, ventricular fluid pressure and the volume–pressure response were reduced equally. Mannitol, however, caused a greater reduction in the volume–pressure response than in ventricular fluid pressure. The intravenous administration of mannitol therefore produces a beneficial effect on intracranial capacitance which is greater than observation of intracranial pressure alone indicates.

In a previous experimental study it was established that a measure of the reserve capacity of the intracranial contents to compensate for volume addition to the cranium may be obtained by observing the response of the ventricular fluid pressure (VFP) to an induced change in the volume of the lateral ventricle. During continuous brain compression in baboons this measurement, termed the volume–pressure response (VPR), was found to correlate closely with VFP (before induced ventricular volume change) and with balloon volume (Leech and Miller, 1974a). Measurement of the VPR also provides useful information in patients during continuous monitoring of intracranial pressure (Miller *et al.*, 1973).

In the present study, measurements of VFP and VPR were used to explore the effect on intracranial volume–pressure relationships of two methods in clinical use for the reduction of raised intracranial pressure, hypertonic mannitol solution, and induced hypocapnia. Intravenous mannitol was administered not only at normocapnia but also at hypercapnia, and the results compared with those observed during hypocapnia, produced by imposed hyperventilation.

EXPERIMENTAL METHODS

Ten anaesthetized ventilated baboons (body weight 8 to 11·5 kg) were studied. The anaesthesia, surgical preparation, and methods of recording systemic arterial pressure (SAP) and VFP have been described previously (Leech and Miller, 1974a). The VPR was calculated from the change in mean VFP after an injection into the lateral ventricle of 0·05 ml normal saline over one second. Cerebral blood flow (CBF) was measured from the right cerebral hemisphere by the intracarotid ^{133}Xe technique (Rowan *et al.*, 1970) over a 10 minute period of isotope clearance. Arterial blood gases were checked throughout the study with a direct reading electrode system.

Cerebral compression was achieved by slowly inflating an extradural balloon in the right frontal region using a variable speed infusion pump (Slow Infusion Apparatus—SRI 5200). Inflation was started at 1 ml in six minutes and continued at this rate until VFP increased to 40 mmHg (at this stage the balloon volume was approximately 6 ml); the rate of inflation of the balloon was then adjusted to maintain a constant level of increased VFP. In a

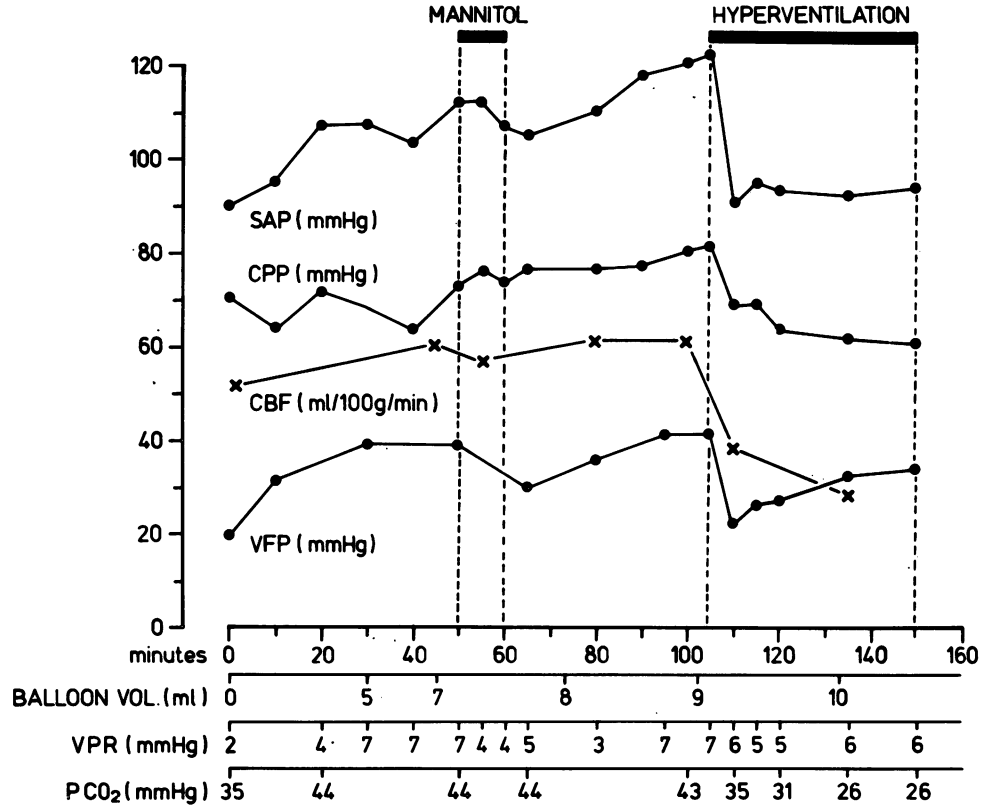

FIG. 1. *Studies of the changes in intracranial volume–pressure relationships caused by mannitol and hyperventilation, data from one baboon. Note that mannitol reduces VPR more than VFP, but has little effect on CBF. Hyperventilation reduces VPR and VFP equally, and also reduces CBF and SAP.*

control experiment, steady state conditions of VFP, VPR, and SAP were maintained for 2½ hours by this method, the only change being an increase in the clearance time of the volume addition. It was against this background that the agents for reducing VFP were assessed (Fig. 1).

Statistical analysis of results was performed using the paired *t* test.

PROTOCOL

MANNITOL AT NORMOCAPNIA (10 baboons) When VFP was elevated ($M \pm SE = 46{\cdot}3 \pm 3{\cdot}7$ mmHg) and normocapnia obtained ($M \pm SD = 41{\cdot}5 \pm 1{\cdot}7$ mmHg), the control measurements were made. An intravenous infusion of 20% mannitol (0·5 g/kg) was then administered over 10 minutes. At 5, 10, 15, 30, and 45 minutes after the commencement of the mannitol, measurements of VFP, VPR, and SAP were recorded. CBF was measured at five and 30 minutes in six of the 10 animals.

MANNITOL AT HYPERCAPNIA (five baboons) The effect of mannitol was also studied at hypercapnia in five of the 10 animals in the normocapnia series, the order of the two studies being randomized. To produce hypercapnia, carbon dioxide was added to the inspired gases and the end tidal CO_2 monitored using an infra-red analyser. When a steady state was obtained (VFP: $M \pm SE = 61{\cdot}2 \pm 4{\cdot}9$ mmHg; PCO_2: $M \pm SD = 53{\cdot}8 \pm 1{\cdot}3$ mmHg), intravenous mannitol was administered and measurements performed as described for normocapnia.

HYPOCAPNIA (five baboons) The five animals used to study mannitol at normocapnia, but not at hypercapnia, were hyperventilated to produce hypocapnia (Fig. 1). Again the order of the two studies was

TABLE 1

MANNITOL AT NORMOCAPNIA (M ± SE)

Time (min)	*VFP (mmHg)*	*VPR (mmHg)*	*SAP (mmHg)*	*CPP (mmHg)*	*CBF (ml/100 g/min)*
0	46·3 ± 3·7	7·6 ± 1·0	95·0 ± 4·8	48·7 ± 5·1	40·3 ± 4·8
5	42·8 ± 3·8	3·3 ± 0·7***	93·0 ± 4·4	50·2 ± 5·1	39·6 ± 3·8
10	37·5 ± 4·1**	3·1 ± 0·7***	92·0 ± 4·1	54·5 ± 5·1	
15	36·9 ± 4·4**	3·6 ± 0·6***	92·1 ± 4·4	55·2 ± 6·2	
30	39·1 ± 4·4*	3·3 ± 0·4**	91·2 ± 4·8	52·1 ± 6·2	38·8 ± 4·8
45	44·4 ± 4·2	4·1 ± 0·7*	96·8 ± 5·0	52·4 ± 3·9	
N	10	10	10	10	6

Significance of differences from values at control (0 minutes). *** P < 0·001. ** P < 0·02. * P < 0·05.

TABLE 2

MANNITOL AT HYPERCAPNIA (M ± SE)

Time (min)	*VFP (mmHg)*	*VPR (mmHg)*	*SAP (mmHg)*	*CPP (mmHg)*
0	61·2 ± 4·9	6·6 ± 0·9	106·4 ± 8·2	45·2 ± 11·0
5	59·4 ± 5·7	4·0 ± 0·6	107·4 ± 11·9	48·0 ± 16·3
10	55·6 ± 6·1	4·8 ± 1·3*	104·8 ± 11·1	49·2 ± 14·1
15	53·6 ± 5·1	4·6 ± 1·4**	97·8 ± 5·8	44·2 ± 8·6
30	53·6 ± 5·1*	4·0 ± 1·3**	98·4 ± 6·5	44·8 ± 10·7
45	62·5 ± 4·6	3·5 ± 0·9***	89·5 ± 4·8	27·0 ± 12·3
N	5	5	5	5

Significance of differences from values at control (0 minutes). *** P < 0·001. ** P < 0·02. * P < 0·05.

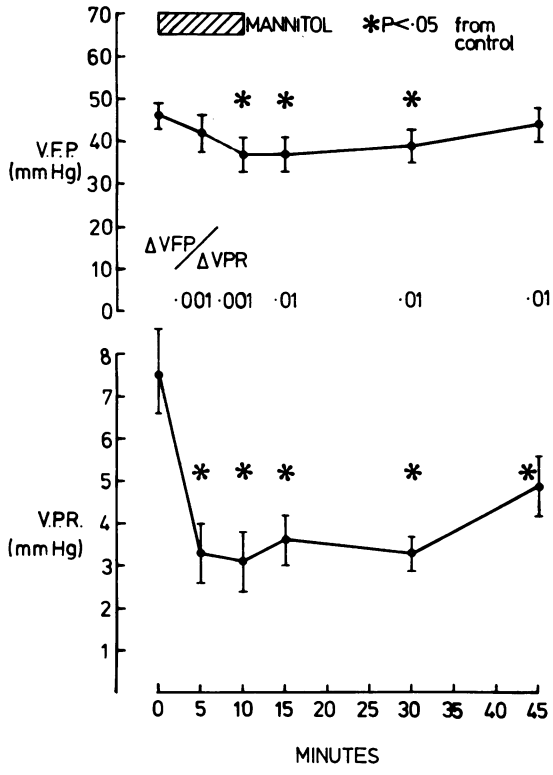

FIG. 2. *Mannitol at normocapnia (N = 10, M ± SE). Both VFP and VPR are significantly reduced by mannitol. Asterisk indicates P value at least less than 0·05 from control (at 0 minutes). Greater reduction in VPR than in VFP throughout the study. P values for ΔVFP/ΔVPR are shown. See Table 1.*

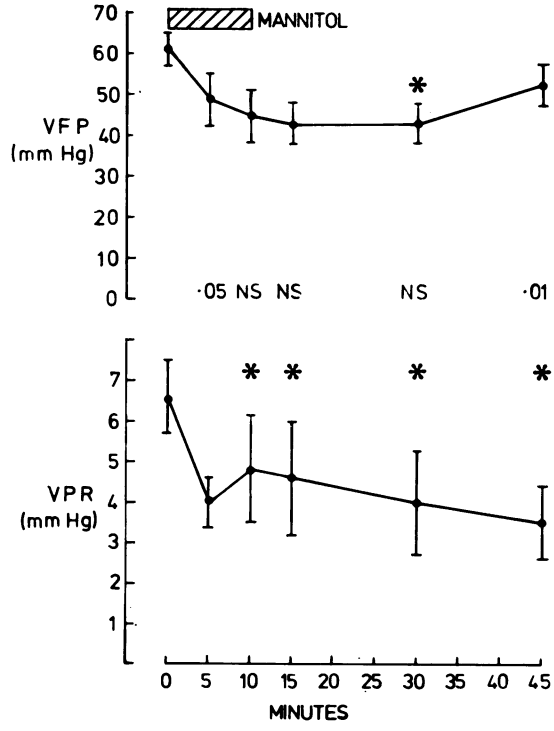

FIG. 3. *Mannitol at hypercapnia (N = 5, M ± SE). Reductions in VFP and VPR less marked than at normocapnia. Asterisk indicates P value at least less than 0·05 from control (at 0 minutes). Greater reduction in VPR than in VFP recorded at five and 45 minutes after commencing mannitol. P values for ΔVFP/ΔVPR are shown. Note control VFP at hypercapnia greater than control VFP at normocapnia (Fig. 2). See Table 2.*

TABLE 3

HYPOCAPNIA (M ± SE)

Time (min)	*VFP (mmHg)*	*VPR (mmHg)*	*SAP (mmHg)*	*CPP (mmHg)*	*CBF (ml/100 g/min)*	*CVR (mmHg/ml/100 g/min)*	*$PaCO_2$ (mmHg) M ± SD*
0	43·6 ± 6·8	6·8 ± 0·6	102·4 ± 7·2	58·8 ± 7·3	38·6 ± 6·1	1·60 ± 0·23	41·8 ± 1·9
5	29·0 ± 3·2*	5·0 ± 0·9**	85·4 ± 4·2	56·4 ± 5·0	31·6 ± 3·1	1·80 ± 0·24	27·6 ± 4·2
10	30·8 ± 4·1**	4·8 ± 0·9**	87·6 ± 4·7	56·8 ± 5·1			
15	35·0 ± 5·0*	4·8 ± 0·6*	88·6 ± 3·4	53·6 ± 5·2			
30	38·2 ± 6·3	5·8 ± 0·6	87·0 ± 6·2	48·8 ± 7·4	26·8 ± 3·2	1·81 ± 0·20	22·8 ± 2·9
45	42·8 ± 7·5	6·2 ± 0·9	88·4 ± 8·1	45·6 ± 9·2			
N	5	5	5	5	5	5	5

Significance of differences from values at control (0 minutes). ** $P < 0.02$. * $P < 0.05$.

randomized. After reaching a steady state (VFP: M ± SE = 43·6 ± 6·8 mmHg; PCO_2: M ± SD = 41·8 ± 1·9 mmHg), the tidal volume delivered by the ventilator was abruptly increased without changing the stroke rate. Arterial PCO_2 fell to 27·6 ± 4·2 mmHg in five minutes, and to 22·8 ± 2·9 mmHg after 30 minutes of hyperventilation. Starting five minutes after the onset of hyperventilation, measurements of VFP and VPR were performed at the same time intervals and in the manner as previously described. CBF was measured as before, after five and 30 minutes of hypocapnia.

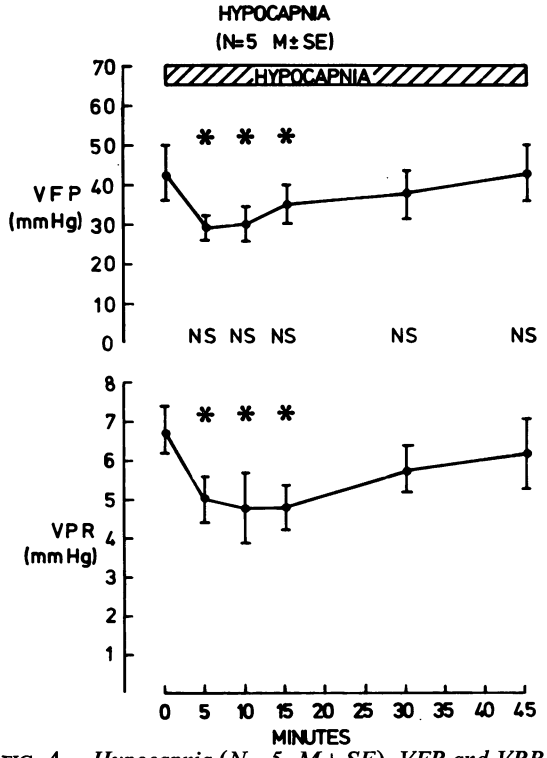

FIG. 4. *Hypocapnia (N = 5, M ± SE). VFP and VPR are reduced equally. Asterisk indicates P value at least less than 0·05 from control (at 0 minutes). No significant difference between ΔVFP and ΔVPR recorded throughout the study. See Table 3.*

RESULTS

VENTRICULAR FLUID PRESSURE (VFP) Significant reductions in VFP were produced by each of the manoeuvres in this study. Mannitol at normocapnia (Table 1; Fig. 2) produced the maximum reduction at 10 minutes (19%) and 15 minutes (20%) after commencement of the infusion. During hypercapnia (Table 2; Fig. 3) mannitol had less effect on VFP, with maximum reduction of 12% at 15 and 30 minutes. During hypocapnia (Table 3; Fig. 4), the most pronounced reductions in VFP were observed five minutes (33%) and 10 minutes (29%) after commencement of hyperventilation. Despite continuing hypocapnia, VFP rose towards control levels at 45 minutes.

VOLUME–PRESSURE RESPONSE (VPR) Between five and 30 minutes after the commencement of mannitol at normocapnia, VPR was reduced by more than 50% (Table 1; Fig. 2). The maximum response of VPR to mannitol at hypercapnia was a reduction greater than 39% at five, 30, and 45 minutes after commencement of the infusion (Table 2; Fig. 3). During hypocapnia, VPR was reduced maximally at five minutes (26%), 10 minutes (29%), and 15 minutes (29%) after the commencement of hyperventilation (Table 3; Fig. 4).

With mannitol at both normocapnia and hypercapnia, the reduction from control levels in VPR was greater in both duration and magnitude than the reduction in VFP (Figs 2, 3).

At normocapnia, the reduction in VPR was significantly greater than that of VFP at all times at which the two parameters were recorded after commencement of the mannitol. When mannitol was administered at hypercapnia, the reduction in VPR was significantly greater than the reduction in VFP only at the five and 45 minute levels.

During hypocapnia, the reductions in VPR followed a strikingly similar pattern to the reductions in VFP and at no time was there a difference between the behaviour of these two parameters (Fig. 4).

SYSTEMIC ARTERIAL PRESSURE (SAP) SAP remained relatively stable during the mannitol studies, but a fall was observed immediately after the commencement of hyperventilation. This reduced SAP was maintained at a relatively steady level thereafter despite falling PCO_2 and rising VFP.

CEREBRAL PERFUSION PRESSURE (CPP) This was calculated from the difference between SAP and VFP (Miller *et al.*, 1972). CPP rose after mannitol administration at both normocapnia and hypercapnia, but during hypocapnia, because of the fall in SAP, CPP remained steady during the initial phase despite the reduction in VFP. As VFP increased in the later stages of hypocapnia, CPP decreased, the maximum reduction being 13·2 mmHg from control values after 45 minutes of hyperventilation (Table 3).

CEREBRAL BLOOD FLOW (CBF) Mannitol did not significantly alter CBF at either normocapnia or hypercapnia, but a sharp decline in flow was registered during hyperventilation. This fall in CBF was greater than the reduction in CPP, so that there was an increase in cerebrovascular resistance, even allowing for the changes in SAP.

DISCUSSION

In an experimental study of the effect of therapeutic interventions, it is important to consider the relevance of the experimental model in terms of the clinical condition for which these therapeutic manoeuvres are prescribed in patients.

Intracranial hypertension produced in animals both with an inflated balloon and a cryogenic lesion has been reduced by 30–35% by vasoconstriction induced with both hyperventilation and hyperbaric oxygenation (Miller and Ledingham, 1971) and hyperventilation has achieved a 35% reduction in intracranial pressure in patients (Lundberg *et al.*, 1959). In the present study this compares with a reduction in intracranial pressure of 33% observed during hyperventilation. In addition, the reductions in VFP seen in the current study of 19% at 10 minutes and 20% at 15 minutes after commencing mannitol at normocapnia compare with a reduction in VFP of 22% in the first hour reported in patients by Johnston *et al.* (1972) using the same dose regime (0·5 g/kg).

The effects of hyperosmolar solutions on intracranial pressure have been recognized experimentally (Weed and McKibben, 1919) and exploited clinically (Wise and Chater, 1962) for many years. Few attempts have been made, however, to compare the effects of mannitol with other agents used to reduce raised intracranial pressure. Mannitol has been found to be more effective than hyperbaric oxygen in this respect (Miller, 1973).

Different mechanisms exist whereby intravenous mannitol and induced hypocapnia produce reduction of intracranial pressure. The effectiveness of intravenous mannitol depends, firstly, on an intact blood-brain barrier to permit the establishment of an osmotic gradient, and, secondly, on the volume–pressure status—that is, the amount of pressure reduction obtainable from the removal of a given volume of brain water. The contribution of this latter factor may be assumed to be the same for both methods of ICP reduction in this present study because the mechanism of hyperventilation is to reduce cerebral blood volume by cerebral vasoconstriction. The effectiveness of hypocapnia depends on the degree of responsiveness of cerebral blood vessels to changes in arterial PCO_2, which may vary under conditions of brain damage. Common to both techniques is that the maximum effect is produced on normal brain (Pappius and Dayes, 1965).

Although several studies have examined the

effects of mannitol and hyperventilation on ICP, less attention has been directed to their effect on intracranial volume–pressure relationships. Previous studies in patients have shown a linear correlation between VFP and the VPR (Miller *et al.*, 1973) and experimental studies have shown a direct relationship between VFP and VPR (Leech and Miller, 1974a). If the volume–pressure curve remains unaltered, therefore, a reduction in VFP produced by mannitol should be accompanied by an equal reduction in VPR. In this study, mannitol reduced the VPR considerably more than it reduced VFP, suggesting that the shape of the volume–pressure curve was altered, permitting the intracranial contents to accept a given volume addition more readily. That this effect was both earlier in appearance and longer lasting than reduction of VFP emphasizes the potential benefit of mannitol administration in raised intracranial pressure, particularly where the volume–pressure curve is at or near the critical steeply-rising stage (Langfitt, 1969). Since the volume-adding effect of cerebral vasodilatation will also be better compensated, abolition of plateau waves of raised intracranial pressure by a hyperosmolar solution (Lundberg, 1960) may be partly explained by the observations of this study. Circulatory dynamics do not appear contributory, since changes in SAP and CBF with hyperosmolar solutions were minimal in this and other studies in this laboratory (Harper and Bell, 1963; Johnston and Harper, 1973).

The action of hypocapnia in reducing both intracranial pressure (Lundberg *et al.*, 1959) and cerebral blood flow (Harper and Glass, 1965) are well documented. In this study, by contrast with the changes observed during mannitol administration, the effect of hyperventilation on VPR was a purely passive movement and VFP was strictly parallel, there being no specific influence on the intracranial volume–pressure relationships. Two mechanisms contributed to the fall in VFP. First, active cerebral vasoconstriction as evidenced by the rise in cerebrovascular resistance; second, the reduction in SAP which was produced by hyperventilation in these animals, combined with impaired autoregulation is likely to have been responsible for some reduction of both VFP and CBF. The reduction in arterial pressure during hypocapnia may also have contributed directly to the reduction in VPR (Leech and Miller, 1974b). Although the relative importance of these mechanisms is unclear, the changes recorded in the cerebral circulation are sufficient to account for the reduction in VFP during hyperventilation, and for the change of VPR parallel with that of VFP. Using an entirely different method of assessing intracranial volume–pressure relationships in the dog, Löfgren (1974) has concluded that variations in arterial PCO_2 do not affect intracranial elastance (inverse compliance) (Löfgren *et al.*, 1974). The results of the present study would support this view.

In comparing the effects of the two methods of reduction of raised intracranial pressure on the volume–pressure relationships within the cranium, mannitol may be described as reducing brain water volume and periventricular elastance, and hyperventilation as reducing cerebral blood volume without any influence on elastance. Although both methods have clinical merits and indications, this experimental study suggests that because mannitol has this double action and does not adversely influence the cerebral circulation, it provides a more satisfactory method of protecting the brain against the dangers of raised intracranial pressure.

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