Effects of mannitol and steroid therapy on intracranial volume-pressure relationships in patients

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The intracranial volume-pressure response was measured in 61 patients undergoing continuous monitoring of intraventricular pressure. This test, which determines the increase in intracranial pressure induced by an addition of 1 ml in ventricular CSF volume in 1 second, yields information concerning spatial compensation in patients with intracranial space-occupying processes. On the basis of variability tests, a change in volume-pressure response of 2 mm Hg/ml was accepted as significant. Pronounced enlargement of the ventricles interferes with the test. In patients with intracranial hypertension, intravenous mannitol (0.5 gm/kg) and intramuscular betamethasone (26 mg) both reduce the volume-pressure response significantly more than they reduce intracranial pressure. This suggests that these agents favorably alter the configuration of the volume-pressure curve.

KEY WORDS: volume-pressure response • intracranial pressure • mannitol • corticosteroids

RAISED intracranial pressure (ICP) is a common, though unpredictable, feature of many cerebral disorders, and reduction of increased ICP is an established part of neurosurgical management. Since the mechanism whereby ICP is decreased usually involves reduction in volume of one or more of the intracranial constituents (blood, CSF, or brain water), information concerning intracranial volume-pressure relationships is fundamentally important. This relationship is seen at its simplest during the expansion of an intracranial mass lesion at a steady rate. Initially there is a minimal increase in ICP, but as compensatory capacity is exhausted the curve rapidly steepens, and if expansion of the mass continues a pronounced increase in ICP results. Not only does the precise configuration of the volume-pressure curve differ in individual patients, but it is also influenced by the exact process responsible for intracranial hypertension and its rate of progress (Fig. 1). Despite this, the central clinical problem is a simple one, namely, how to tell whether a patient who has a normal or slightly raised ICP has adequate spatial compensatory reserve or is about to exhibit a marked increase in ICP in response to a small increase in intracranial blood, CSF, or brain water volume.

In previous studies we have shown that valid information concerning intracranial volume-pressure status can be obtained from patients undergoing continuous monitoring of
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FIG. 1. Graph showing three different theoretical curves relating the volume of an expanding mass lesion to intracranial pressure (ICP). At the same resting pressure (x) the addition of the same volume (y) produces three quite different increases in intracranial pressure.

ventricular fluid pressure (VFP) by measuring the increase in VFP produced by a small (1 ml) increase in CSF volume in the lateral ventricle.19,20 This measurement, termed the “volume-pressure response” (VPR),11 is an expression of brain (periventricular) elastance (ΔP/ΔV) and is equivalent to inverse compliance.10 The VPR is related to the height of ICP, showing an approximate linear correlation, with wide individual variation, in unselected patients.19,20 The VPR correlates closely with the volume of an intracranial expanding lesion in experimental animals11 and with the degree of angiographically determined brain shift in patients with head injury.21 This simple technique appears, then, to provide information of clinical benefit in the management of patients with raised ICP. Questions remain, however, concerning the repeatability of the test and influence on the VPR of factors such as ventricular size, arterial blood pressure and pCO2. The first two factors in this investigation receive particular attention. The second two factors have been examined in experimental animals,12-15 but have not been substantially studied in patients.

The effects of hyperosmolar solutions and of glucocorticoids in reducing ICP and producing clinical improvements are well documented3,4,5,17,18,24,27,29,30 On the other hand, there is little information concerning the effects of these agents on the intracranial volume-pressure relationship in patients. In a study carried out in anesthetised baboons subjected to expansion of intracranial extradural balloons we found that mannitol reduced the VPR significantly more than ICP, and suggested that this agent might actually be altering the shape of the volume-pressure curve of these animals subjected to experimental compression of the brain.13

The purpose of the present investigation was to examine this particular aspect of the effects of both mannitol and glucocorticoids administered to patients with raised intracranial pressure. We have been especially interested in the latter agent’s early effects, since patients receiving glucocorticoids sometimes show clinical improvements before any reduction in ICP is evident.7,8

Clinical Material and Methods

Patient Selection and Technique

Sixty-one patients have been observed; all of them were undergoing continuous monitoring of VFP with an intraventricular catheter16 as part of their investigation or management.5 The diagnoses covered a wide spectrum of neurological disorders (Table 1). The VPR was determined by inducing a ventricular CSF volume change of 1 ml in 1 second with a 3-way tap and by measuring the immediate change in mean VFP (calculated from diastolic plus one third of the pulse pressure). In most patients both subtraction and addition of fluid were carried out; volume subtraction was always the initial maneuver but the VPR was normally calculated from volume addition. When ICP was considerably raised (> 40 mm Hg) only volume subtraction was considered advisable. Arterial pressure was measured by sphygmomanometer. Four investigations were carried out.

Description of Studies

Variability Study. In nine patients, 10 series each of 10 consecutive VPR measurements were performed to calculate the random variation to be expected in carrying out this simple maneuver when no deliberate change was induced.

Study of Ventricular Size. An assessment of ventricular size was made in 44 patients, none of whom had large supratentorial mass lesions. Ventricular size was demonstrated by Conray ventriculography in 39 patients and by carotid angiography in the remaining five patients. Two groups were distinguished: 21 patients with normal ventricles and 23 with unequivocal ventricular enlargement. The VPR was elicited during the course of VFP
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TABLE 1

Diagnoses of patients studied

<table>
<thead>
<tr>
<th>Study Carried Out</th>
<th>Variability</th>
<th>Steroids Alone</th>
<th>Ventricular Size Alone</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>supratentorial tumors</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>head injuries</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>hydrocephalus including</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>posterior fossa mass</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>benign intracranial</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cerebrovascular disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td>9</td>
<td>8</td>
<td>4*</td>
<td>40†</td>
</tr>
</tbody>
</table>

* Since three patients received both mannitol and steroids, total number with steroids was seven.
† Since four patients who received mannitol were also included in the ventricular size study, the total number in this study was 44.
‡ There were 68 studies carried out in 61 patients.

monitoring within 24 hours of radiological demonstration of ventricular size in all cases.

Mannitol Study. Eight patients were studied following the administration of 20% mannitol solution given in an intravenous dose of 0.5 gm/kg over 10 minutes. Measurements of VFP, VPR, and arterial blood pressure were carried out prior to and 5, 10, 15, 30, and 45 minutes after the start of mannitol infusion.

Steroid Study. Seven patients were studied prior to and 24 hours following the administration of 26 mg of betamethasone given as 10 mg loading dose and 4 mg/6 hours. In measuring VFP, attention was directed to the resting pressure; the measurements of VPR used in this study were not made during pressure waves. Any change in the frequency of pressure waves following steroid administration was recorded, however.

Results

Variability Study

The mean VFP levels in the nine patients studied ranged from 3.9 to 39.2 mm Hg (Table 2). The variation in resting VFP in individual patients was much smaller, however, at 4.4 ± 3.0 mm Hg standard deviation (sD). The study was repeated in one patient following insertion of a ventriculoperitoneal shunt. The VPR ranged from 0 to 6 mm Hg/ml over the entire study. In each patient mean values and the standard deviation of 10 consecutive measurements of VFP and VPR were recorded (Table 2). The lack of relationship between mean VPR and the standard deviation indicated that the accuracy of measurement was not a function of the level of VPR. Although an average figure for the standard deviation is shown in Table 2, in this situation it is more correct to calculate the within-set standard deviation from the root-mean-square deviation. This yields a figure of 0.79 mm Hg/ml. The 90% and 95% confidence limits (1.6 and 2.0 sD) of this value are therefore 1.27 and 1.58 mm Hg/ml respectively. The 90% and 95% confidence limits for a difference between 2 consecutive measurements each having the variation shown are derived from 0.41

TABLE 2

Variability in 10 consecutive measurements of ventricular fluid pressure (VFP) and volume-pressure response (VPR)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Measurement No.</th>
<th>VFP (mm Hg) Mean ± SD</th>
<th>VPR (mm Hg/ml) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>20.3 ± 0.82</td>
<td>3.3 ± 0.67</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>16.2 ± 0.79</td>
<td>2.7 ± 0.48</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>38.4 ± 6.18</td>
<td>3.3 ± 1.64</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>3.9 ± 1.29</td>
<td>1.5 ± 0.85</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>6.4 ± 0.70</td>
<td>1.5 ± 0.53</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>39.2 ± 3.12</td>
<td>2.0 ± 0.47</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>24.9 ± 1.45</td>
<td>3.6 ± 0.84</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>16.5 ± 1.51</td>
<td>0.4 ± 0.70</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>17.5 ± 0.97</td>
<td>1.5 ± 0.71</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>15.7 ± 1.34</td>
<td>2.0 ± 0.00</td>
</tr>
<tr>
<td>mean</td>
<td>19.90 ± 1.82</td>
<td>2.18 ± 0.69</td>
<td></td>
</tr>
<tr>
<td>standard deviation</td>
<td>±11.67 ± 1.68</td>
<td>±1.02 ± 0.41</td>
<td></td>
</tr>
</tbody>
</table>
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\[ \sqrt{2} \times 1.58 \text{ mm Hg/ml}, \text{ that is } 1.79 \text{ and } 2.23 \text{ mm Hg/ml respectively.} \]

On this basis we regard a difference between successive measurements of VPR in a single patient of 2 mm Hg/ml or more as significant.

**Ventricular Size**

In the group of 21 patients with normal-sized ventricles (Fig. 2) a significant linear correlation was observed between the volume-pressure response and ventricular fluid pressure with:

\[ \text{VPR} = 0.16 \text{ VFP} - 0.08 \]  \(r = 0.84; \ p < 0.001\)

The scatter of data around the regression line was not very large, the 95% confidence limits (2 Sy) being 2.7 mm Hg/ml.

In the 23 patients with enlarged ventricles correlation between VPR and VFP was not significant, the regression equation being:

\[ \text{VPR} = 0.03 \text{ VFP} + 2.12 \]  \(r = 0.23; \ NS\)

NS means "not significant." The gradient of regression line was less and the data was more scattered. The results indicate that when ventricular enlargement is present, patients with raised intracranial pressure may still have low values of VPR. Hydrocephalus therefore limits the usefulness of VPR measurement in its present form.

**Mannitol Study**

The ventricular fluid pressure was reduced in all of the eight patients to whom intravenous mannitol was administered (Fig. 3, Table 3). Mean VFP fell 26% at 5 minutes from the start of the mannitol infusion; the maximum reduction of 34% occurred at 15 minutes and remained at this level throughout the 45 minutes of the study. Arterial blood pressure was not significantly changed by the administration of mannitol in this study.

Significant reductions in the volume-pressure response were recorded throughout the 45-minute periods, starting with 48% reduction at 5 minutes and attaining a maximum value of 70% reduction in VPR at 15 minutes, representing an actual reduction of 5.5 mm Hg/ml. When the percentage reductions in VPR and VFP were compared at each recording point in the study, significantly greater reductions of VPR than of VFP were noted at 10, 15, and 30 minutes from the start of administration of mannitol. It appears from the mean values shown in Table 3 that, after a maximum reduction at 15 minutes, VPR was beginning to rise although VFP remained low, suggesting that the VPR may be presaging a later increase in VFP toward control levels. Inspection of individual results indicated that this was often the case.
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FIG. 3. Graph showing effect of intravenous mannitol (0.5 gm/kg) on ventricular fluid pressure (VFP) and the volume-pressure response (VPR) in eight patients. Asterisks indicate the significance of differences from control. The figures in the center refer to the significance of the differences in the percentage changes in VFP and VPR. Mean values and standard error of the mean are shown.

Steroid Study

The striking feature about these patients was the marked difference between the early effects of steroids on the VFP and on the VPR (Fig. 4, Table 1). There was no change in the mean VFP, since modest reductions in the first five patients were balanced by increases in baseline VFP in the last two patients. However, the first patient, a woman with a frontal meningioma, prior to steroids had frequent plateau waves up to 80 mm Hg in height; their frequency and height were markedly reduced even after 24 hours of steroids. Two other patients with infrequent plateau-like waves prior to steroids had none by the following day. Steroid therapy did not affect arterial blood pressure.

The volume-pressure response was clearly reduced in all patients after 24 hours of steroid therapy; the mean reduction of 4.3 mm Hg/ml (61%) was highly significant. The greatest reduction in VPR was observed in the first patient, already referred to. The mean percentage change in VPR was significantly greater than the change in VFP (p < 0.02).

Discussion

Assessing the significance of changes such as those produced in this study by mannitol and steroids using the paired t-test may be misleading. Quite small changes, if they are consistent, can yield high significance values, and yet be less than the random variation observed with repeated testing under steady state conditions. For this reason we felt it important to establish a value for a significant change in VPR based on a variability study.

The changes in VPR produced by both mannitol and steroids in this study are therefore significant not only as regards the directional change in the mean value, but also in terms of the magnitude of the changes observed.

Since the VPR (ΔP/ΔV) is an index of inverse compliance of the intracranial contents and since the volume changes take place in

<table>
<thead>
<tr>
<th>Time of Observation</th>
<th>VFP mm Hg</th>
<th>p from Control</th>
<th>VPR mm Hg/ml</th>
<th>p from Control</th>
<th>p % Δ VPR</th>
<th>% Δ VFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>32.9 ± 4.8</td>
<td>—</td>
<td>7.9 ± 0.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>24.4 ± 3.0</td>
<td>&lt;0.01</td>
<td>4.1 ± 1.2</td>
<td>&lt;0.01</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>23.2 ± 3.7</td>
<td>&lt;0.01</td>
<td>3.2 ± 0.7</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>15</td>
<td>21.7 ± 3.1</td>
<td>&lt;0.01</td>
<td>2.4 ± 0.5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>30</td>
<td>21.9 ± 2.7</td>
<td>&lt;0.01</td>
<td>3.2 ± 0.7</td>
<td>&lt;0.001</td>
<td>&lt;0.02</td>
<td>NS</td>
</tr>
<tr>
<td>40</td>
<td>22.1 ± 1.9</td>
<td>&lt;0.02</td>
<td>3.6 ± 0.7</td>
<td>&lt;0.01</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

* Dosage = 0.5 gm/kg; values given are mean ± standard error; N=8; NS = not significant.
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the lateral ventricle, the volume of the ventricular system might be expected to influence the volume-pressure relationship, just as lung compliance is affected by lung volume. This did appear to be the case in the present study, and it helps to explain our earlier observation of wide variation in the relationship between VFP and VPR, since several of the patients studied at that time had ventricular enlargement. It is evident now that measurement of the VPR, as presently described, is not very helpful in the presence of hydrocephalus.

The extent to which mannitol reduced ICP in this study (26% to 34%) is similar to the 25% reduction recorded by Johnston, et al., using the same dosage schedule in patients, and to the 20% reduction observed by us in baboons subjected to brain compression. Greater reductions in ICP have been reported using larger doses of mannitol.

The striking effect of mannitol in this study, however, was the dramatic reduction in the volume-pressure response. The results in these patients were in this respect similar to results we found in baboons with extradural balloons. If an agent is administered to reduce ICP and it does not alter the actual volume-pressure relationship, then the fall in ICP should be matched by a proportionate fall in VPR. We have observed this during hypocapnia in primates subjected to brain compression, and Lofgren has found that changes in arterial pCO₂ in either direction do not alter the intracranial volume-pressure curve of dogs subjected to cisterna magna infusion of artificial CSF. The greater reduction in the VPR following mannitol administration suggests that the actual configuration of the intracranial volume-pressure curve was changed to render the intracranial contents more tolerant to volumetric additions, even though the actual reduction in ICP was modest.

The glucocorticoids betamethasone and dexamethasone have a less obvious immediate effect on ICP than mannitol, but in favorable cases, notably of chronic focal cerebral edema, the clinical improvement is rapid and dramatic. Previous studies emphasize a gradual response of ICP over 2 to 5 days, with a drop in the frequency of plateau waves and a shift of the frequency distribution of ICP values toward the lower range.

The responses observed in the present study are interesting in that VPR was significantly reduced in the first 24 hours, prior to any effect on baseline ICP. Again the data suggest that the configuration of the volume-pressure curve is being favorably altered by corticosteroids to permit greater spatial compensation. This is supported by diminution in the frequency of plateau waves observed in our own and others' studies, since plateau waves appear to be associated with vasodilatation in the presence of a tight brain, though not with increased CBF.
Conclusions

Both mannitol and steroids produced similar effects on brain elastance in this study; however, different mechanisms cause the brain water content reduction that both are thought to induce. Mannitol produces its osmotic effect across an intact blood-brain barrier and is therefore more likely to reduce water content in normal brain. The focal nature of the expanding lesions in many of the patients in this series may therefore have provided a favorable environment for the beneficial effects of mannitol. Steroids are thought to act in areas of focal brain swelling and certainly reduce the bulk of areas affected by brain edema. Other effects may contribute to the overall effect, however, such as the inhibition of CSF formation and improvements in local tissue perfusion in edematous areas.

The importance of the relationship between intracranial pressure and the volumes of the intracranial contents was first recognized by Monro in 1783 and was recently re-emphasized. The demonstration that both mannitol and steroids can so favorably influence the intracranial volume-pressure curve underlines their usefulness in the management of raised ICP, and may at least partly explain why improvement in the patient's neurological status may be found following their administration, even when there is little obvious effect on intracranial pressure itself.

References

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Intracranial volume-pressure relationships


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