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Intracranial volume–pressure relationships during experimental brain compression in primates

1. Pressure responses to changes in ventricular volume

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SYNOPSIS Intermittent additions of 0·05 ml saline were made into the lateral ventricle of anaesthetized, ventilated baboons at regular intervals during continuous inflation of a supratentorial extradural balloon. Close correlation was observed both between the increase in ventricular fluid pressure (VFP) immediately after the injection and the volume in the balloon ($P < 0·001$); and between the increase in ventricular pressure and the pressure immediately before the injection ($P < 0·001$). This change in ventricular fluid pressure, which is termed the volume–pressure response (VPR), helps to delineate the stage reached on the intracranial volume–pressure curve, and is therefore a measure of the capacity of the intracranial contents to compensate for the volume changes produced by an expanding intracranial lesion. The VPR is currently being used in patients and the clinical implications of confirming its validity experimentally are therefore discussed.

Intracranial hypertension is common in neurosurgical practice, and it is often necessary to manage patients with raised intracranial pressure by reducing the volume of part of the intracranial contents. Information concerning the volume–pressure relationships within the cranium is therefore of fundamental importance. During the early stages of the steady expansion of an intracranial mass lesion, the increase in intracranial pressure is minimal, because a volume of cerebrospinal fluid (CSF) and venous blood equivalent to that of the lesion can be displaced from the cranium to accommodate the mass. Only when this compensatory capacity of the intracranial contents is exhausted do further increases in volume produce progressively sharper rises in intracranial pressure (ICP) (Fig. 1) (Langfitt *et al.*, 1965; Langfitt, 1969). The clinical importance of this process has been appreciated since the middle of the last century (Burrows, 1846), and was widely promulgated by Cushing (1926).

Whereas early predictions of the effect of mass lesions on intracranial pressure were largely confined to brain tumours or discrete intracranial haematomas, increasing use of continuous monitoring of ICP in neurosurgical patients clearly shows that sudden sharp increases in ICP are common in a wide range of conditions. In addition to the frequent waves of increased ICP seen in patients with brain tumours, head injury, or intracranial haemorrhage (Lundberg, 1960; Lundberg *et al.*, 1965; Johnston *et al.*, 1970; Richardson *et al.*, 1970), equally dramatic pressure changes have been observed in patients with benign intracranial hypertension (Johnston and Paterson, 1972) and post-hypoxic brain damage (Langfitt *et al.*, 1971). Not only are such sudden pressure changes common, they are also unpredictable; although continuous monitoring of ICP can record pressure waves when they occur, it cannot forecast their appearance.

Since sharp increases in ICP are presumably related to the intracranial compensatory capacity available at that time, a logical development of continuous monitoring of ICP would be to devise a method of assessing this capacity to respond to the stress of additional intracranial volume. Ideally this should take the form of a complete range of changes in intracranial volume

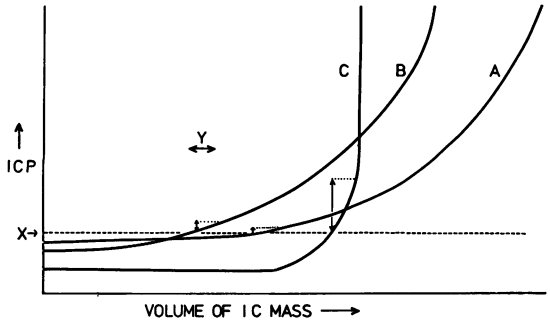

FIG. 1. *Three possible configurations of intracranial volume–pressure curves. At the same intracranial pressure* (X), *a constant volume addition* (Y) *will cause a greater elevation of* ICP *in curve* B *than in* A, *and in curve* C *than in* B. *This information is not available from knowledge of resting* ICP.

plotted against ICP, but for obvious ethical reasons an extensive intracranial volume–pressure curve cannot be obtained for patients. As an alternative, we have suggested that measuring the change in ventricular fluid pressure (VFP) in response to infusion or withdrawal of 1 ml fluid from the measuring catheter in the lateral ventricle during one second might provide a useful index (Miller and Garibi, 1972) (Fig. 1).

In patients this small change in pressure, which we now term the volume–pressure response (VPR), has been shown to be correlated with the resting VFP (Miller *et al.*, 1973a). More important, studies in individual patients show significant changes in the VPR after the removal of mass lesions (Miller *et al.*, 1973a), and in patients with head injuries the height of the VPR is closely correlated with the degree of shift of intracranial structures demonstrated angiographically (Miller and Pickard, 1974). The VPR, therefore, provides information which appears to relate to the intracranial volume–pressure compensatory capacity.

A difficulty in the clinical evaluation of the VPR is that neither the volume nor the rate of expansion of the underlying mass lesion can be measured in patients. Moreover, other variables which may affect intracranial blood and CSF volume, such as ventricular size, blood pressure, and respiration, are largely uncontrolled. For these reasons, a series of volume–pressure experiments was designed in animals; intracranial balloons were expanded to a known volume at a steady measured rate with the possibility of exercising some control over other relevant parameters.

METHODS

Eight adult baboons, body weight 9–13 kg, were anaesthetized with phencyclidine (1 mg/kg) and intravenous thiopentone (10 mg/kg) and maintained with nitrous oxide and oxygen (75:25), supplemented by phencyclidine (2 mg every 30 minutes). After intubation, the animals received succinylcholine (100 mg) and were ventilated using a modified Starling pump, the stroke volume of which was adjusted to maintain normocapnia (40 mmHg).

Systemic arterial pressure (SAP) was monitored from an aortic catheter introduced via the femoral artery. Ventricular fluid pressure (VFP) was measured bilaterally from catheters introduced into the frontal horns of the lateral ventricles by small drill holes in the cranium. Sagittal sinus wedge pressure (SSWP) was measured with a catheter introduced into the sinus through a burr hole in the occipital region and advanced until it wedged in the anterior part of the sinus.

Arterial blood gases ($PaCO_2$, PaO_2, apH) were measured at regular intervals using a direct-reading electrode system (Radiometer BMS 3) and values corrected for any temperature difference between the animal and the recording system (Severinghaus, 1966).

Cerebral blood flow was measured using the intracarotid ^{133}Xe technique; after bolus injection of 0·5 mC ^{133}Xe into the right internal carotid artery, clearance of radioactivity was monitored from the parietotemporal region of the right hemisphere using a well-collimated 1 inch sodium iodide crystal as described previously (Rowan *et al.*, 1970).

A small balloon, fashioned from glove rubber, was inserted into the extradural space via a burr hole; the balloon was placed in the right frontal region in four baboons and in the temporal region in the remaining four animals. All bone defects were then sealed with acrylic dental cement. All pressures (SAP, SSWP, and VFP right and left) were monitored continuously using pressure transducers (Bell and Howell) and a multichannel heated stylus chart recorder (Devices M4). Throughout the experiments, normal saline was slowly infused intravenously and body temperature was maintained using heating lamps. Each pressure was expressed as a mean (diastolic pressure + ⅓ pulse pressure). Statis-

tical analysis of results was undertaken using linear and Spearman's rank correlation tests and paired *t* testing. The coefficient of linear correlation is referred to as 'r' and the Spearman's rank correlation coefficient as 'r_s'.

EXPERIMENTAL PROTOCOL After control measurements of cerebral blood flow and all pressures, the extradural balloon was slowly distended using a continuous infusion pump adjusted to deliver 1 ml during 15 minutes (4 ml/hr); as inflation proceeded at a steady rate, after each millilitre of balloon volume—that is, every 15 minutes—an additional aliquot of 0·05 ml was injected into one of the ventricular catheters over a period of one second, using a three-way tap. This produced a sharp, well-defined change in VFP; the VPR was calculated in mmHg from the change registered between the mean VFP before the injection and mean VFP immediately afterwards. The VPR was therefore measured at regular intervals throughout the period of brain compression. In addition, in suitable cases, the rate of return of the post-injection VFP to the base-line level was made by measuring the half-time of a plot of logarithmic VFP against linear time after the ventricular volume addition. Cerebral blood flow measurements were made at intervals during the period of brain compression.

When VFP had been increased to within 30 mmHg of systemic arterial pressure—that is, when cerebral perfusion pressure was less than 30 mmHg—the balloon was deflated. This produced an immediate initial fall in VFP, but in five animals there was then some tendency for VFP to increase spontaneously; when this occurred, SAP was deliberately increased by administration of intravenous noradrenaline which produced a considerable passive increase in VFP. When steady levels of increased SAP and VFP were attained, a further aliquot of 0·05 ml was injected into the lateral ventricle and the change in VFP measured once again. It was thus possible, in these five baboons, to compare the VPR at the same level of intracranial hypertension produced by a focal expanding lesion, and by a diffuse process.

RESULTS

As the balloon increased steadily in volume, VFP rose in an exponential fashion, slowly at first but more rapidly after 3–4 ml had been infused (Fig. 2). No difference was noted between VFP on the side of the balloon and in the opposite ventricle;

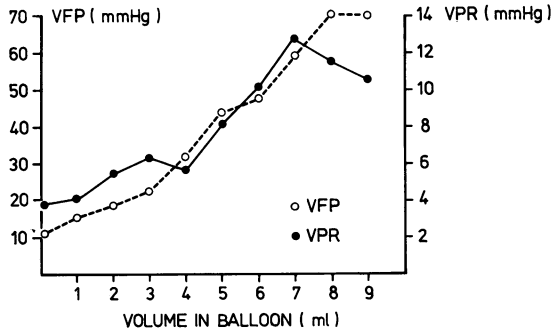

FIG. 2. *Mean ventricular fluid pressure* (VFP) *before injection and mean volume–pressure response* (VPR) *during steady rate inflation of extradural balloons* (*values for scatter are shown in Table 1*). VPR *and* VFP: *Rs=0·927; P<0·001.* VPR *and balloon volume: Rs=0·915; P<0·001.*

TABLE 1

CHANGES IN VENTRICULAR FLUID PRESSURE (VFP), VOLUME–PRESSURE RESPONSE (VPR), SYSTEMIC ARTERIAL PRESSURE (SAP), CEREBRAL PERFUSION PRESSURE (CPP), SAGITTAL SINUS WEDGE PRESSURE (SSWP), CEREBRAL BLOOD FLOW (CBF), AND CEREBROVASCULAR RESISTANCE (CVR) DURING CONTINUOUS INFLATION OF EXTRADURAL BALLOON (N=8, M±SE)

Volume in balloon (ml)	*VFP (mmHg)*	*VPR (mmHg)*	*SAP (mmHg)*	*CPP (mmHg)*	*SSWP (mmHg)*	*CBF (ml/100 g/ min)*	*CVR (mmHg/ ml/100 g/ min)*
0	10·9±4·5	3·9±1·3	96·2±3·9	85·2±7·6	18·9±3·0	50·8±5·5	1·9±0·3
1	16·5±5·5	4·1±1·6	98·0±2·7	81·5±6·7	24·0±3·1		
2	19·5±5·5	5·5±2·1	99·5±4·1	80·0±8·0	27·4±2·9		
3	23·6±5·6	6·4±1·6	102·1±4·4	78·5±9·0	31·8±3·7	47·0±4·3	1·7±0·2
4	32·0±6·2	5·6±1·4	107·1±4·2	75·1±9·2	37·7±4·6		
5	44·1±7·0	8·1±1·5	117·4±6·7	73·2±9·7	56·4±8·1	51·7±4·8	1·5±0·2
6	47·6±4·6	9·7±1·5	109·9±7·3	62·2±9·7	56·1±4·2		
7	60·2±9·6	12·5±2·0	128·4±12·5	68·1±9·3	55·7±5·3	47·4±4·9	1·4±0·1
8	71·5±8·2	11·5±2·6	110·4±11·0	38·9±8·9	77·6±9·2		
9	70·4±5·3	10·5±1·4	103·7±14·2	33·3±11·3	61·7±9·0	17·2±9·7	1·9±0·1

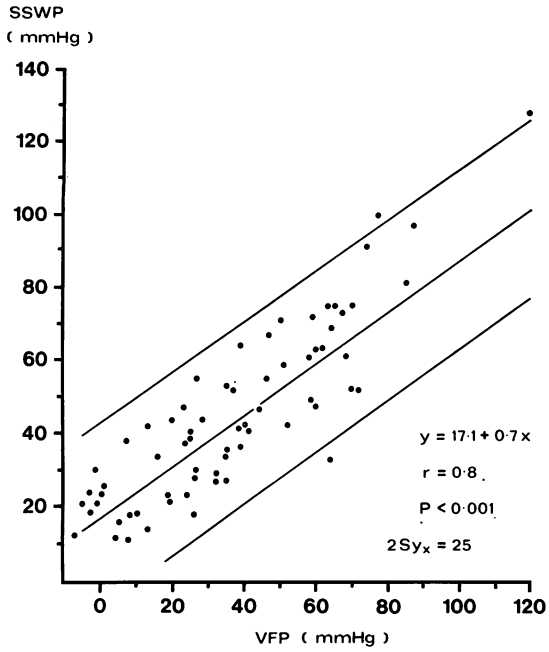

FIG. 3. *Relationship between ventricular fluid pressure and sagittal sinus wedge pressure during inflation of extradural balloons. The regression line is shown. With 95% confidence limits.*

neither did the position of the balloon influence the results.

As VFP increased, there was a corresponding rise in VPR, although the two values did not increase in parallel in individual experiments (Figs 2, 4; Table 1). Overall, there was, however, a close ranking correlation between VPR and VFP during inflation of the intracranial balloon ($r_s = 0{\cdot}927$; $P < 0{\cdot}001$), and between the VPR and the volume in the balloon ($r_s = 0{\cdot}915$; $P < 0{\cdot}001$). The close relationship between VPR and the volume of the expanding intracranial lesion persisted until the final stages of inflation, when VFP approached the level of SAP, at which stage there was a decrease in VPR.

Sagittal sinus wedge pressure also increased with VFP, but not exactly in parallel with it. A plot of SSWP against VFP yielded the regression equation:

$$SSWP = 0{\cdot}74\ VFP + 17{\cdot}1\ mmHg$$
$$(r = 0{\cdot}85;\ P < 0{\cdot}001)\ (Fig.\ 3).$$

Systemic arterial pressure increased steadily with VFP as inflation of the balloon proceeded ($r_s = 0{\cdot}794$; $P < 0{\cdot}01$), although by only a small amount, so that cerebral perfusion pressure steadily decreased despite the rise in SAP (Table 1).

Cerebral blood flow did not change significantly as cerebral perfusion pressure fell from $82{\cdot}5 \pm 7{\cdot}5$ to $68{\cdot}1 \pm 9{\cdot}3$ mmHg, indicating well-preserved autoregulation. When perfusion pressure fell to $33{\cdot}3 \pm 11{\cdot}3$ mmHg, however, CBF was sharply reduced to $17{\cdot}2 \pm 9{\cdot}7$ ml/100 g/min (Table 1). It was at this stage, when cerebral perfusion pressure and cerebral blood flow were both reduced, that the VPR tended to fall despite continuing inflation of the balloon.

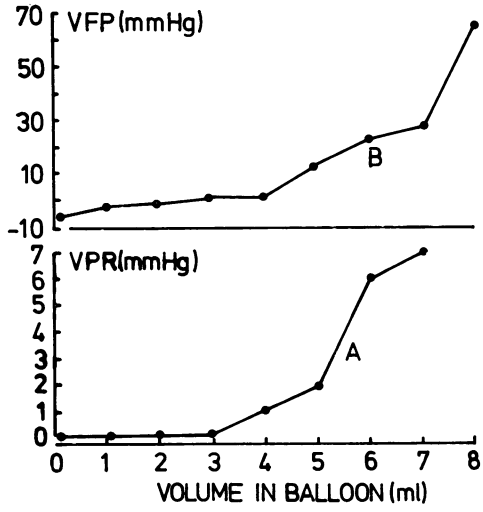

FIG. 4. *Ventricular fluid pressure* (VFP) *and volume–pressure response* (VPR) *during steady inflation of an extradural balloon in a single baboon. Note increase in* VPR (A) *before the sharp rise in* VFP (B).

When it was possible to measure the rate of return of VFP to base-line after recording the VPR, this appeared to be inversely related to the VFP and the volume in the balloon; the greater the volume and the higher the VFP, the slower the return of VFP to base-line. In several instances, a sharp rise in VPR was seen 10 to 15 minutes before a wave of increased VFP (Fig. 4).

In the period after deflation of the balloon,

TABLE 2

VENTRICULAR FLUID PRESSURE (VFP) AND VOLUME–PRESSURE RESPONSE (VPR) WITH AND WITHOUT INTRACRANIAL MASS LESION

Expt. no.	*VFP (mmHg)*		*VPR (mmHg)*	
	Balloon inflated	*Balloon deflated**	*Balloon inflated*	*Balloon deflated**
3	64	66	7	0
4	64	61	17	8
5	26	25	5	0
7	46	48	13	4
8	51	45	4	0
M	50·2	49·0	9·2	2·4
SE	±7·0	±7·1	±2·5	±1·6
P	NS		<0·01	

* Vasomotor paresis with systemic arterial hypertension.

when ICP was passively increased by infusing nor-adrenaline to increase SAP, the VPR was significantly less than that obtained at similar levels of VFP during inflation of the balloon ($t=6·668$; $P<0·01$; Table 2). Thus, at the same levels of VFP, the presence of an intracranial expanding lesion was associated with a higher VPR.

DISCUSSION

The results of this study not only provide information on the volume–pressure relationships within the cranium, but also confirm several observations made separately by other groups of investigators.

The exponential form of the intracranial volume–pressure curve resulting from inflation of the intracranial balloons in primates was shown by Langfitt and his colleagues (1965), and the fall-off of the curve as VFP approaches SAP has been noted by Nakatani and Ommaya (1972). The relationship between SSWP and VFP found in the present study corresponds closely with that recorded at normal ICP levels in dogs by Shulman (1965). He quotes a slope factor of 0·68 compared with 0·74 in the present study and his y-intercept of 12 mmHg compares with 17 mmHg. Maintenance of constant CBF despite an increase in ICP of more than 60 mmHg produced by inflation of an intracranial balloon confirms earlier reports from this laboratory (Johnston *et al.*, 1973; Miller *et al.*, 1973b). Final reduction of CBF when the difference between arterial and intracranial pressures falls below 40 mmHg has also been reported by these two groups, using two different animal models (baboon and dog) and two methods of measuring CBF (^{133}Xe and cerebral venous outflow).

The results of measurement of the VPR during progressive expansion of an intracranial mass lesion can therefore be correlated with the other measurements with some confidence. Correspondence of the VPR with the volume in the intracranial balloon is encouraging for the clinical applications of this simple measurement. Since the VPR is in part a measure of the elastance, or inverse compliance, of the intracranial contents, it is not surprising that it increases with rising VFP. Löfgren and his colleagues (1973) have noted a change in elastance with rising ICP using rapid infusion of saline into the cisterna magna to assess the intracranial volume–pressure relationship in dogs. What is more important, therefore, is the demonstration in the present study that, even at the same VFP, the VPR can be dissimilar according to whether the ICP is elevated by a mass lesion or a diffuse process. This may have a parallel in the observation of a closer correlation between VPR and brain shift than between VPR and VFP in patients with head injuries (Miller and Pickard, 1974).

A valid model has been devised in the baboon with which to examine the pathophysiology of the intracranial volume–pressure response and its efficacy as a measure of the intracranial volumetric compensatory capacity—that is, of the volume–pressure status at the time of testing. Further experimental observations of VPR will be reported, but the importance of this study rests with its clinical application where, added to observations on the ICP itself, the VPR may be of assistance in the management of patients with raised intracranial pressure.

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