

Effects of hypercapnia and arterial hypotension and hypertension on cerebrospinal fluid pulse pressure and intracranial volume-pressure relationships

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SUMMARY In twelve anaesthetised, ventilated dogs the effects of hypercapnia and pharmacologically induced arterial hypotension and hypertension on the interrelation between volume-pressure response (VPR) and cerebro-spinal fluid (CSF) pulse pressure were studied during continuous inflation of a supratentorial extradural balloon. Hypercapnia did not significantly affect the intracranial volume-pressure relationships, but did cause a significant increase in gradient of the relationship between CSF pulse pressure and intracranial pressure (ICP). Alteration of the arterial blood pressure showed opposite effects on VPR and CSF pulse pressure. A decrease in VPR and an increase in pulse pressure were observed during arterial hypotension; the reverse was found during arterial hypertension. The discrepancy between the effects on VPR and CSF pulse pressure of the variables under study was explained by changes in the transient increase in cerebral blood volume per cardiac cycle. On the basis of the results of this study it will be possible, during clinical ICP monitoring, to interpret changes in the CSF pulse pressure to ICP ratio in terms of changes in intracranial volume-pressure relationships.

Definitions of abbreviations and symbols

ICP	Intracranial pressure
VFP	Ventricular fluid pressure
SAP	Systemic arterial pressure
Δ SAP	Systemic arterial pulse pressure
P_{eq}	Equilibrium pressure, physiological steady state ICP
ΔP	CSF pulse pressure or VPR
V	Change in total volume of the craniospinal compartment
ΔV	Injected volume during a volume pressure test or the transient increase in CBV per cardiac cycle
CBV	Cerebral blood volume
VPT	Volume-pressure test
VPR	Volume-pressure response
E	Elastance of the craniospinal compartment
E_1	Elastance coefficient
CBF	Cerebral blood flow
HR	Heart rate
$PaCO_2$	Arterial carbon dioxide tension

In previous clinical and experimental studies^{1,2} the interrelation between the cerebrospinal fluid (CSF) pulse pressure and the volume-pressure response (VPR) was established. These studies had been designed to investigate whether the CSF pulse pressure could be used as a continuous parameter of the intracranial volume-pressure relationships during clinical intracranial pressure (ICP) monitoring. The height of the CSF pulse was shown to be determined by two factors: (a) the slope of the intracranial volume-pressure curve and (b) the magnitude of the transient increase in cerebral blood volume (CBV) per cardiac cycle (ΔV). During experimental brain compression in dogs this volume change was shown to be constant up to a mean ICP of 60 mm Hg and we consequently concluded that changes in the CSF pulse pressure to ICP ratio, occurring below this pressure, truly reflect changes in the slope of the volume-pressure curve. In the pressure range above 60 mm Hg ΔV was found to increase progressively. The origin of the transient increase in CBV was attributed to the interaction between the cerebral

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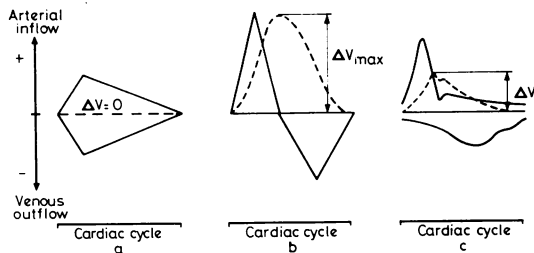


Fig 1 Concept of transient increase in cerebral blood volume per cardiac cycle (ΔV). The cerebral arterial inflow and venous outflow curves are schematically drawn; the change in cerebral blood volume is indicated by the dashed curve. The magnitude of ΔV is determined by the interaction between inflow and outflow. If both flow profiles were identical, the resulting volume change would be nil (a). If inflow and outflow were completely separated, ΔV would be maximal (b). Inflow and outflow, however, have different pulsatile flow patterns, thus producing an intermediate volume change (c.)

arterial inflow and venous outflow of blood during a cardiac cycle (fig 1). One of the main determinants of these flow profiles is the cerebrovascular resistance, and the increase in ΔV above the ICP of 60 mm Hg was therefore explained by failure of cerebral blood flow (CBF) autoregulation and progressive vasomotor paralysis.

Factors influencing cerebral hemodynamics, such as the arterial carbon dioxide tension (PaCO_2) and the systemic arterial pressure (SAP), may be expected to affect ΔV and consequently the height of the CSF pulse. Hypercapnia is known to increase the pulse pressure.^{3,4,5} This effect, however, is rather complex, as hypercapnia also produces a rise in ICP and SAP. Conflicting results have been reported with regard to the effects of changes in SAP on the CSF pulse pressure. Hamer *et al*⁵ found an increase of the pulse height during arterial hypertension. An increased transmission of pulse from cerebral artery to vein, implying a consequent increase of the CSF pulse pressure, was observed during hypotension by Symon.⁴ Moreover, with regard to the effect on the CSF pulse pressure, clear distinction is often not made between the level of SAP and the height of the arterial pulse. The blood pressure has also been claimed to influence the intracranial elastance,^{6,7} which constitutes another mechanism through which the CSF pulse pressure may be affected.

Critically ill patients are exposed to changes in both PaCO_2 and SAP. Because of the complex effects of these variables on the CSF pulse pressure and the intracranial elastance, the role of the pulse pressure in the assessment of the in-

tracranial volume-pressure relationships during clinical ICP monitoring tends to be obscured. For this reason an experimental study was designed in dogs to establish the effects of hypercapnia as well as arterial hypotension and hypertension on the interrelation between the CSF pulse pressure and the VPR as a measure of intracranial elastance during rising ICP produced by an expanding extradural balloon.

Methods

Twelve anaesthetised, ventilated adult mongrel dogs of both sexes (body weights 14 to 28 kg) were studied. The anaesthesia, surgical preparation, and methods of continuously recording ventricular fluid pressure (VFP), cisterna magna pressure, SAP, and central venous pressure have been described previously.² After all pressures had stabilised an extradural balloon in the right frontal region was gradually distended by infusion of normal saline at a rate of 1 ml/40 minutes. As a measure of the elastance the VPR⁸ was used. At regular intervals throughout the experiment clusters of four volume-pressure tests (VPT) each were carried out by rapid injections of 0.05 ml of normal saline into the lateral ventricle. The VPR was calculated from the immediate change in mean VFP. To reduce variability the mean value of the four VPTs of each cluster was taken as the VPR for that interval and related to the mean preinjection VFP. Eight CSF pulse pressures were calculated by taking the average value of the pulse pressures over the last respiratory cycle before and the first cycle after each VPT. The means of the four pulse pressures before and after each test were related to the mean preinjection and postinjection VFP respectively. As a result of this procedure each time interval yielded one VPR and two pulse pressures. Arterial blood gases were measured throughout the study using a direct reading electrode system (Radiometer BMS 3) and the readings were corrected for temperature differences between the animal and the recording system.⁹

After conclusion of the experiments the animals were killed and the brains removed. After weighing (weights between 71 and 102 g) the brains were fixed in formalin and thereafter sectioned coronally at 5-mm intervals. The correct position of the VFP recording needles was verified and major brain lesions other than those produced by the expanding balloon were excluded.

The twelve animals were divided into two

groups of six each. In the first group the effects of hypercapnia and in the second those of arterial hypotension and hypertension on the CSF pulse pressure and the VPR were studied. The experimental design was such that each animal served as its own control.

Protocol hypercapnia Brain compression was started at normocapnia. Hypercapnia was produced by administering 5% carbon dioxide to the inspired gases for five minutes, after which period a steady state was obtained as indicated by an infrared analyser monitoring the end-tidal CO_2 . During the following 15 minutes the animal was allowed to stabilise at a normal normocapnic level. At time 0 and 5 minutes volume-pressure tests were done and blood gases taken. The same manoeuvre was repeated at intervals of 20 minutes until the VFP approached the level of the blood pressure, at which time the experiment was terminated. In this way VPRs and CSF pulse pressures were obtained at normocapnic ($\text{PaCO}_2 = M \pm \text{SD} = 40.9 \pm 2.7$ mm Hg) and hypercapnic ($\text{PaCO}_2 = 57.8 \pm 3.3$ mm Hg) levels throughout the period of brain compression.

Protocol arterial hypotension and hypertension Brain compression was started at arterial normotension. SAP was reduced over 5 minutes by intravenous titration of a 0.1% solution of trimethaphan (Arfonad). For the next 5 minutes SAP was increased by continuous intravenous infusion of angiotensin (Hypertensin-CIBA, 3 $\mu\text{g}/\text{ml}$). Thereafter the animal was allowed to stabilise at a normotensive level for 10 minutes. VPTs were performed at 0, 5, and 10 minutes. The same procedure was repeated every 20 minutes. In this way VPRs and CSF pulse pressures were obtained throughout the period of brain compression at arterial normotension ($M \pm \text{SD} = 135.5 \pm 5.9$ mm Hg), hypotension (89.0 ± 5.2 mm Hg), and hypertension (175.3 ± 9.2 mm Hg). PaCO_2 was maintained within normal limits (37–43 mm Hg) during this experiment.

Data analysis The mathematical model used to analyse the data of this study has been extensively described and experimentally verified in a previous study.² The intracranial volume-pressure relationship was defined by a monoexponential function:

$$P = P_{\text{eq}} e^{\frac{E_1 V}{P}} \quad (1)$$

Where $P = \text{ICP}$, P_{eq} = a constant equal to the ICP at the equilibrium point—that is, the normal, physiological steady state ICP— E_1 = the

elastance coefficient, a constant defining the slope of the volume-pressure curve, and V = the change in total volume of the craniospinal compartment. From this equation the relationships of both VPR and CSF pulse pressure to the ICP were derived:

$$\Delta P = P \left[e^{\frac{E_1 \Delta V}{P}} - 1 \right] \quad (2)$$

where $\Delta P = \text{VPR}$ or CSF pulse pressure and ΔV = the injected volume during a VPT (0.05 ml) as well as the transient increase in CBV per cardiac cycle. For both VPR and pulse pressure this was demonstrated to be a linear function up to a break point occurring at a mean ICP of 60 mm Hg. E_1 and ΔV were therefore concluded to be constant below the break point. These parameters can be calculated from the slopes of the VPR and CSF pulse pressure versus ICP regression lines using equation 2, which can then be rewritten as:

$$E_1 = \frac{1}{\Delta V} \ln \left[\frac{\Delta P}{P} + 1 \right] \quad (3)$$

where $\frac{\Delta P}{P}$ = the slope of the VPR versus ICP regression line and ΔV = the injected volume during a volume-pressure test, and:

$$\Delta V = \frac{1}{E_1} \ln \left[\frac{\Delta P}{P} + 1 \right] \quad (4)$$

where ΔV = the transient increase in CBV per cardiac cycle, $\Delta P/P$ = the slope of the CSF pulse pressure versus ICP regression line and E_1 = the elastance coefficient calculated from equation 3.

Above the break point the VPR remained constant, implying a constant elastance (E) and thus a linear volume-pressure relationship:

$$E = \frac{\Delta P}{\Delta V} = \text{constant and } P = EV. \quad (5)$$

Since the pulse pressure continued to increase linearly with the ICP, we concluded that this was caused by a progressive increase in the volume change per cardiac cycle.

Results

EFFECTS OF HYPERCAPNIA ON THE VOLUME-PRESSURE RESPONSE AND THE CSF PULSE PRESSURE Figure 2 illustrates, in a single animal, the

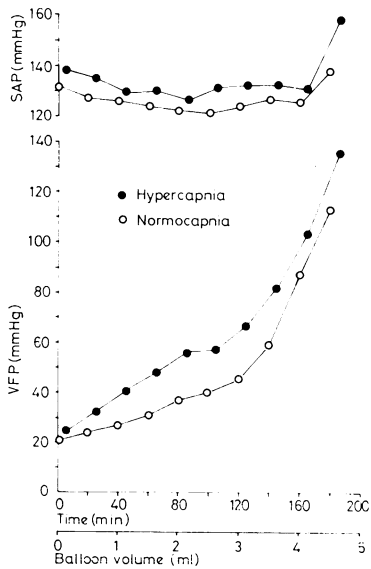


Fig 2 Ventricular fluid pressure (VFP) and systemic arterial pressure (SAP) at normocapnia (Mean PaCO₂ (±SD) 36.3 ± 2.7 mm Hg) and at hypercapnia (PaCO₂ = 53.8 ± 5.4 mm Hg) during steady rate inflation (1 ml/40 min) of an extradural balloon in a single animal. Hypercapnia produced progressively larger rises in VFP. Above VFP of 45 mm Hg, however, CO₂ response decreased.

effect of hypercapnia on the ventricular fluid pressure during gradual inflation of the extradural balloon. Hypercapnia produced a progressive increase in VFP, but at a particular level of ICP the CO₂ response started to

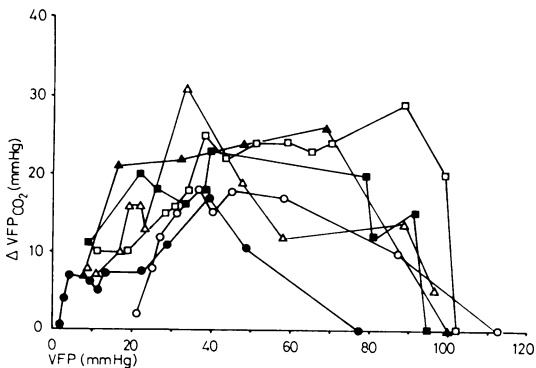


Fig 3 Increase in ventricular fluid pressure in each time interval produced by hypercapnia (ΔVFP_{CO₂}; see also fig 2) against VFP during cerebral compression in six dogs. Average increase in VFP reached its maximum around VFP of 50 mm Hg corresponding with the break point pressure in the relationship between volume-pressure response and VFP (53.5 mm Hg; see text).

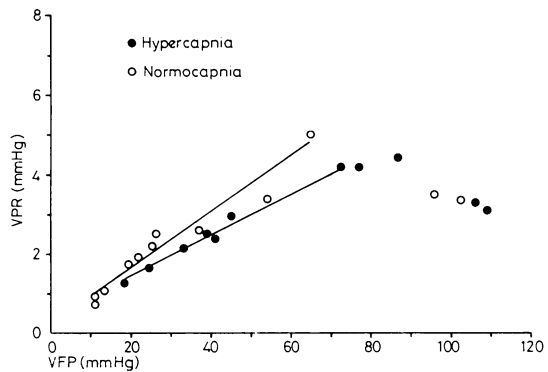


Fig 4 Plot of the volume-pressure response (VPR) against the ventricular fluid pressure (VFP) during hypercapnia (mean PaCO₂ (±SD) 60.7 ± 4.3 mm Hg) compared with normocapnia (PaCO₂ = 43.6 ± 2.9 mm Hg) in single animal. A linear relationship is shown up to a breakpoint above which the VPR slightly decreases. Regression lines are shown: $y = 0.07x + 0.3$ ($r = 0.97$, $p < 0.001$) for normocapnia and $y = 0.05x + 0.5$ ($r = 0.99$, $p < 0.001$) for hypercapnia. Gradients of the regression lines are not significantly different (F test).

decrease and finally CO₂ could no longer increase the VFP. This is clearly demonstrated when the increase in VFP, produced by hypercapnia in each time interval, is plotted against the VFP at normocapnia (fig 3).

During both normocapnia and hypercapnia the VPR increased linearly with rising VFP until a breakpoint was reached above which the VPR levelled off and sometimes slightly decreased (fig 4). Close to the level of the blood pressure the VPR started to increase again, but this pressure range was not further studied. The "normocapnic" breakpoint occurred at a mean VFP of 53.4 mm Hg (range 42.8–64.6 mm Hg) and the "hypercapnic" break point at a VFP of 60.8 mm Hg (range 47.8–72 mm Hg). The difference in break point VFP was statistically significant (Wilcoxon matched-pairs test: $p < 0.05$). Below the breakpoint significant linear relationships between VPR and VFP were always obtained ($p < 0.05$). Consequently the monoexponential volume-pressure model could be applied. The elastance coefficients (E_1) were calculated from the slopes of the regression lines using equation 3 and the results are given in table 1. Hypercapnia produced a decrease of E_1 , indicating a flattening of the volume-pressure curve, in five animals and an increase of E_1 in one, but none of these differences attained statistical significance (F test applied to the slopes of the regression lines).

Table 1 *Elastance coefficient (E_1) and transient increase in cerebral blood volume per cardiac cycle (ΔV) below and elastance and increase in ΔV above the break point, arterial carbon dioxide tension (P_{aCO_2}), systemic arterial pressure (SAP), systemic arterial pulse pressure (ΔSAP), and heart rate (HR) during normocapnia and hypercapnia. Values are means \pm SD*

Animal no	E_1 (1/ml)	ΔV (ml)	P_{aCO_2} (mm Hg)	SAP (mm Hg)	ΔSAP (mm Hg)	HR beats/min	Elastance (mm Hg/ml)	Increase in ΔV (ml/mm Hg)
<i>Normocapnia</i>								
1	1.5	0.113	36.3 \pm 2.7	126.5 \pm 5.0	58.1 \pm 4.5	136.7 \pm 23.0	98	0.0023
2	1.9	0.059	43.0 \pm 2.8	135.1 \pm 7.3	54.3 \pm 6.3	70.7 \pm 8.2	110	0.0015
3	1.4	0.036	43.6 \pm 2.9	145.8 \pm 7.4	52.2 \pm 5.6	105.8 \pm 14.2	68	0.0021
4	1.4	0.077	39.7 \pm 0.8	132.4 \pm 4.0	44.6 \pm 5.2	83.3 \pm 7.5	88	0.0017
5	1.2	0.074	40.4 \pm 1.9	166.3 \pm 4.7	71.0 \pm 3.3	91.0 \pm 9.9	82	0.0028
6	1.2	0.142	42.4 \pm 2.4	147.7 \pm 2.7	62.1 \pm 4.1	87.0 \pm 4.2	76	0.0047
Mean	1.4	0.084	40.9 \pm 2.7	142.3 \pm 14.3	57.1 \pm 9.0	95.8 \pm 23.1	87	0.0025
<i>Hypercapnia</i>								
1	1.4	0.200	53.8 \pm 5.4	131.2 \pm 3.3	65.9 \pm 2.8	133.8 \pm 19.5	104	0.0027
2	2.1	0.071	61.2 \pm 4.0	161.1 \pm 10.6	65.8 \pm 6.2	72.4 \pm 5.4	114	0.0018
3	1.0	0.098	60.7 \pm 4.3	155.4 \pm 8.1	57.4 \pm 4.7	108.4 \pm 7.1	84	0.0014
4	1.0	0.107	60.4 \pm 3.1	143.8 \pm 3.5	47.1 \pm 3.9	91.0 \pm 6.2	80	0.0020
5	0.8	0.200	55.6 \pm 2.5	182.5 \pm 5.6	77.2 \pm 4.1	93.0 \pm 8.5	94	0.0024
6	1.0	0.220	55.3 \pm 3.3	152.1 \pm 6.1	63.6 \pm 2.9	81.0 \pm 3.0	80	0.0043
Mean	1.2	0.149	57.8 \pm 3.3	154.4 \pm 17.3	62.8 \pm 10.0	96.6 \pm 21.9	93	0.0024

The ICP range above the break point was in view of the levelling-off phenomenon of the VPR (and in agreement with the results of a previous study²) conceived as a pressure range

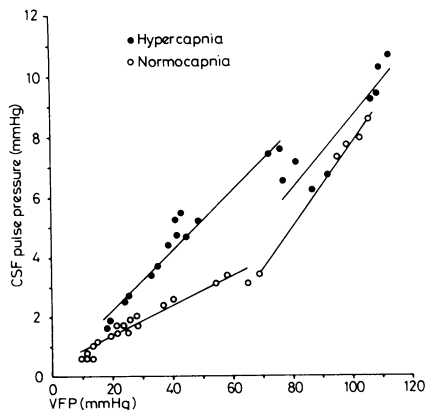


Fig 5 *Effect of hypercapnia on relationship between CSF pulse pressure and ventricular fluid pressure (VFP) in single animal (same animal as in fig 4). Regression lines are shown for pressure ranges on both sides of break points in VPR—VFP relationships. Below break point CSF pulse pressure increased significantly faster (F test, $p < 0.001$) during hypercapnia ($y = 0.10x + 0.2$, $r = 0.97$, $p < 0.001$) than during normocapnia ($y = 0.05x + 0.4$, $r = 0.97$, $p < 0.001$). Above break points gradients of relationships at hypercapnia ($y = 0.12x - 3.3$, $r = 0.92$, $p < 0.001$) and at normocapnia ($y = 0.14x - 6.3$, $r = 1.00$, $p < 0.001$) were not significantly different. When slopes above break points were compared with those of below break points, significant change was observed during normocapnia only (F test, $p < 0.001$).*

with a constant elastance to which therefore a linear volume-pressure model should be applied. The elastance (E) was calculated from the mean VPR using equation 5 (table 1). In none of the animals did hypercapnia produce a significant change in the high pressure elastance.

A typical example of the effect of hypercapnia on the relationship between CSF pulse pressure and VFP is shown in fig 5. All the animals behaved in this way. In the analysis of the pulse pressure data the same break points were taken into account as were found in the VPR—VFP relationships. On either side of the break point there was a significant positive linear correlation (p always < 0.001) between CSF pulse pressure and VFP, but the effect of hypercapnia was different. Below the break point the gradient of the hypercapnic regression line was always steeper compared to normocapnia. In five animals the difference attained statistical significance (F test: $p < 0.05$ in one and $p < 0.001$ in four). Above the break point, however, the effect of CO_2 on the pulse pressure was less pronounced. In four animals the slope of the hypercapnic relationship was only slightly steeper, in one it was weaker, whereas in the remaining animal there was no difference in slope between hypercapnia and normocapnia. None of these differences were statistically significant. The break point was operative in still another way. During normocapnia the pulse pressure always increased more rapidly above than below the break point, the difference in gradient of the regression lines attaining

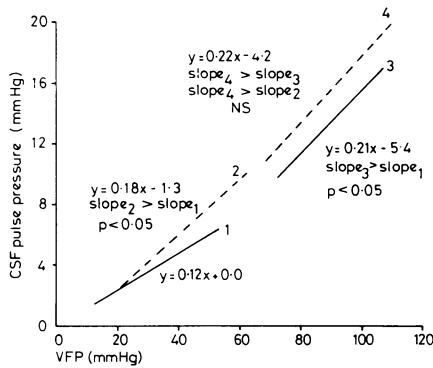


Fig 6 Composite graph of effect of hypercapnia on relationship between CSF pulse pressure and ventricular fluid pressure (VFP) during cerebral compression in six dogs. Mean regression lines and corresponding regression equations are shown for hypercapnia (dashed line) and normocapnia (uninterrupted line) on both sides of break points. Difference in gradient between various relationships was statistically evaluated by applying Wilcoxon's matched-pairs test to the regression lines of individual animals.

statistical significance in five animals (F test: $p < 0.05$ in two and $p < 0.001$ in three). During hypercapnia the pulse pressure showed a significantly steeper rise above the break point in two animals only (F test: $p < 0.05$ and $p < 0.001$). These results are summarised in fig 6, where the mean regression lines of the whole group of animals are given. According to the analytical model the linear correlations of both VPR and CSF pulse pressure with the VFP below the break point imply a constant change in CBV per cardiac cycle (ΔV). The magnitude of ΔV was calculated from the slopes of the regression lines using equation 4. In each animal hypercapnia produced a significant increase in the intracranial volume change per cardiac cycle (table 1). The rapid increase of the pulse pressure above the break point can, in view of the constant elastance in this pressure range, be caused only by a progressive increase in ΔV . The increase in ΔV per mm Hg was calculated using equation 5 and the results are given in table 1, showing no significant differences between normocapnia and hypercapnia.

Hypercapnia also produced a slight rise in blood pressure as well as in arterial pulse pressure (table 1). This should be taken into account in discussing the effects of hypercapnia on both VPR and pulse pressure. The heart rate remained unchanged.

EFFECTS OF ARTERIAL HYPOTENSION AND HYPERTENSION ON THE VOLUME-PRESSURE RESPONSE AND THE CSF PULSE PRESSURE

The hypotensive, normotensive, and hypertensive levels of the SAP in the various animals together with the corresponding arterial pulse pressures (ΔSAP) and heart rates (HR) are given in table 2. The typical reactions of the ventricular fluid pressure to the administration of trime-thaphan and angiotensin are shown in fig 7a and b. The VFP first changed concomitantly with the SAP, but generally after 10–30 seconds the VFP began to move into the opposite direction. This was considered to be the effect of a vasomotor response to the change in cerebral perfusion pressure consisting of vaso-constriction and vasodilatation respectively. So long as this response was effective the net effect on the ICP was small. At a certain level of ICP, however, the response started to diminish and finally disappeared, and thereafter the VFP closely followed the SAP (fig 8).

When the VPR was plotted against the VFP for all three levels of SAP the same type of relationship was found as in the previous series: a linear (p always < 0.01) increase of the

Table 2 Elastance coefficient (E_1), transient increase in cerebral blood volume per cardiac cycle (ΔV), systemic arterial pressure (SAP), systemic arterial pulse pressure (ΔSAP), heart rate (HR) during arterial normotension, hypotension, and hypertension. Values are means \pm SD

Animal no	E_1 (1/ml)	ΔV (ml)	SAP (mm Hg)	ΔSAP (mm Hg)	HR beats/min
<i>Normotension</i>					
1	1.4	0.090	129.1 \pm 7.8	46.6 \pm 5.9	120.5 \pm 15.2
2	0.8	0.062	132.6 \pm 7.4	32.8 \pm 4.9	157.3 \pm 7.7
3	1.0	0.050	140.2 \pm 5.6	32.2 \pm 4.8	138.4 \pm 9.0
4	1.9	0.055	145.1 \pm 7.0	54.5 \pm 3.0	143.3 \pm 9.0
5	1.9	0.016	133.6 \pm 6.0	28.3 \pm 2.6	143.1 \pm 25.4
6	1.7	0.017	132.6 \pm 3.6	26.5 \pm 8.0	135.5 \pm 21.6
Mean	1.5	0.048	135.5 \pm 5.9	36.8 \pm 11.2	139.7 \pm 12.0
<i>Hypotension</i>					
1	1.4	0.084	87.9 \pm 8.7	39.3 \pm 6.4	123.3 \pm 12.5
2	0.6	0.099	86.9 \pm 6.0	26.3 \pm 1.4	143.6 \pm 6.6
3	1.0	0.134	90.0 \pm 5.4	28.4 \pm 1.8	114.5 \pm 4.0
4	1.4	0.097	96.0 \pm 4.5	39.5 \pm 2.5	152.0 \pm 24.2
5	1.4	0.036	92.5 \pm 6.2	29.1 \pm 2.9	124.8 \pm 17.0
6	0.8	0.062	80.9 \pm 8.4	24.5 \pm 2.9	127.0 \pm 10.3
Mean	1.1	0.085	89.0 \pm 5.2	31.2 \pm 6.6	130.9 \pm 14.0
<i>Hypertension</i>					
1	2.3	0.038	175.9 \pm 15.1	48.7 \pm 5.6	98.0 \pm 14.7
2	1.2	0.025	164.7 \pm 6.1	27.8 \pm 6.3	156.8 \pm 13.1
3	1.5	0.019	174.9 \pm 10.1	23.5 \pm 4.0	121.8 \pm 11.7
4	1.7	0.066	190.5 \pm 3.6	49.9 \pm 5.8	129.9 \pm 7.7
5	2.4	0.008	178.5 \pm 9.6	29.5 \pm 6.0	125.1 \pm 14.1
6	1.5	0.006	167.3 \pm 8.0	22.7 \pm 3.1	132.0 \pm 5.6
Mean	1.8	0.027	175.3 \pm 9.2	33.7 \pm 12.4	127.3 \pm 18.9

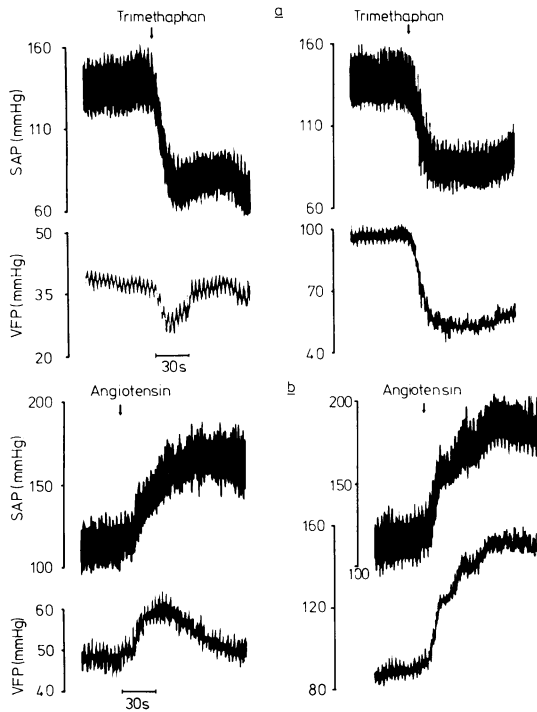


Fig 7 Tracings of systemic arterial pressure (SAP) and ventricular fluid pressure (VFP) during intravenous administration of trimethaphan (a) and angiotensin (b) before (left) and after (right) the break point. Typical response of VFP to change in perfusion pressure before break point is believed to represent intact cerebrovascular reactivity. After break point VFP closely followed SAP, indicating impaired autoregulation.

VPR below and a constant VPR above a break point (fig 9). In all the animals an increase in VPR with rising SAP was observed. When the slopes of the regression lines at the three blood pressure levels were compared, a significant difference was found between normotension and hypotension in three animals ($p < 0.01$) and between normotension and hypertension in the other three animals ($p < 0.05$). Only when hypotension was compared with hypertension was a significant change in slope found in all the animals ($p < 0.1$ in one, $p < 0.05$ in two, and $p < 0.01$ in the remaining animals). The overall results, however, indicate a rise in VPR with increasing blood pressure, as shown in table 3, where the mean regression lines are given. The elastance co-efficients were calculated from the slopes of the individual regression lines using equation 3 (table 2). Hypertension generally produced an increase in E_1 and hypotension a

decrease, implying a steeper and a flatter intracranial volume-pressure curve respectively.

The break points occurred at a mean VFP of 45.7 mm Hg (range 41.4–48.8 mm Hg) for hypotension, 55.1 mm Hg (range 38.3–69.6 mm Hg) for normotension, and 58.3 mm Hg (range 45.6–73.8 mm Hg) for hypertension. The break point pressures at hypotension and at hypertension were significantly different (Wilcoxon matched-pairs test, $p < 0.05$). The corresponding cerebral perfusion pressures were 42.7 mm Hg, 79.6 mm Hg, and 119.8 mm Hg. The break point pressure at normotension corresponded with the VFP at which the vasomotor response disappeared (fig 8) and this was confirmed in each animal. In this series the ICP range above the break point was not further studied; too few data points were available as the SAP changes caused large fluctuations in ICP.

The plots of the CSF pulse pressure against VFP showed linear correlations for each blood pressure level (p always < 0.01 ; fig 10). Comparison of the slopes of the regression lines yielded the reverse result, as was found in the

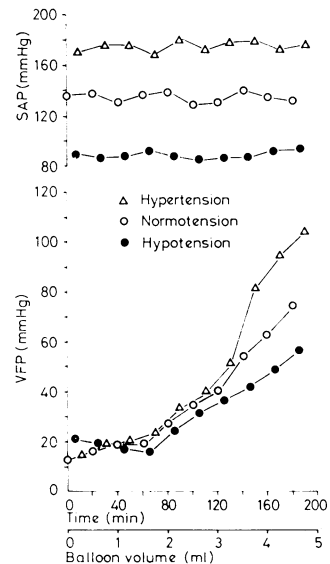


Fig 8 Composite plot of ventricular fluid pressure (VFP) and systemic arterial pressure (SAP) at arterial normotension and drug induced hypotension and hypertension during steady rate inflation (1 ml/40 min) of extradural balloon in six dogs. From mean VFP of 55 mm Hg onwards changes in SAP produced significant changes in VFP. In every animal this event coincided with disappearance of vasomotor response (fig 7a, b) and with break point in VPR–VFP relationship.

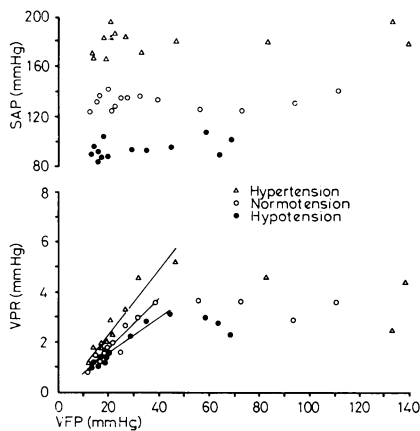


Fig 9 Effects of arterial hypotension and hypertension on relationship between volume-pressure response (VPR) and ventricular fluid pressure (VFP) in single animal. Various levels of systemic arterial pressure (SAP) are shown. At all three levels of SAP a break point in relationship was observed. Below break point linear correlations were obtained with $y=0.10x - 0.2$ ($r=0.96$, $p<0.001$) for normotension, $y=0.07x + 0.3$ ($r=0.98$, $p<0.001$) for hypotension, and $y=0.13x - 0.2$ ($r=0.95$, $p<0.001$) for hypertension. The slopes were significantly different between hypotension and normotension and hypotension and hypertension (F test, $p<0.01$). Above break points VPR remained constant or slightly decreased.

VPR against VFP plots: a decrease in slope with increasing SAP level (table 3). A significantly weaker slope at hypertension compared to normotension was found in five animals (F test, $p<0.05$). In the remaining animal the slope was steeper at hypertension, but the difference was not significant. Hypotension produced a steeper slope than normotension in all but one animal, but in only three animals did the difference attain statistical significance (F test, $p<0.05$). Only when hypertension was compared with hypotension was a uniform change in slope found in all the animals (F test, $p<0.05$ in five animals). The transient change in CBV per cardiac cycle was calculated for each blood pressure level in each animal using equation 4 (table 2). The difference in ΔV between the various blood pressure levels is larger than the difference in slope of the regression lines. The reason is that ΔV is also proportional to the inverse of E_1 , and E_1 is, in contrast to the pulse pressure, increasing with rising blood pressure. Both arterial pulse pressure and heart rate remained fairly constant during changes in SAP (table 2) and cannot therefore account for the differences in ΔV .

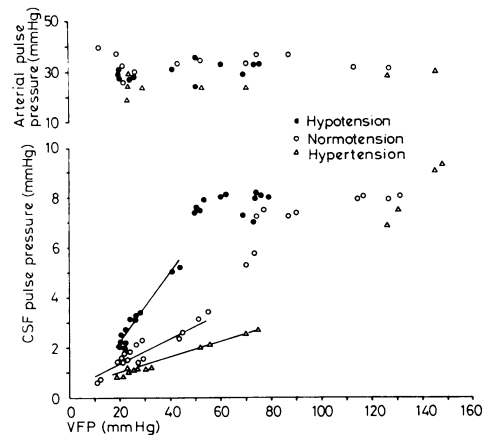


Fig 10 Effects of arterial hypotension and hypertension on relationship between CSF pulse pressure and ventricular fluid pressure (VFP) in single animal. Three mean (\pm SD) blood pressure levels were: 140.2 ± 5.6 mm Hg, 90.0 ± 5.4 mm Hg, and 174.9 ± 10.1 mm Hg. Corresponding arterial pulse pressures are shown. Only data below break points were analysed. Linear relationships were found with following regression equations: $y=0.05x + 0.4$ ($r=0.90$, $p<0.001$) for normotension, $y=0.14x - 0.5$ ($r=0.95$, $p<0.001$) for hypotension, and $y=0.03x + 0.4$ ($r=0.97$, $p<0.001$) for hypertension. The slopes were significantly different from each other (F test, $p<0.01$). Above break points pulse pressures seem to converge.

Table 3 Mean regression equations of relationships between volume-pressure response (VPR) and ventricular fluid pressure (VFP) and between CSF pulse pressure and VFP during systemic arterial normotension, hypotension, and hypertension

	VPR—VFP	CSF pulse pressure—VFP
Normotension	$y=0.08x+0.2$	$y=0.07x+0.0$
Hypotension	$y=0.06x+0.7$	$y=0.09x+0.2$
Hypertension	$y=0.09x+0.2$	$y=0.05x+0.4$

Discussion

The results of this study obtained at normal levels of carbon dioxide and blood pressure are consistent with those of a previous report.² During cerebral compression caused by steady rate inflation of an extradural balloon both VPR and CSF pulse pressure behave differently on either side of a break point ICP. Their linear relationships with the ICP below the break point confirm the validity of the analytical model implying a monoexponential intracranial volume-pressure curve and a constant transient increase in cerebral blood volume per cardiac cycle. The finding of a constant elastance and

a more rapid increase of the pulse pressure above the break point supports the concept of a linear volume-pressure model and a progressive increase in ΔV , once the break point ICP has been passed. The mean break point ICPs of 53.4 mm Hg in the first and 55.1 mm Hg in the second series do not significantly differ from the earlier reported pressure of 59.8 mm Hg. The physiological explanation for the occurrence of the break point was previously derived from the concepts on the mechanisms underlying VPR and the change in intracranial volume per cardiac cycle (fig 1).² It was then suggested that the break point is associated with cerebral vasoparesis and failure of CBF autoregulation.

Our present investigations have yielded arguments in favour of the above explanation. Hypercapnia is known to raise the ICP through an increase in cerebral blood volume produced by cerebral vasodilatation¹⁰⁻¹². During the initial period of cerebral compression CO₂ produced increasingly larger rises in ICP (figs 2 and 3). Here, two opposite effects are operative. The gradual decrease in cerebral perfusion pressure induces an autoregulatory vasodilatation and thus reduces the capacity for further dilatation in response to CO₂ stimulus. On the other hand, the CO₂ induced increments in CBV cause progressively larger rises in ICP, because of the exponential shape of the volume-pressure curve. This last effect apparently is the stronger one up to a pressure corresponding with the break point ICP (fig 3). Above the break point, the CO₂ effect on the ICP levelled off and finally disappeared. In view of the explanation for the break point two factors can be held responsible for this phenomenon: the linear nature of the volume-pressure relationships (constant VPR) and the gradual loss of CO₂ reactivity of the cerebral vessels due to vasoparesis and subsequently vasoparalysis¹³. This does not conflict with the assumption of failure of autoregulation commencing at the break point, as it is well documented that cerebrovascular reactivity to CO₂ is retained when autoregulation is abolished.¹³⁻¹⁶ The significantly higher break point ICP during hypercapnia compared with normocapnia may be related to the increased blood pressure level. The autoregulatory constrictor stimulus induced by raised SAP increases the residual vasodilator capacity thus delaying maximal vasodilatation with consequent impairment of autoregulation. The break point therefore seems to be related to the cerebral perfusion pressure, rather than

to the level of ICP. Further evidence for relating the break point in the relationships of both VPR and CSF pulse pressure to the ICP to failure of autoregulation can be derived from the second series of experiments, in which changes in SAP were induced. Below the break point, variations in SAP had little influence on the ICP (fig 8). This provides indirect evidence that the cerebrovascular reactivity to changes in perfusion pressure was unimpaired. The typical shape of the VFP tracings each time the SAP was raised or lowered (fig 7a, b) shows that, in spite of the recurrent infliction of arterial hypotension and hypertension, the autoregulatory vasomotor response of the animal preparations was intact. The absence of the response above the break point ICP indicates that the cerebral vessels behaved in a pressure-passive manner to changes in SAP. As a result, the blood pressure variations produced exaggerated changes in ICP (fig 8). These observations are consistent with those of previous reports.^{12,17} It is interesting to note that the break points at arterial hypotension normotension, and hypertension occurred at successively higher intracranial pressures. Again, the explanation follows from the assumption that the break point is related to disturbance of autoregulation: by raising the SAP the lower limit of autoregulation is shifted towards a higher ICP. The perfusion pressures at the break points, however, differ considerably, the break point at hypertension occurring when the perfusion pressure is still relatively high. This is presumably caused by damage to the flow regulating structures as cerebral compression progresses.

Our main aim was to study the effects of changes in PaCO₂ and SAP on the amplitude of the CSF pulse during rising ICP. Since we are mainly interested in the CSF pulse pressure in so far as it is a measure of intracranial elastance, which in its turn may be influenced by the variables under investigation, we had to study the intracranial volume-pressure relationships as well. The volume-pressure test was chosen for the evaluation of these relationships, because of its clinical relevance. Hypercapnia did not significantly alter the elastance coefficient (E_1) in the individual animals, which implies that the shape of the volume-pressure curve remained unchanged. These results are in line with those of Löfgren,⁸ who recorded the volume-pressure curve by rapid infusion into the cisterna magna of dogs with varying degrees of hypercapnia. He found a slight, though not

significant, decrease of the elastance. Leech and Miller¹⁸ and Rowed *et al*¹⁹ also demonstrated that hypocapnia, induced by hyperventilation, has no effect on the elastance. However, the group results of the present study, a reduction of E_1 in five animals, do suggest a slight flattening of the volume–pressure curve. This might have some meaning, if the positive influence on E_1 of the raised blood pressure at hypercapnia is taken into account, as will be discussed later.

In contrast to the effect on the VPR, hypercapnia produced a significant increase in the amplitude of the CSF pulse. This is in agreement with various other reports.^{3,5} Symon^{4,20} used the ratio of venous to arterial pulse height (pulse index) in the pial circulation within the middle cerebral arterial field to assess regional vascular reactivity. The author found an increased pulse index in response to increased PaCO₂. Since the venous pulsations in particular are easily transmitted to the CSF, these observations probably also hold for the CSF pulse. It follows from the experimental design of the present study that the increased pulse height is a pure CO₂ effect, not related to the CO₂ induced rise in ICP. As the elastance coefficient remained unaltered, the explanation for the increase in pulse pressure should, according to the analytical model, be sought in an increase in magnitude of the change in CBV per cardiac cycle during hypercapnia. The CO₂ induced cerebral vasodilatation reduces the arterial inflow resistance. On account of the “easier” inflow of blood the time lag between inflow and outflow increases, resulting in a larger ΔV (fig 1). An additional factor may be a simultaneous change in the venous outflow profile, because of the slightly raised central venous pressure. Apart from the timing mechanism, the CO₂ induced increase in CBF per se should cause a larger change in CBV per cardiac cycle, so long as the heart rate remains constant. At the same time, this explains why hypercapnia did not produce a significant effect on the increase in ΔV , and consequently on the increase in CSF pulse pressure, above the break point, where vasoparesis has occurred and CO₂ gradually loses its vasodilatory action. This is clearly demonstrated by fig 6. The gradients of the relationships between CSF pulse pressure and VFP above the break point are not significantly different, implying an equal increase in ΔV at normocapnia and at hypercapnia. Moreover, the break point is virtually absent in the hypercapnic relationship. This is because under hypercapnic conditions the cerebral vessels are

widely dilated all the time and the increase in pulse pressure, when autoregulation becomes impaired, is therefore less marked than during normocapnia.

The reason why ΔV steadily increases above the break point is that the venous outflow resistance continues to increase because of the so-called cuff constriction of the cerebral veins at their junction with the dural sinuses^{21–23} as well as because of compression of the sinuses themselves.^{24,25} As a result, the cerebral arterial inflow and venous outflow during a cardiac cycle separate into two processes causing a progressively larger change in CBV (fig 1*b*). It might be argued that also below the break point ΔV is not truly constant, as the inflow resistance is gradually reduced as part of the autoregulatory process. In that case the relationship between pulse pressure and ICP should be non-linear and, indeed, such an approximation might well have fitted the data of this study, as was also shown by Guinane.²⁶ However, the effect of the decrease in cerebrovascular resistance on ΔV below the break point is apparently so small that the description of the relationship by means of a linear function, and consequently a constant ΔV , is also valid.

The small rise in arterial pulse height during hypercapnia may be a contributory factor to the increase in CSF pulse pressure but cannot account for the whole phenomenon, as it was also present in animals with only a minimal difference in arterial pulse pressure (table 1). On the other hand, the concomitantly increased blood pressure level tends to reduce the CSF pulse pressure, as will be discussed next, and is thus in competition with the effect of the arterial pulse. Above the break point, however, under conditions of vasoparesis, the increased arterial pulse height may have been responsible for the constant difference in ΔV and consequently in CSF pulse pressure between normocapnia and hypercapnia (fig 6). Moreover, the slight increase in perfusion pressure causes a rise in CBF resulting in a larger ΔV , as the heart rate remained constant.

In contrast to changes in arterial carbon dioxide tension, variations in arterial blood pressure did affect the intracranial volume–pressure relationships, as has been reported by others.^{6,7} Raising the SAP from hypotensive to hypertensive levels increased the elastance coefficient by approximately 50%, which is in agreement with the findings of the earlier mentioned investigators, if the same SAP range is considered. Looking at the individual animals,

however, it was either hypotension or hypertension which produced a significant change in E_i compared to normotension. Only when the extremes, hypotension and hypertension, were compared was a significant difference found in every animal. This implies that in the blood pressure range encountered clinically minor changes in SAP do not necessarily produce a noticeable effect on brain elastance.

The influence of SAP on the elastance can be understood by considering the underlying mechanisms of the VPR. A rapid volume addition to the CSF compartment causes a compression of the venous outflow section and thus a corresponding increase in the outflow resistance. The outflow of blood will consequently be reduced, whereas the inflow remains unaffected, resulting in an increase in CBV with a corresponding rise in CSF pressure. In order that the equilibrium between inflow and outflow be restored the CSF pressure rises to the extent that the perfusion pressure over the inflow tract is decreased proportionally to the increase in outflow resistance. For this reason, the CSF pressure shows a larger rise at higher arterial pressures. The height of the VPR seems therefore to be primarily related to the perfusion pressure over the inflow section of the vascular bed and not to the inflow resistance and the CBF. This may explain why CO_2 , increasing CBF by reducing the inflow resistance, does not significantly affect the VPR. These arguments seemingly contradict the findings of Leech and Miller,⁷ who described a significant positive correlation between SAP and VPR as well as between CBF and VPR. Once intracranial hypertension had been established, however, their experimental animals showed failure of autoregulation and the CBF thus responded in a pressure-passive manner to changes in SAP. Although we did not measure the CBF, we assume, for reasons mentioned above, that autoregulation was intact up to the break point ICP.

The results of the current study show that, by contrast to the effect on the VPR, the level of SAP is inversely related to the height of the CSF pulse (table 3). The reason for this must be a decrease in the transient change in CBV per cardiac cycle with rising SAP, since according to the analogy between VPR and CSF pulse pressure an increase in pulse height with rising SAP would have been expected. Thus, during rising SAP two opposite forces are effective on the amplitude of the CSF pulse: an increase of the elastance coefficient and a decrease in ΔV .

The effect on ΔV apparently prevails, as in most animals the CSF pulse pressure significantly decreased when SAP was raised from hypotensive over normotensive to hypertensive levels and vice versa. These findings cannot be explained by changes in the arterial pulse height, since ΔSAP was relatively little affected when SAP was altered (table 2). Besides, the small changes that occurred were mostly into the same direction as the blood pressure, so that their influence on the CSF pulse pressure was opposite to that of the blood pressure. The arterial pulse pressure is one of the factors determining the pulsatile inflow profile and consequently affects the CSF pulse pressure through the mechanism of ΔV . The difference in mean ΔV between arterial normotension in this series and normocapnia in the first series can therefore be explained by the difference in ΔSAP .

The explanation of the SAP-induced changes in ΔV follows the same argument as outlined above. The alterations in cerebral perfusion pressure elicit an autoregulatory response consisting of vasodilatation during hypotension and vasoconstriction during hypertension with corresponding changes in the inflow resistance and the shape of the pulsatile inflow curve, thus causing an increase and a reduction in ΔV respectively (fig 1). Fig 10 shows that the difference in CSF pulse height between the various SAP levels tends to disappear above the break point, where cerebral vasoreactivity becomes impaired. Contrary to the results of this study, Hamer *et al*⁵ described an increase in CSF pulse height with rising SAP. From their tracings, however, it appears that this was due to a concurrent rise both in ICP and in arterial pulse pressure. Moreover, presumably the increase in SAP did not last long enough for the autoregulatory vasoconstrictor response to develop, so that ΔV was not negatively influenced. It might still be argued that the vasomotor response, as shown in the ICP tracings (fig 7a, b) was not a true autoregulatory response, but merely the result of a direct action of angiotensin and trimethaphan on the cerebral vasculature and that consequently the present results hold true only for drug-induced alterations in SAP. This criticism can be answered by referring to the previously mentioned work of Symon⁴ with regard to the pulse transmission in the middle cerebral field. Lowering the input arterial pressure by exsanguination or temporarily occluding the carotid vessels in the neck caused reduction in pial arterial pressure but a definite increase in the pulse index, which is consistent with an increase

in CSF pulse pressure. From comparison between intracarotid and intravenous infusion of angiotensin in patients various authors^{27, 28} have concluded that the increase in cerebrovascular resistance was secondary to the increase in blood pressure, representing autoregulation, and not the result of a direct effect on the cerebral vessels. The same was demonstrated for trimethaphan.²⁹ Finally, additional evidence for the vasomotor response representing true autoregulation is found by studying the time lag between the change in SAP and the change in ICP in the opposite direction (fig 7a, b). This was always in the order of 10 to 30 seconds, which is in agreement with the reported time intervals necessary for autoregulation to adjust.³⁰⁻³³

This study was directed toward clinical applicability. The idea of using the CSF pulse pressure to ICP ratio as a continuous parameter of intracranial volume-pressure relationships was first launched by two of us in a preliminary clinical report¹ and subsequently further developed in an extensive experimental study.² However, in both patients and experimental animals, the gradient of the relationship between pulse pressure and ICP did not correlate with the slope of the volume-pressure curve as defined by the elastance coefficient. This was not surprising, as it had been mathematically demonstrated that the gradient of the relationship also depends on the magnitude of the change in CBV per cardiac cycle. Since ΔV shows a biological variation between individuals, their volume-pressure relationships cannot be accurately assessed on the basis of the CSF pulse pressure alone. In the same individual, however, ΔV has been shown to remain constant when ICP rises, provided that autoregulation is maintained. This has important implications for the clinical practice of ICP monitoring. At the beginning of a pressure recording the elastance coefficient can be calculated on the basis of a few volume-pressure tests. Thereafter, any change in the CSF pulse pressure to ICP ratio, which can be monitored by means of on-line computer analysis, indicates a change in elastance coefficient. This, of course, holds true only so long as the condition of the patient is stable with regard to both intracranial and extracranial haemodynamics, since they will, through the mechanism of ΔV , also affect the CSF pulse pressure. It has already been shown that loss of autoregulation and sudden cerebral vasodilatation, such as those occurring during plateau waves, causes an abrupt increase in pulse

pressure.^{1, 2} This study has evaluated the influence on ΔV of some other major factors: arterial CO₂ tension, blood pressure, arterial pulse pressure, and heart rate. Since these variables are routinely monitored in patients in whom continuous ICP recording is indicated, information on variations in ΔV will be constantly available. This may help to interpret changes in the slope of the relationship between CSF pulse pressure and ICP in terms of changes in intercranial volume-pressure relationships.

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