Systemic vascular responses to increased intracranial pressure

1 Effects of progressive epidural balloon expansion on intracranial pressure and systemic circulation

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SUMMARY This paper details the results of experimental studies, on 16 dogs with artificially-induced intracranial space-occupying lesions, of the systemic vascular responses and the intracranial pressure changes (both in the supratentorial and infratentorial compartments) induced by increasing intracranial pressure. The changes produced were divided into two phases such that phase 1 detailed the alterations observed from the start of the balloon inflation up to the initiation of the systemic pressor response. Phase 2 recorded those alterations which occurred during, and immediately after, the period of systemic hypertension (see Fitch *et al.*, 1977). The changes observed during phase 1, and presented in this communication, were those of increasing intracranial pressures and decreasing mean arterial pressure and heart rate. These alterations were associated with decreases in supratentorial perfusion pressure and increases in transtentorial pressure gradient and arrhythmia index.

In the classical experiments in which systemic hypertension and bradycardia were related to increased intracranial pressure, the increase in intracranial pressure was produced by the infusion of fluid into the subarachnoid space (Naunyn and Schreiber, 1881; Cushing, 1901; Kocher, 1901). Under such conditions, the increase in intracranial pressure is uniformly distributed throughout the intracranial space. For example, when this method of increasing intracranial pressure is used, the pressure in the subarachnoid space overlying the anterolateral surface of one hemisphere has been found to be equal to the pressure in the cisterna magna over the range 0-100 mmHg (Coroneos *et al.*, 1971). In clinical practice, however, this is a rare form of increased intracranial pressure, although conditions pertaining during pneumoencephalography may approximate closely to it. Much more commonly, the clinician is concerned with alterations in intracranial pressure produced by space-occupying pathology such as tumour or haematoma. Thus, the question of the greatest interest to the clinician is that regarding the re-

lationship between the systemic circulatory changes and intracranial pressure when the latter is abnormal due to the effects of intracranial space-occupying pathology with concomitant distortion of intracranial structures.

The following experiments were performed in order to obtain further information on the relationships existing between the systemic vascular changes noted with increasing intracranial pressure and the intracranial pressure changes found in different intracranial compartments in the presence of an intracranial mass lesion.

Methods

Two groups of investigations were carried out on anaesthetised dogs. In each animal an artificial space-occupying lesion was created by the placement of a small balloon in the extradural space. Volume changes of this artificial mass lesion were produced by the addition of fluid to the balloon.

Group A In six dogs, the extradural balloon was inflated *rapidly* with 1 ml increments of fluid, each increment being added over 2 min and being separated from the preceding increment by approximately 30 min (Fig. 1). Intracranial and systemic pressure changes were monitored and, in

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Accepted 29 March 1977

Fig. 1 Diagram of protocols used in the six animals of group A (upper trace) and in the 10 animals of group B (lower trace).

addition, cardiac output was determined. *Group B* In a further 10 dogs, the extradural balloon was inflated slowly by a constant infusion pump at a rate of 1 ml fluid added over 20 min (Fig. 1). As in the previous group, systemic and intracranial pressure changes were observed.

DETAILED METHODOLOGY

Group A (Rapid inflation)

In each animal, anaesthesia was induced with thiopentone sodium (20 mg/kg) injected intravenously, and was maintained subsequently with 70% nitrous oxide in oxygen. Halothane 0.5–1.0% was added to the inspired gas mixture during the surgical preparation. Muscular relaxation was produced by the intermittent intramuscular injection of suxamethonium (100 mg), and all the animals were ventilated artificially by a Palmer large animal ventilator, the minute volume of ventilation and the inspired oxygen concentration being adjusted as necessary to produce normocapnia and normoxia. The end-tidal carbon dioxide concentration was monitored continuously using an infra-red analyser (URAS 4; Hartmann and Braun) and arterial pH, PCO_2 , and PO_2 were measured at intervals throughout each investigation using appropriate, suitably calibrated electrodes (Radiometer). Body temperature was measured with an oesophageal temperature probe (Ellab) and was maintained between 36° and 37.5°C with the help of heating lamps. Correction was made, where

indicated, for any temperature difference existing between the animal and the electrode system (Severinghaus, 1966).

The temporal muscles were reflected from both sides of the skull and two burr holes (10 mm diameter) were made, one over each parietal area. A thin-walled loose balloon was inserted through one burr hole and was placed so as to lie in the subarachnoid space over the frontal cortex; 0.5 ml fluid was added to this balloon and it was used for the measurement of supratentorial intracranial pressure. The burr hole on the opposite side of the skull admitted a second balloon which acted as the artificial space-occupying lesion. This latter balloon was placed extradurally and lay over the parietal cortex. Once both balloons had been positioned satisfactorily, the skull was closed with dental cement.

In two of the animals a catheter was inserted (under direct vision) into the cisterna magna and was used for the measurement of posterior fossa (infratentorial) intracranial pressure.

Systemic arterial pressure was measured electronically (Bell and Howell: L221 transducer) from the abdominal aorta through a catheter inserted via the left femoral artery. Other catheters were inserted into the inferior vena cava via the left femoral vein and into the right femoral artery and vein. Intravenous fluids were administered through the venous catheter and blood was withdrawn for the measurement of arterial blood-gas tensions and for the determination of cardiac output through the arterial catheter. Cardiac output was estimated by a dye dilution technique using indocyanine green. In addition the electrocardiogram was monitored (Lead 2) and the QRS complex used to trigger an instantaneous heart rate meter (Devices).

Each investigation consisted of the stepwise inflation of the extradural balloon by increments of 1 ml fluid, delivered over a 2 min period. Each addition to the balloon was separated from the subsequent increment by approximately 30 min. All measurements, including that of cardiac output, were made according to the pattern depicted diagrammatically in Fig. 1. A measurement of each variable under study was made 3 min before the start of each balloon inflation (A¹), at the end of the period of inflation (B¹), and again 5 min after the end of the balloon inflation (C¹). Finally, some 20 min later, another series of measurements was made (A²). This group of results not only served as the final series of measurements for one change of balloon volume, but also as the first (pre-inflation or control) set of measurements for the subsequent balloon inflation. This experimental

protocol was repeated throughout each investigation and, to ensure reproducibility, the time for each stage was given on a continuously running tape-recorded commentary. In this way the volume of the extradural balloon was increased by 1 ml each 30 min, although it should be noted that the actual change in balloon volume took place rapidly (over 2 min).

In addition to the variables measured and discussed above, the following indices were derived from the data available, as described below:

- (a) Stroke volume (ml): Cardiac output (ml/min)/heart rate (beats/min).
- (b) Systemic vascular resistance (dyne sec cm⁻⁵): Mean arterial pressure (mmHg) × 79,920/cardiac output (ml/min).
- (c) Arrhythmia index (%): From an analysis of the R-R interval on the ECG trace the alterations in the sinus arrhythmia could be noted and the arrhythmia index calculated. This was defined as the sinus arrhythmia (observed over a period of 30 sec) expressed as a percentage of the mean heart rate such that
Arrhythmia index =
$$\frac{\text{Maximum heart rate} - \text{minimum heart rate}}{\text{mean heart rate}} \times 100$$
- (d) Cerebral perfusion (kPa : mmHg). Calculated as the difference between the mean arterial pressure and the mean intracranial pressure (either supratentorial or infratentorial).
- (e) Transtentorial pressure gradient (kPa: mmHg). This was determined as the difference between the mean supratentorial intracranial pressure and the mean infratentorial (posterior fossa) intracranial pressure.

Group B (Slow inflation)

In 10 unselected mongrel dogs (20–30 kg), the effects of slower expansion of the extradural balloon were studied. The detailed methodology of this series of investigations has been presented previously (Fitch and McDowall, 1971) and only the salient features will be re-emphasised in this presentation. Anaesthesia was provided as described for the animals studied in group A. The extradural balloon was placed over the antero-lateral surface of one hemisphere. In five of the animals it was positioned so as to overlie the parietal cortex, while in the other five animals it lay over the frontal cortex. Supratentorial sub-arachnoid pressure was measured as in group A. In addition, in each animal, a catheter was inserted into the cisterna magna under direct vision and via this catheter infratentorial pressure was monitored.

In this series of investigations, the extradural

balloon was inflated slowly by a constant infusion pump at a rate of 1 ml fluid in 20 min. At the end of the 20 min period of inflation, the pump was stopped and halothane 1.0% was added to the inspired gas mixture for the subsequent 10 min. At 30 min (from the start of the balloon inflation) the halothane was discontinued and the infusion pump re-started and the sequence of events repeated over the next 30 min (Fig. 1). The results of the addition of halothane to the inspired gas mixture have been presented elsewhere (Fitch and McDowall, 1971).

Once again, in addition to the measurements of supratentorial and infratentorial intracranial pressure, the changes in systemic arterial pressure and heart rate were monitored and the alterations in pulse pressure, arrhythmia index, cerebral perfusion pressure, and transtentorial pressure gradient calculated.

Results

The values are presented as mean ± SEM. When presented, supratentorial and infratentorial perfusion pressures have been calculated as the difference between the mean arterial pressure and the mean intracranial (supratentorial or infratentorial) pressure. Mean pressure has been determined as the diastolic pressure plus one-third of pulse pressure. Probability values have been assessed using Student's *t* test for paired and unpaired data; *P* < 0.05 was taken as significant.

As the volumes of the individual artificial mass lesions were increased progressively by the injection of increments of 1 ml fluid, supratentorial intracranial pressure was observed to increase in the manner shown in Fig. 2. In each of these studies, an initial compensatory phase with a gradual increase in intracranial pressure was followed by a phase in which small changes in balloon volume produced markedly greater increases in supratentorial pressure. As a consequence of these alterations in supratentorial pressure, changes in systemic arterial pressure and heart rate were noted (Fig. 3). As a result of these findings, the events taking place in the animals of both groups have been divided into two phases, such that (Fig. 3)

Phase 1 was characterised by a period during which systemic arterial pressure changed little and was accompanied by a progressive decrease in heart rate, whereas

Phase 2 was characterised by a period during which the systemic hypertensive or 'Cushing' response was evident. This systemic arterial pressor response was accompanied by marked

Fig. 2 Mean values, with standard errors, for supratentorial intracranial pressure at each balloon volume in six animals in group A (X), five animals in group B with frontal lesions (●), and five animals in group B with parietal lesions (○).

and persistent increases in heart rate.

For clarity of presentation the results pertaining to phase 1 will be considered in this presentation, while those relating to the changes observed during phase 2 are described by Fitch *et al.* (1977).

GROUP A (RAPID INFLATION)

The changes observed, both in the intracranial and cardiovascular indices, in the six animals subjected to rapid inflation (1 ml fluid given over 2 min) of the artificial supratentorial mass lesion are presented in Table 1a (intracranial indices) and Table 1b (cardiovascular indices).

Table 1a Changes (mean $\pm$ SEM) in supratentorial intracranial pressure and supratentorial perfusion pressure observed in six animals due to rapid inflation of the extradural balloon (group A)

	Baseline	Before onset of SHR	Significance (P)
Mean supratentorial intracranial pressure kPa (mmHg)	1.3 $\pm$ 0.27 (10 $\pm$ 2)	10.1 $\pm$ 0.53 (76 $\pm$ 4)	< 0.001
Mean supratentorial perfusion pressure kPa (mmHg)	16.4 $\pm$ 0.93 (123 $\pm$ 7)	3.1 $\pm$ 0.53 (23 $\pm$ 4)	< 0.001

SHR = systemic hypertensive response.

Table 1b Changes (mean $\pm$ SEM) induced in the cardiovascular indices of six animals by rapid inflation of the extradural balloon (group A)

	Baseline	Before onset of SHR	Significance (P)
Heart rate (beats/min)	171 $\pm$ 12	67 $\pm$ 12	< 0.005
Mean arterial pressure kPa (mmHg)	17.8 $\pm$ 0.8 (134 $\pm$ 6)	13.2 $\pm$ 0.4 (99 $\pm$ 3)	< 0.005
Systolic arterial pressure kPa (mmHg)	21.1 $\pm$ 1.2 (159 $\pm$ 9)	17.2 $\pm$ 0.4 (129 $\pm$ 3)	< 0.05
Diastolic arterial pressure kPa (mmHg)	16.1 $\pm$ 0.8 (121 $\pm$ 6)	11.2 $\pm$ 0.67 (84 $\pm$ 5)	< 0.001
Pulse pressure kPa (mmHg)	5.1 $\pm$ 1.1 (38 $\pm$ 8)	6.0 $\pm$ 0.8 (45 $\pm$ 6)	ns
Cardiac output (litre/min)	3.29 $\pm$ 0.28	2.31 $\pm$ 0.34	ns
Stroke volume (ml/beat)	20 $\pm$ 2	33 $\pm$ 8	ns
Systemic vascular resistance (dyn sec cm ⁻⁵)	3358 $\pm$ 190	3840 $\pm$ 450	ns

SHR = systemic hypertensive response. ns = not significant.

Fig. 3 Effects, in one animal, of increasing balloon volume on mean supratentorial intracranial pressure (x - - x), heart rate (●—●), systolic and diastolic arterial pressure. Hatched area represents pulse pressure.

Intracranial indices

At zero balloon volume, mean supratentorial pressure ranged from 0.67 kPa (5 mmHg) to 2.3 kPa (17 mmHg) (average value 1.3 kPa $\pm$ 0.27 (10 mmHg $\pm$ 2)) in the individual animals. At this point mean cerebral perfusion pressure in the supratentorial compartment varied between 14.1 kPa (106 mmHg) and 19.3 kPa (145 mmHg). Immediately before the onset of the systemic hypertensive response (SHR), the mean balloon volume had been increased to 8.0 ml $\pm$ 0.5, by which time mean supratentorial pressure had increased significantly to 10.1 kPa $\pm$ 0.53 (76 mmHg $\pm$ 4). This was associated with a significant decrease

in the perfusion pressure in the supratentorial compartment, due in the main to the alterations in the intracranial pressure, but also partly to a significant decrease in mean arterial pressure (Table 1b). Immediately before the onset of the SHR, mean supratentorial perfusion pressure ranged from 1.1 kPa (8 mmHg) to 4.9 kPa (37 mmHg) (average value $3.1 \text{ kPa} \pm 0.53$ (23 mmHg ± 4)). In this particular group of animals there were only two in which infratentorial pressure was measured and in which values of infratentorial pressure and transtentorial pressure gradient could be calculated. Mean infratentorial pressure increased in these animals from values of 0.53 kPa (4 mmHg) and 0.67 kPa (5 mmHg) to 1.9 kPa (14 mmHg) and 6.5 kPa (49 mmHg) respectively, and was associated thus with decreases in infratentorial perfusion pressure from initial values of 14.5 kPa (109 mmHg) and 19.3 kPa (145 mmHg) to final values (immediately before the onset of the SHR) of 9.8 kPa (74 mmHg) and 6.8 kPa (51 mmHg). As a result of the changes in the two intracranial pressures, transtentorial pressure gradient (initial values of 0.34 kPa (3 mmHg) and 0 kPa (0 mmHg)) increased to 8.8 kPa (66 mmHg) and 4.1 kPa (31 mmHg) respectively.

Cardiovascular indices

Before inflation of the balloon, mean arterial pressure ranged from 15.0 kPa (113 mmHg) to 20 kPa (150 mmHg) in the individual animals and as a result of the progressive increase in the volume of the artificial mass lesion and the accompanying changes in intracranial pressure, mean arterial pressure decreased in each of the animals studied (Fig. 3). Systolic and diastolic arterial pressures were observed to decrease significantly, pulse pressure remaining relatively unchanged (Table 1b). It would seem likely that the decrease in mean arterial pressure could be ascribed to the significant decrease in heart rate, since there were no significant alterations in either cardiac output or systemic vascular resistance. However, it should be noted that while there was no overall significant change in cardiac output, it had decreased in five

of the six animals (range -0.93 l/min to -2.37 l/min), and in these animals this could also have been a factor in producing the decrease in mean arterial pressure.

In each of the animals studied there was an increase in the arrhythmia index and in all but one animal an increase in the absolute arrhythmia. The mean changes for these two variables are shown in Table 2.

Table 2 Changes (mean $\pm$ SEM) observed in the absolute arrhythmia (AA) and the arrhythmia index (AI) in the animals of groups A and B

	Baseline	Before onset of SHR	P
Rapid inflation			
AA (beats/min)	23 $\pm$ 7	60 $\pm$ 4	< 0.025
AI (%)	13 $\pm$ 4	94 $\pm$ 27	< 0.25
Slow inflation (parietal)			
AA (beats/min)	7 $\pm$ 3	46 $\pm$ 10	< 0.025
AI (%)	6 $\pm$ 3	68 $\pm$ 18	< 0.05
Slow inflation (frontal)			
AA (beats/min)	16 $\pm$ 2	48 $\pm$ 6	< 0.005
AI (%)	11 $\pm$ 2	49 $\pm$ 7	< 0.01

GROUP B (SLOW INFLATION)

Parietal lesions

Five animals with parietally-placed artificial space-occupying lesions were subjected to slow inflation (1 ml fluid administered over 20 min) of the balloon and, of these, four animals developed subsequently a marked systemic hypertensive response. In one animal there was a moderate increase in mean arterial pressure of 2.9 kPa (22 mmHg) towards the end of the investigation.

The changes observed in all five animals from the initial baseline stage to the point immediately before the onset of the SHR are displayed in Table 3a (intracranial indices) and in Table 3b (cardiovascular indices).

Intracranial indices

At baseline values, mean supratentorial pressure ranged from 0.27 kPa (2 mmHg) to 1.2 kPa (9 mmHg) (average value $0.8 \text{ kPa} \pm 0.13$ (6 mmHg)

Table 3a Changes (mean $\pm$ SEM) induced in the intracranial indices of five animals with parietal lesions by slow inflation of the extradural balloon (group B).

	Baseline	Before onset of SHR	Significance (P)
Mean supratentorial intracranial pressure kPa (mmHg)	0.8 $\pm$ 0.13 (6 $\pm$ 1)	8.5 $\pm$ 1.5 (64 $\pm$ 11)	< 0.005
Mean infratentorial intracranial pressure kPa (mmHg)	0.27 $\pm$ 0.08 (2 $\pm$ 1)	4.3 $\pm$ 0.93 (32 $\pm$ 7)	< 0.01
Transtentorial pressure gradient kPa (mmHg)	0.40 $\pm$ 0.13 (3 $\pm$ 1)	4.3 $\pm$ 0.93 (32 $\pm$ 7)	< 0.02
Mean supratentorial perfusion pressure kPa (mmHg)	16.5 $\pm$ 0.53 (124 $\pm$ 4)	6.3 $\pm$ 2.0 (47 $\pm$ 15)	< 0.005
Mean infratentorial perfusion pressure kPa (mmHg)	17.0 $\pm$ 0.40 (128 $\pm$ 3)	10.5 $\pm$ 1.3 (79 $\pm$ 10)	< 0.01

SHR = systemic hypertensive response.

Table 3b Changes (mean $\pm$ SEM) induced in the cardiovascular indices of five animals with parietal lesions by slow inflation of the extradural balloon (group B)

	Baseline	Before onset of SHR	Significance (p)
Heart rate beats/min	180 $\pm$ 19	72 $\pm$ 7	< 0.01
Mean arterial pressure kPa (mmHg)	17.3 $\pm$ 0.4 (130 $\pm$ 3)	14.8 $\pm$ 0.67 (111 $\pm$ 5)	< 0.025
Systolic arterial pressure kPa (mmHg)	20.8 $\pm$ 0.8 (156 $\pm$ 6)	20.1 $\pm$ 0.4 (151 $\pm$ 3)	ns
Diastolic arterial pressure kPa (mmHg)	15.6 $\pm$ 0.27 (117 $\pm$ 2)	12.5 $\pm$ 0.93 (94 $\pm$ 7)	< 0.01
Pulse pressure kPa (mmHg)	5.2 $\pm$ 0.67 (39 $\pm$ 5)	7.6 $\pm$ 0.8 (57 $\pm$ 6)	ns

SHR = systemic hypertensive response. ns = not significant.

± 1)), mean infratentorial pressure ranged from 0.13 kPa (1 mmHg) to 0.4 kPa (3 mmHg) (average value 0.27 kPa $\pm$ 0.08 (2 mmHg $\pm$ 0.6)), and mean cerebral perfusion pressure ranged from 15.2 kPa (114 mmHg) to 17.6 kPa (132 mmHg) in the supratentorial compartment and from 15.8 kPa (119 mmHg) to 18.1 kPa (136 mmHg) in the posterior fossa.

In this group of animals 8 ml $\pm$ 0.6 fluid had been added to the balloon before there was evidence of the beginning of the SHR, by which point both supratentorial and infratentorial pressures had increased significantly to 8.5 kPa $\pm$ 1.5 (64 mmHg $\pm$ 11) and 4.3 kPa $\pm$ 0.93 (32 mmHg $\pm$ 7) respectively. Since mean supratentorial pressure had increased to a greater extent than infratentorial pressure, the transtentorial pressure gradient increased significantly also from a baseline value of 0.40 kPa $\pm$ 0.13 (3 mmHg $\pm$ 1) to a value of 4.3 kPa $\pm$ 0.93 (32 mmHg $\pm$ 7). As a result of the alterations in the two intracranial pressures and in the mean arterial pressure (*vide infra*), cerebral perfusion pressure in the supratentorial compartment decreased significantly by 10.2 kPa $\pm$ 3.9 (77 mmHg $\pm$ 29) to a value of 6.3 kPa $\pm$ 2.0 (47 mmHg $\pm$ 15) (range 2.4 kPa (18 mmHg) to 13.4 kPa (101 mmHg)). It was noted, however, that in one animal, the animal which did not show any significant SHR, there was a decrease of only 3.3 kPa (29 mmHg) in the supratentorial perfusion pressure. If one removes the result for this particular animal from the mean values, mean cerebral perfusion pressure in this group of animals equals 4.5 kPa $\pm$ 0.93 (34 mmHg $\pm$ 7) (range 2.4 kPa (18 mmHg) to 6.7 kPa (50 mmHg)). Infratentorial perfusion pressure decreased also significantly, although to a lesser extent, to a new value of 10.5 kPa $\pm$ 1.3 (79 mmHg $\pm$ 10).

Cardiovascular indices

Before the initial infusion of fluid into the balloon, mean arterial pressure ranged from 16.4 kPa (123 mmHg) to 18.4 kPa (138 mmHg) (average value 17.3 kPa $\pm$ 0.4 (130 mmHg $\pm$ 3)) and, as was noted previously in the animals of group A, mean arterial pressure decreased significantly

by 2.5 kPa $\pm$ 0.67 (19 mmHg $\pm$ 5) immediately before the onset of the SHR. In this group there was no significant change in the systolic arterial pressure although diastolic arterial pressure did decrease significantly (Table 3b). Pulse pressure increased in all but one of the animals (range 6.7 kPa (5 mmHg) to 5.3 kPa (40 mmHg)) but the overall change was not significant.

Heart rate decreased in each animal, the decreases ranging from -29 beats/min to -157 beats/min. The absolute arrhythmia increased significantly and this plus the decrease in mean heart rate produced increases in arrhythmia index in each animal (range 8% to 127%) (Table 2).

FRONTAL LESIONS

The findings in the five animals with frontally-placed lesions were essentially similar to those observed in the animals with parietally-placed lesions, although in this group the changes took place more quickly and were present at lower balloon volumes. The onset of the systemic pressor response occurred at a balloon volume of 5.8 ml $\pm$ 0.4, which is significantly smaller ($p < 0.05$) than that required to initiate the response in either of the two other groups. The results of this group of animals are presented in Table 4a (intracranial indices) and Table 4b (cardiovascular indices).

Intracranial indices

Significant increases were observed in both the supratentorial pressure and in the infratentorial pressure to new values of 8.8 kPa $\pm$ 2.7 (66 mmHg $\pm$ 2) and 4.8 kPa $\pm$ 0.4 (36 mmHg $\pm$ 3) with a resultant increase in the transtentorial pressure gradient to 4.0 kPa $\pm$ 0.4 (30 mmHg $\pm$ 3). Supratentorial perfusion pressure decreased significantly to 3.2 kPa $\pm$ 0.93 (24 mmHg $\pm$ 7) (range 1.1 kPa (8 mmHg) to 6.5 kPa (49 mmHg)) while infratentorial pressure decreased less, although still significantly to 8.0 kPa $\pm$ 1.1 (60 mmHg) (range 5.5 kPa (41 mmHg) to 11.4 kPa (86 mmHg)).

Cardiovascular indices

Systolic and diastolic arterial pressures decreased significantly with a resultant decrease in the mean

Table 4a Changes (mean±SEM) induced in the intracranial indices of five animals with frontal lesions by slow inflation of the extradural balloon (group B)

	Baseline	Before onset of SHR	Significance (p)
Mean supratentorial pressure kPa (mmHg)	1.6±0.27 (12±2)	8.8±0.27 (66±2)	< 0.001
Mean infratentorial pressure kPa (mmHg)	1.5±0.13 (11±1)	4.8±0.4 (36±3)	< 0.001
Transtentorial pressure gradient kPa (mmHg)	0.13±0.13 (1±1)	4.0±0.4 (30±3)	< 0.005
Mean supratentorial cerebral perfusion pressure kPa (mmHg)	16.0±0.67 (120±5)	3.2±0.93 (24±7)	< 0.001
Mean infratentorial cerebral perfusion pressure kPa (mmHg)	16.0±0.67 (121±5)	8.0±1.1 (60±8)	< 0.001

SHR = systemic hypertensive response.

Table 4b Changes (mean±SEM) induced in the cardiovascular indices of five animals with frontal lesions by slow inflation of the extradural balloon (group B)

	Baseline	Before onset of SHR	Significance (p)
Heart rate beats/min	152±17	93±16	< 0.05
Mean arterial pressure kPa (mmHg)	17.4±0.53 (131±4)	12.6±0.67 (95±5)	< 0.001
Systolic arterial pressure kPa (mmHg)	20.9±0.53 (157±4)	16.5±0.53 (124±4)	< 0.001
Diastolic arterial pressure kPa (mmHg)	15.8±0.53 (119±4)	10.8±0.8 (81±6)	< 0.001
Pulse pressure kPa (mmHg)	5.1±0.4 (38±3)	5.7±0.67 (43±5)	ns

SHR = systemic hypertensive response. ns = not significant.

pressure of 4.8 kPa±0.4 (36 mmHg±3) (range 3.7 kPa (28 mmHg) to 5.5 kPa (41 mmHg)). As in the other groups studied, heart rate decreased in each animal (range -6 beats/min to -106 beats/min), the mean change being significant. The arrhythmia index increased in each animal (range 21% to 64%), the overall change being an increase of 38%±8 (Table 2).

Pupillary changes

An examination of the pupillary changes occurring in the 16 animals revealed that in 12 animals unilateral dilatation of the pupil ipsilateral to the lesion had taken place before the onset of the systemic pressor response. In three of the animals, both pupils were fully dilated and unreactive by this stage, and in only one animal—that already discussed which did not show any marked pressor response—were the pupils still small. In the animals subjected to rapid infusion, the first sign of unilateral dilatation of the pupil appeared after 6.3 ml±0.4 had been added to the balloon. In those animals with parietally-placed lesions subjected to slow inflation, this feature was evident once 7.6 ml±0.8 had been added. There is no significant difference between these two results ($P<0.10$). However, in the animals with frontally-placed lesions, unilateral pupillary dilatation occurred when significantly less fluid had been added to the balloon (4.6 ml±0.3) ($P<0.01$).

Discussion

Significant decreases in mean arterial pressure and heart rate, associated with significant increases in

absolute arrhythmia and arrhythmia index, have been observed in animals subjected to progressive increases in the volume of artificial intracranial mass lesions. These particular alterations took place before the onset of the SHR. It was noted that the changes occurred whether the balloon was inflated rapidly or more slowly, although differences did exist in the speed of onset of the changes depending on the site of the artificial space-occupying lesion.

INTRACRANIAL INDICES

Supratentorial pressure As the volume of the intracranial balloon was increased progressively, the supratentorial pressure increased from normal baseline values of around 1.3 kPa (10 mmHg) to values of between 7.7 kPa (58 mmHg) and 10.6 kPa (80 mmHg) in all but one animal. The rate of change, however, differed significantly between those animals in which the artificial mass lesion was placed over the frontal cortex and those with parietally-placed lesions. In a study by Jennett *et al.* (1969) it was shown that halothane had a more marked effect on the intracranial pressure of patients presenting with frontally-placed lesions than those with parietal tumours. They explained this finding by suggesting that in those patients with frontally-placed lesions, the space-occupying pathology had been present for a longer time and had reached a greater volume before producing symptoms than was the case with lesions in other areas. At the time of surgery, therefore, the frontal lesions were probably larger, intracranial compression more advanced, and the effect of the halothane consequently greater. How-

ever, the present study has shown that, in the dog, frontally-placed lesions led to marked intracranial hypertension and large transtentorial pressure gradients at smaller balloon volumes than did the parietally-placed lesions. The explanation for these differences seems likely to lie in the different anatomy of the dog compared with man, the narrow frontal pole of the dog's skull contrasting with the much more spacious frontal area of man. In these circumstances, compensation for the expansion of a frontally-placed balloon would be limited in the dog, and the displacement of the brain produced by a given balloon volume greater. The earlier establishment of tentorial impaction in those animals with a lesion in the frontal area would tend to support this possibility, evidence of impaction being deduced from the earlier appearance of transtentorial pressure gradients (Kaufmann and Clark, 1970) and the more rapid onset of unilateral pupillary dilatation in that group of animals.

Transtentorial pressure gradients As noted by others (Langfitt *et al.*, 1964; Weinstein *et al.*, 1968; Gonzalez *et al.*, 1972; Goodman *et al.*, 1972), supratentorial pressure was not transmitted uniformly to the posterior fossa with the result that marked transtentorial pressure gradients appeared. The level at which the apparent tentorial block occurred varied in the different groups. Tentorial impaction (as determined by unilateral pupillary dilatation) occurred at transtentorial pressure gradients which ranged from $2.8 \text{ kPa} \pm 0.4$ ($21 \text{ mmHg} \pm 3$) in the group B animals with frontal lesions to $4.5 \text{ kPa} \pm 2.3$ ($34 \text{ mmHg} \pm 17$) in group A. (Average value (11 animals) $3.2 \text{ kPa} \pm 0.4$ ($24 \text{ mmHg} \pm 3$).) The existence of such inter-compartmental pressure gradients in a state of increased intracranial pressure has been documented in the past (von Bergmann, 1885; Smyth and Henderson, 1938; Kaufmann and Clark, 1970). Gradients may occur at either of two sites, across the tentorium, as in the present study, and across the foramen magnum as described by Smyth and Henderson (1938). The development of such gradients seems to depend on the obliteration of the subarachnoid space at these sites by the displacement of brain tissue. If the subarachnoid space can be reconstituted, then the gradients may be reversed (Langfitt *et al.*, 1964).

Cerebral perfusion pressure As a result of the increase in supratentorial pressure and the concomitant decrease in mean arterial pressure, supratentorial perfusion pressure decreased markedly in 15 of the 16 animals, the exception being the dog which failed to develop a marked SHR. Immediately before the onset of the SHR,

the average supratentorial perfusion pressure (15 animals) was $3.7 \text{ kPa} \pm 0.4$ ($28 \text{ mmHg} \pm 3$). However, it should be noted that the value for the supratentorial perfusion pressure given above was that value existing at the point immediately before the onset of the systemic pressor response as judged by the arterial pressure record, and was not, therefore, necessarily the lowest cerebral perfusion pressure recorded in each individual animal. If one abstracts from the records the lowest supratentorial perfusion pressure values in each of the 15 animals, an average value of $2.8 \text{ kPa} \pm 0.27$ ($21 \text{ mmHg} \pm 2$) is obtained (range $+0.4 \text{ kPa}$ (3 mmHg) to $+5.1 \text{ kPa}$ (38 mmHg)). Thus the values obtained for perfusion pressure in the supratentorial compartment were less than the values ($4.0\text{--}6.7 \text{ kPa}$: $30\text{--}50 \text{ mmHg}$) at which signs of cerebral tissue hypoxia and a pronounced acidosis in the cerebral extracellular fluids can be observed (Zwetnow, 1968; Zwetnow *et al.*, 1968). Infratentorial perfusion pressure ranged from 5.5 kPa (41 mmHg) to 12.9 kPa (97 mmHg) which would be sufficient to maintain adequate blood flow in the posterior fossa (Harper, 1966). As low supratentorial perfusion pressures were recorded immediately or almost immediately before the onset of the SHR, it may be that the low perfusion in the supratentorial compartment played some part in the genesis of the hypertensive response.

CARDIOVASCULAR INDICES

The haemodynamic changes associated with increasing intracranial pressure have been the subject of many previous studies. However, in most of these investigations, the intracranial pressure has been increased acutely, over a few seconds or minutes, and the primary interest of the investigators has been in the associated systemic pressor response. In such studies, an assessment of the sequence of events preceding the SHR was not possible, although in a few studies (Campbell *et al.*, 1949; Hedges and Weinstein, 1964; Ducker and Simmons, 1968) a decrease in heart rate was observed immediately before the onset of the systemic hypertension. Decreases in heart rate have, however, been recorded by Langfitt *et al.* (1966) in the rhesus monkey, by Hekmatpanah (1970) in cats, and by Gonzalez *et al.* (1972) in dogs during a gradual increase in intracranial pressure and before the appearance of systemic hypertension. In contrast, Hayreh and Edwards (1971) found a linear relationship between heart rate and CSF pressure in the rhesus monkey—as the CSF pressure increased so did the heart rate. In the present study, a decrease in heart rate was noted in all animals and was in evidence after

the first addition of fluid to the balloon. This decrease was found to be progressive from the first balloon inflation until the onset of the SHR.

Another feature noted in the present study was the alteration in the sinus arrhythmia related to the rate of the ventilator; heart rate increased during positive pressure inspiration and decreased during expiration. This ventilator-related arrhythmia was present before the balloon was inflated at all, but with each inflation of the balloon the extent of the arrhythmia increased. In many animals the increase in arrhythmia index paralleled the decrease in heart rate, as one would anticipate since heart rate is the denominator of the equation. Table 2 displays both the arrhythmia indexes and the absolute arrhythmias found in the three groups of animals in the present study and it is clear that marked and significant increases in absolute arrhythmia occurred as well as in arrhythmia index. It is interesting to note that the one animal out of the 16 which did not develop major intracranial hypertension or a marked SHR showed the smallest changes in arrhythmia index.

In the present studies, mean arterial pressure decreased significantly from baseline values by the beginning of the SHR. It is possible that this effect was the result of a progressive deterioration in the experimental preparation with time or it may have been secondary to the bradycardia which we have noted already. However, support is given to the suggestion that the changes observed in mean arterial pressure are a feature of the initial stages of increasing intracranial pressure by the findings of other workers who observed similar changes (Hedges and Weinstein, 1964; Langfitt *et al.*, 1966; Hekmatpanah, 1970; Goodman *et al.*, 1972). Hayreh and Edwards (1971) noted a decrease in the arterial pressure of rhesus monkeys at low levels of intracranial pressure but, as the mean intracranial pressure increased to around 4.7 kPa (35 mmHg), they observed a slight increase in the mean arterial pressure. A decrease in diastolic pressure alone was reported by Gonzalez *et al.* (1972) whereas Ducker and Simmons (1968) found no change in mean arterial pressure in dogs and monkeys before the onset of the SHR.

Clinically, widening of the pulse pressure has been reported as an early sign of increasing intracranial pressure (Lewin, 1966), and a similar observation has been made by Tarlov *et al.* (1959) in dogs. However, in the present study no significant changes were noted in the pulse pressure in any of the groups, although in most of the animals (12) pulse pressure did increase. In a further two animals the pulse pressure decreased, and in two

it remained unchanged.

No significant alterations were noted in either cardiac output, stroke volume, or systemic vascular resistance as the intracranial pressure was increased to value of around 9.3 kPa (70 mmHg). Ducker *et al.* (1968) found no significant change in cardiac output and systemic vascular resistance with increase in mean intracranial pressure up to 10.0 kPa (75 mmHg), and similarly, Gonzalez *et al.* (1972) found no significant alterations in cardiac output with intracranial pressure up to 8.0 kPa (60 mmHg).

CLINICAL IMPORTANCE

The animals in the present study were studied while paralysed and on controlled ventilation, conditions which tend to militate against the collection of data of clinical relevance in the head-injured patient, or in the patient with acute neurological problems. This applies especially to the estimation of conscious level and limb movements. However, the present study has shown that certain changes do take place under conditions of artificial ventilation, and it is possible that an assessment of these changes could be of clinical value. This would be particularly true of the measurement of the arrhythmia index (or of absolute arrhythmia) if these particular indices were shown to be as sensitive in man as they are in the dog. It is also of clinical importance to emphasise again the finding that these changes preceded the appearance of the systemic pressor response, and in the majority of animals, such changes also preceded bilateral pupillary dilatation, changes which appear to be late and possibly agonal responses (Fitch *et al.*, 1977). It is true that the study has been concerned with the changes taking place in dogs and direct extrapolation to the clinical situation may not be relevant without further studies. However, certain features do exist which may be of value in the assessment of patients with head injuries or other acute neurological problems such as cerebral infarction, subarachnoid haemorrhage, and intracerebral haematoma and which may be worthy of further study in the clinical setting.

The authors wish to acknowledge the help received from Dr G. M. Paterson and Dr W. R. Hain. They thank also the technical and biochemical staff of the University Department of Anaesthesia, The University of Leeds. The Department of Medical Illustration, Southern General Hospital, Glasgow, prepared the illustrations. Secretarial assistance was given by Miss Diane E. McCorkindale. Dr Fitch was in receipt

of a grant from the Medical Research Council throughout the period of this work.

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