

Vascular responses to acute intracranial hypertension

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SUMMARY In 27 rhesus monkeys the cerebrospinal fluid pressure (CSFP) was raised by injections into the cisterna magna to about 40 to 50 mm Hg in steps of 5 mm Hg every five minutes. During the initial phase of the rise of the CSFP to about 15 mm Hg normal animals showed a significant fall in the systolic arterial blood pressure. With a further elevation of the CSFP the BP rose till the CSFP reached 30 to 40 mm Hg. If the CSFP were raised higher than that, a large number of the animals showed a significant fall in the BP. In animals which were shocked before the CSFP was raised there was no drop in the systolic BP during the initial phase. This study indicates that vascular decompensation occurs in the majority of animals when the CSFP goes higher than 30 to 40 mm Hg; there is a significant rise in the pulse rate, superior sagittal sinus pressure (SSP), and internal jugular vein pressure (JVP). The JVP was related to the SSP, indicating that the JVP most probably reflected the pressure changes in the intracranial venous sinuses. Four animals suddenly collapsed at the highest CSFP. In the remaining 23 animals, on a sudden lowering of the CSFP to zero from the highest level, 13 monkeys died in less than half an hour and four in about an hour, while six animals stood this elevation of the CSFP well, with a good recovery. This indicates that, once the vascular decompensation has set in, the prognosis is generally poor even after lowering the CSFP to normal. The drop of the CSFP to zero produced no significant change in the pulse rate but a significant fall in the BP. The SSP rose when its pre-lowering level was less than 7.5 mm Hg and fell when the level was at or above 7.5 mm Hg level. The JVP showed a significant correlation with the variations in the SSP. The fundus examination at the end of the experiment revealed no abnormality.

Classical signs and symptoms of raised intracranial pressure include headache, vomiting, raised systemic arterial blood pressure (BP), bradycardia, slowing of the respiratory rate, raised temperature, oedema of the optic disc, stupor, unconsciousness, and coma. Kocher (1901) subdivided the progressive manifestations of brain compression into four stages:

1. STAGE OF ACCOMMODATION due to displacement of the cerebrospinal fluid and encroachment upon the cerebral venous bed.

2. STAGE OF EARLY MANIFEST SYMPTOMS Compression of capillaries results in relative anoxaemia of vital bulbar centres leading to slight rise in BP and vagal

stimulation causing slow pulse and respiration, and distension and tortuosity of the retinal veins.

3. STAGE OF ADVANCED MANIFEST SYMPTOMS Arteriolar stasis and more severe anaemia of the medullary centres leading to high BP, slow pulse, Cheyne-Stokes respiration, and choked optic disc.

4. STAGE OF MEDULLARY COLLAPSE Over-stimulated vital centres become exhausted, causing fall of BP, pulse acceleration, irregular apnoeic respiration, and shock.

Figures 1a and 1b represent the two usual clinical concepts prevalent in the literature. Some workers, however, do not think that the above symptoms and signs are seen in raised intracranial tension (Gurdjian, 1933; Alava and Stat, 1934; Browder and Meyers, 1938).

The present study was carried out in rhesus monkeys with a view to investigating and correlating

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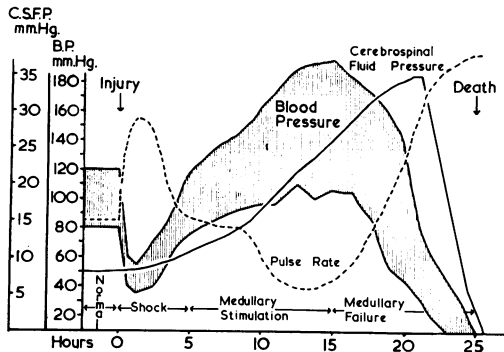


FIG. 1a. This diagram illustrates the pattern which is commonly accepted in clinical practice as occurring after the rise in intracranial pressure following a head injury (after Browder and Meyers, 1938).

the effects of raised intracranial pressure on the systemic and ophthalmic arterial and venous pressures, superior sagittal sinus pressure (SSP), pulse rate, and the changes at the optic disc. This study formed a part of studies on the pathogenesis of oedema of the optic disc in raised intracranial pressure (Hayreh, 1964, 1965, 1968). The effects of raised intracranial pressure on ophthalmic arterial and venous pressures are discussed at length elsewhere (Hayreh and Edwards, 1971).

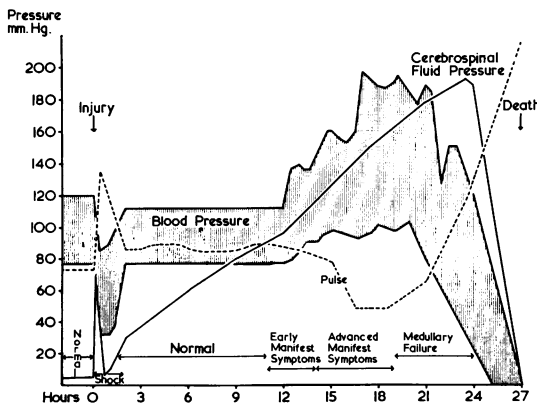


FIG. 1b. This diagram shows the pattern of responses of the blood pressure and pulse rate following an experimental rise in intracranial pressure in animals, as described by Kocher (1901), Cushing (1901), and Eyster (1906), etc. Note the absence of such responses until the intracranial pressure reached the diastolic and/or mean arterial pressure (after Browder and Meyers, 1938).

METHODS

Twentyseven adult, healthy, rhesus monkeys, weighing 4 to 8 kg, were anaesthetized by intraperitoneal nembutal, 40 mg/kg, and placed on an electrically warmed animal operating table. Atropine 1% and phenylephrine 10% were instilled in each eye to dilate the pupil and the lids were then sutured together to preserve corneal transparency, so that the fundus could be examined at the end of the experiment for any changes.

The ophthalmic artery and vein were exposed for cannulation at the right supraorbital margin, with the aid of a Zeiss operating microscope, followed by the superior sagittal sinus at the vertex, the right jugular vein in the neck at about the level of the thyroid cartilage, and the femoral artery and vein just below the inguinal ligament. The vessels were then cannulated in the following order:

1. FEMORAL VEIN It was cannulated in order to inject 5,000 i.u. heparin to minimize clotting of the cannulae and subsequently to administer maintenance doses of nembutal.

2. FEMORAL ARTERY A 1 mm bore nylon tube was pushed in to reach the abdominal aorta.

3. INTERNAL JUGULAR VEIN A glass T-cannula was used. Each arm of the T carried a soft PVC tube about 2 cm long and with a 1.5 mm bore to prevent the collapse of the wall of the vein where it had been exposed for cannulation and had lost the support of surrounding tissue, and to maintain the flow of blood to the heart. The right vein was used because it is in direct line with the superior vena cava and right atrium.

4. OPHTHALMIC VEIN An 0.5 mm bore nylon tube was pushed about 2 cm down the intraorbital section of the vessel.

5. OPHTHALMIC ARTERY An 0.2 mm bore nylon tube was inserted 0.5 to 1 cm into its intraorbital part.

6. SUPERIOR SAGITTAL SINUS A 1 mm bore nylon tube was introduced through a small incision in its superficial wall. The cannula was pushed in for 4 to 5 cm.

7. The animal was turned over to lie on its left side and a short bevel No. 11 serum needle was introduced into the cisterna magna (cerebello-medullary cistern) to enable the cerebrospinal fluid pressure (CSFP) to be recorded and elevated.

The cannulae, filled with normal saline, were connected to six pressure transducers whose amplified outputs were fed to six mirror galvanometers in an ultra-violet recorder, using 12 in. wide paper. The pulse rate was also measured in 17 animals by using another recorder to record, at frequent intervals throughout the experiment, the aortic pressure at high speed, so that the individual pulse waves per minute could be counted.

Normal pressures were recorded first. A tap connecting a saline-filled reservoir to the CSFP transducer was then opened so that the pressure could be elevated to any

TABLE 1

MEAN AND STANDARD DEVIATION OF CHANGES PRODUCED IN BLOOD PRESSURE BY RAISED CEREBROSPINAL FLUID PRESSURE DURING VARIOUS PHASES

Change in BP in mm Hg	Mean SD	Initial phase				Middle phase				Final phase			
		Normal animals		Shocked animals		Normal animals		Shocked animals		Normal animals		Shocked animals	
		Syst.	Diast.	Syst.	Diast.	Syst.	Diast.	Syst.	Diast.	Syst.	Diast.	Syst.	Diast.
		-7.31	+1.12	+4.90	+4.50	+43.43	+19.81	+34.80	+17.20	-26.47	-28.94	+8.20	-6.50
		37.22	27.20	25.3	16.57	63.05	30.02	36.38	22.55	59.39	26.54	70.23	40.28

SD = Standard deviation. Syst. = Systolic. Diast. = Diastolic. + = Rise of blood pressure. - = Fall of blood pressure.

desired level by raising the reservoir. The pressure was raised initially to 10 mm Hg and subsequently increased in steps of 5 mm Hg about every five minutes. The maximum elevation depended upon the response of the animal, so that in some experiments the CSFP did not reach the planned level of 50 mm Hg or more, because the monkey showed signs of distress or collapsed. In 15 experiments the pressure was raised to 50 mm Hg, in four to 45 mm Hg, in three to 40 mm Hg, in one to 35 mm Hg, in one to 55 mm Hg, in two to 60 mm Hg, and in one to 70 mm Hg. In 22 animals the CSFP was raised above normal for

periods varying between 45 and 92 minutes, while in the remaining five experiments it varied between 36 and 120 minutes. The total duration of elevation of pressure in any particular experiment generally depended on how long the maximum pressure was tolerated by the animal. After this, the reservoir was lowered rapidly to zero to record the effect of sudden decompression after an acute intracranial hypertension. Most of the monkeys collapsed immediately or shortly after the pressure drop. At the end of the experiment the fundus was examined for evidence of any changes.

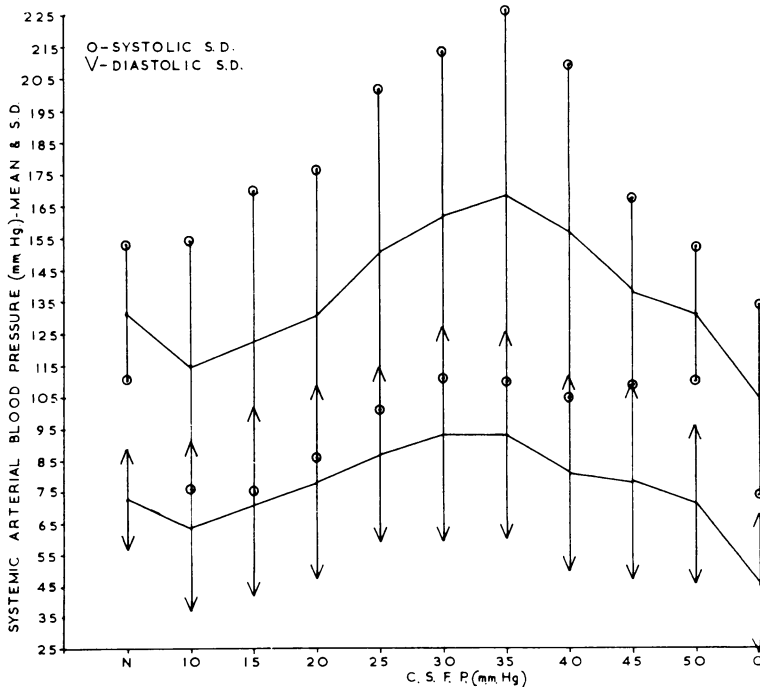


FIG. 2. A graphic plot of the mean systolic and diastolic systemic arterial blood pressure, with their standard deviations, at the various levels of the cerebrospinal fluid pressures in unshocked animals.

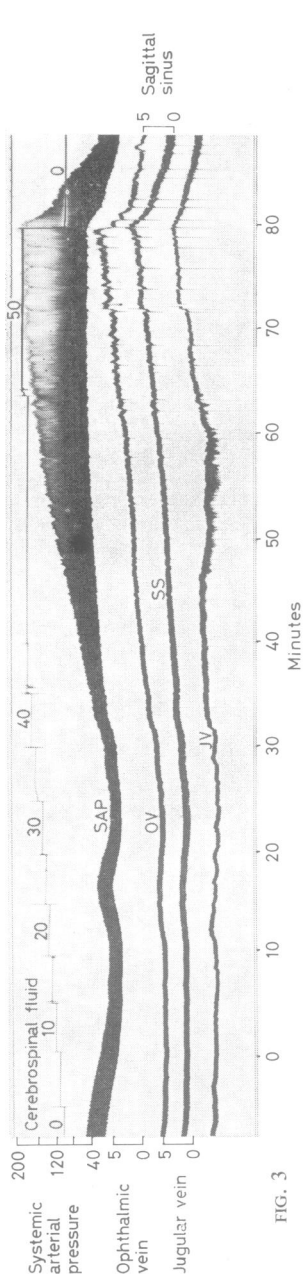


FIG. 3

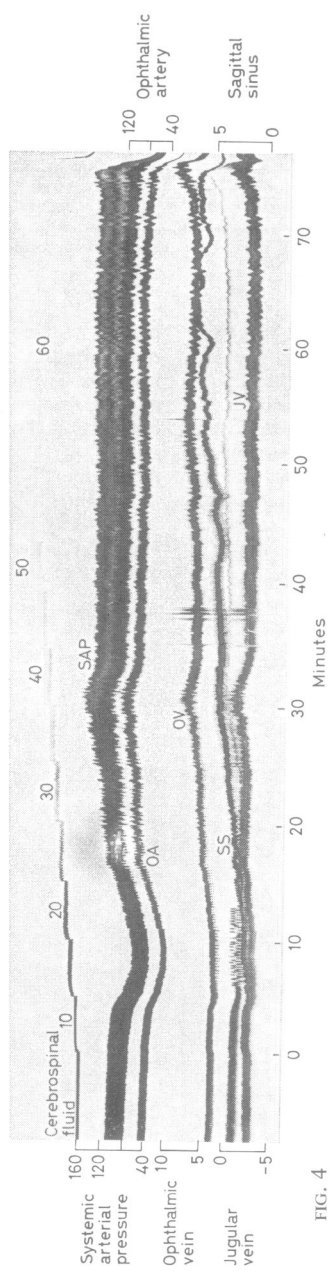


FIG. 4

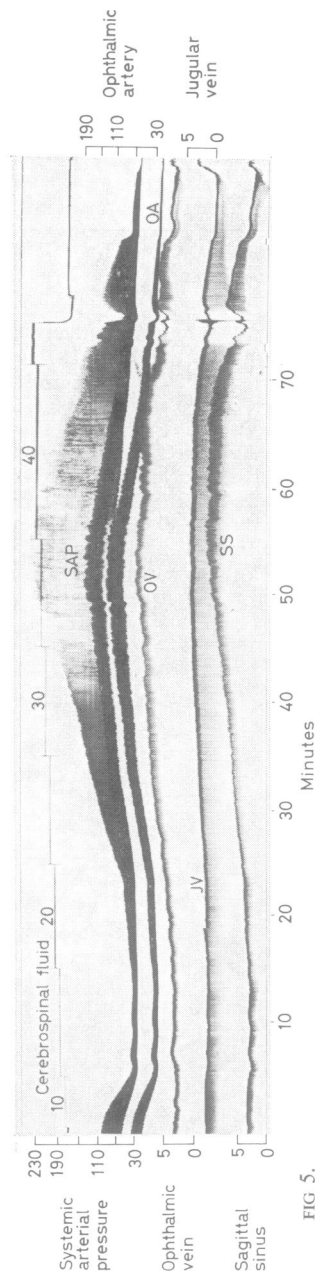


FIG. 5.

FIGS. 3-7. *Experimental records of the various vascular responses to rise of the cerebrospinal fluid pressure. All pressures are in mm Hg. In Figure 6, the fall in the internal jugular vein pressure from five to 25 minutes is an artefact due to a block in its cannula. Fig. 4 shows the animal suddenly collapsing at 60 mm Hg cerebrospinal fluid pressure, and in Fig. 5, soon after lowering the cerebrospinal fluid pressure to zero.*

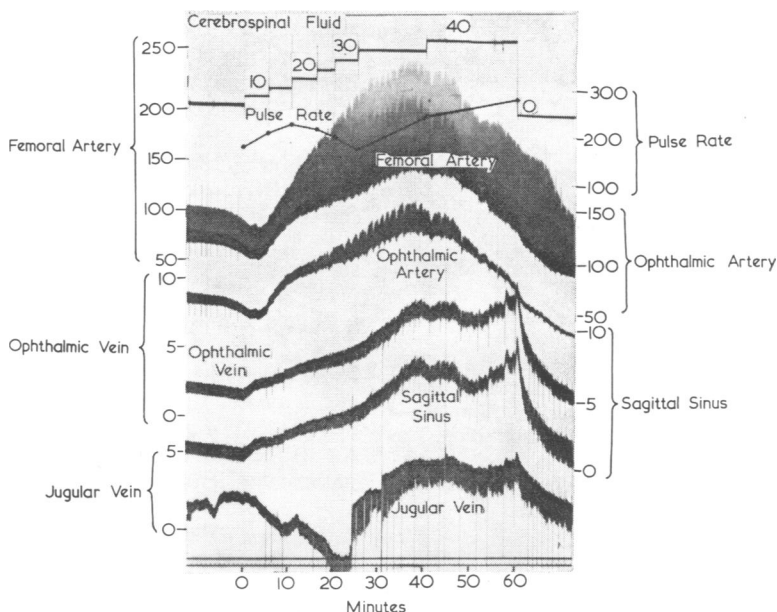


FIG. 6

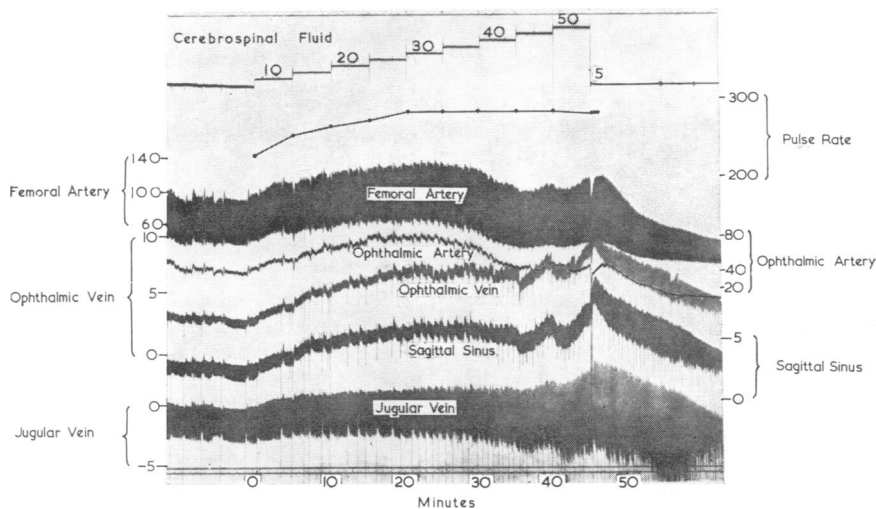


FIG. 7

OBSERVATIONS

The preparation of the animal for the recording of these various pressures took two to three hours and the trauma of the extensive dissections resulted in a varying degree of surgical shock in 37% of the animals (group B). In this group were included the animals with a diastolic BP of 60 mm Hg or less when associated with a systolic BP of less than 110 mm Hg. In this condition the monkey

may perhaps be compared with a person suffering from shock as a result of extensive injuries. The experimental rise of intracranial pressure in these animals may, therefore, simulate a rapid rise of intracranial pressure associated with multiple injuries and shock. Hence, the observations in this group may help to provide some information about the responses of such cases to raised intracranial pressure and sudden surgical decompression. These observations may also indicate the possible differ-

ence in response to raised intracranial pressure in these shocked animals (group B) compared with the normal animals (group A).

The responses of the rhesus monkeys to the acutely raised CSFP varied widely, but the majority showed a considerable similarity. The arterial responses tended to divide themselves into three phases. These were:

1. INITIAL PHASE in which the CSFP was elevated from normal to 15 mm Hg.
2. MIDDLE PHASE with the CSFP from 15 to 30-40 mm Hg.
3. FINAL PHASE with the CSFP from 30 to 40 mm Hg to a level which depended on how well the animal tolerated the high intracranial pressure.

The effects of the sudden drop of CSFP have been presented separately.

From the continuous recordings the levels of the various pressures and the pulse rate were estimated at the normal CSFP and at each step just before raising it by 5 mm Hg—that is, 10 to 15 mm Hg, 15 to 20 mm Hg, and so on. The data thus collected have been subjected to detailed statistical analysis, including the Friedman two-way analysis of variance.

EFFECTS OF ACUTE INTRACRANIAL HYPERTENSION

1. SYSTEMIC ARTERIAL BLOOD PRESSURE The BP was measured from the abdominal aorta with the cannula introduced through the femoral artery. The responses of the BP are reported separately in the normal (group A) and shocked (group B) animals. The normal systolic and diastolic BP in the two groups were:

Group A—Systolic BP: 132.2 ± 13.4 mm Hg
Diastolic BP: 71.3 ± 14.1 mm Hg

Group B—Systolic BP: 74.8 ± 20.4 mm Hg
Diastolic BP: 45.0 ± 11.6 mm Hg

The changes produced by the raised CSFP on the BP in the two groups during the initial, middle and final phases are shown in Table 1.

A graphic plotting of the mean systolic and diastolic BP, with their standard deviations, at the various levels of the CSFP in the group A animals is shown in Fig. 2. The highest systolic and diastolic BP was recorded at the highest CSFP in nine animals (at 50 mm Hg or more CSFP—Figs. 3, 4); while in the remaining 18 these reached the highest levels before the CSFP reached its highest level (40 mm Hg or less—Figs. 5, 6, 7).

A statistical analysis of the responses by the animals from groups A and B revealed that: (a) *During the initial phase* only group A animals showed a significant ($P = < 0.01$) drop in systolic BP, whereas the drop in diastolic BP was not significant in either group. (b) *During the middle and final phases* there was no significant difference in the behaviour of the two groups.

The *t* test was performed (after the Friedman analysis of variance had shown significance in the data) on the changes of the systolic and diastolic BPs (of group A and of the combined group A + B) at the following three levels:

1. *Between the normal and 10 mm Hg CSFP—that is, the initial phase* A large number of the animals showed a fall in the BP during this phase.

For group A. In this group the *t* was statistically significant only for the systolic BP ($P = < 0.01$).

For the entire series (group A + B). The *t* for the systolic and diastolic BP was not significant.

2. *Between 10 and 35 mm Hg CSFP—that is, the middle phase* All the animals showed a rise during this phase. For group A and the entire series (group A + B) the *t* for both systolic and diastolic BP was statistically significant ($P = < 0.01$).

3. *Between 35 and 50 mm Hg CSFP—that is, the final phase* During this phase the majority of the animals showed a fall in both the systolic and diastolic BPs in group A (Fig. 2), as well as in the entire series. However, the *t* was significant ($P = < 0.05$) for the diastolic BP only in both groups. Although a non-significant result was present in the absolute values of the systolic BP, it appeared that a test for the rates of change in the BP would be more appropriate. With this in view, a comparison of the rates of change in the BP (both systolic and diastolic) from 15 to 25, 25 to 35, and 35 to 45 mm Hg CSFP was carried out by the Friedman analysis. This showed that the rates of change were significantly different ($P = < 0.05$). After this result, a Wilcoxon matched pairs sign-rank test showed that the rate of change in the BP during 25 to 35 mm Hg CSFP was significantly different from that during 35 to 45 mm Hg CSFP, whereas the rate of change in the BP during 15 to 25 mm Hg CSFP was *not* significantly different from that during 25 to 35 mm Hg CSFP. In other words, this indicates that the rates of change in the BP induced by the raised CSFP did not vary significantly during the course of the middle phase, but the rate of change in the BP after 35 mm Hg CSFP was different from the rate of change before 35 mm Hg CSFP. Thus, 35 mm Hg CSFP seems to be an important level, the BP showing a rise before and a fall after that level. No correlation was observed between the initial BP, the variation of the BP with the rise of CSFP, and the highest level of the BP reached.

2. PULSE RATE The normal rate in rhesus monkeys was 206 ± 45 per minute (Table 2). The mean pulse rates with standard deviations at different levels of the CSFP are shown in Fig. 8. The correlation

the CSFP are shown (Fig. 9). The correlation coefficients between SSP and CSFP in the various animals are statistically significant (Table 4).

Taking the ophthalmic artery pressure (OAP) as an index of the internal carotid artery pressure (Hayreh and Edwards, 1971), a correlation was looked for between the SSP and the OAP during the different phases of the raised CSFP. At the normal and 10 mm Hg CSFP the correlation coefficient was significant ($P = <0.05$), but not above that level.

A significant correlation ($P = <0.01$) was seen between the SSP and ophthalmic vein pressure (OVP) in normal animals and with raised CSFP (Hayreh and Edwards, 1971).

4. INTERNAL JUGULAR VEIN PRESSURE (JVP) The normal JVP is 1.07 ± 3.11 mm Hg (Table 2). Figure 10 is a graphic plot of the mean JVP and standard deviations at different CSFP levels.

JVP is taken as an index of the systemic venous pressures near the inlet of the thorax and the heart.

The correlation coefficient between JVP and BP (both systolic and diastolic) was not significant. Similarly correlation between the JVP and pulse rate was not significant. The correlation coefficient between JVP and CSFP was significant in the majority of the animals (Table 5).

The rates of change of the JVP between three equal CSFP intervals of the present series—that is, normal to 20 mm Hg, 20 to 35 mm Hg, and 35 to 50 mm Hg CSFP—were examined by Friedman's analysis of variance. This was done with a view to finding out whether there was any difference in the rate of change of the JVP during the initial, middle, or final phase of the raised CSFP. No significant difference in these different phases was observed. This suggests that there is a constant rise in the JVP with the rise of the CSFP without the rise being more marked during any particular stage.

The correlation coefficient between SSP and JVP was significant ($P = <0.05$) at normal and high CSFP.

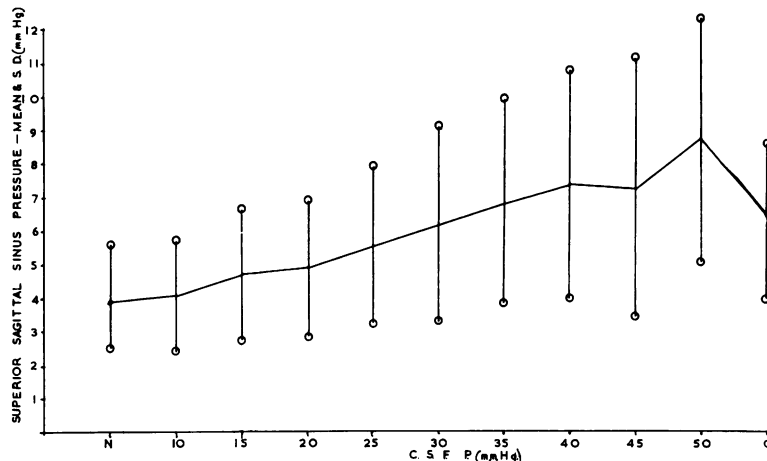


FIG. 9. A graphic plot of the mean and standard deviations of the superior sagittal sinus pressures at different levels of the raised cerebrospinal fluid pressure.

TABLE 4

SPEARMAN'S RANK CORRELATION COEFFICIENT (r) BETWEEN SUPERIOR SAGITTAL SINUS PRESSURE AND CEREBROSPINAL FLUID PRESSURE

r	1.0	0.99	0.98	0.97	0.95	0.93	0.92	0.91	0.90	0.89	0.87	0.86	0.85	0.81	0.73	0.60	0.50	0.45	0.26
No. of animals	1	3	1	3	1	1	1	1	1	1	1	1	2	2	2	1	1	1	1
Significance																at 0.05			None

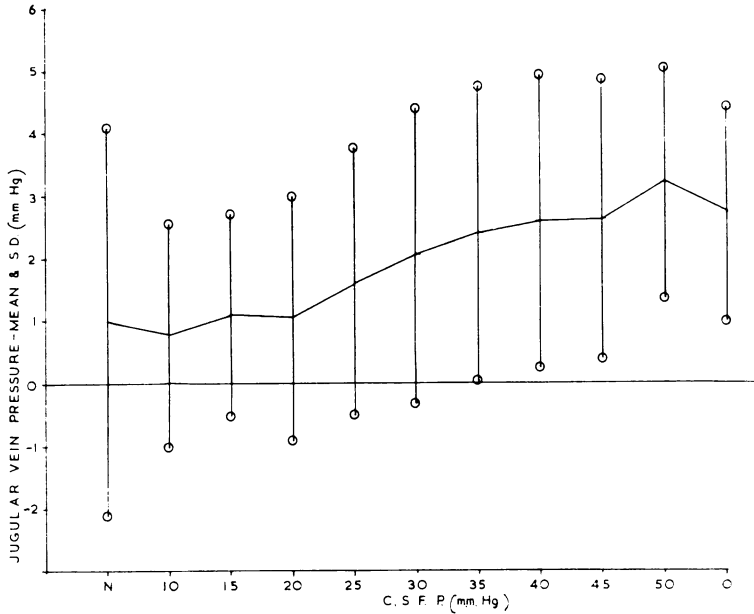


FIG. 10. A graphic plot of the mean and standard deviations of the internal jugular vein pressures at different levels of the raised cerebrospinal fluid pressures.

EFFECTS OF SUDDEN LOWERING OF CSFP

Table 6 summarizes the responses of the BP, pulse rate, SSP, and JVP to the sudden lowering of the CSFP after acute intracranial hypertension. Four animals suddenly collapsed due to the effects of the intracranial hypertension and died at the highest CSFP of 35, 45, 50, and 60 mm Hg respectively (Fig. 4). Out of the remaining animals, 13 died in less than half an hour (Fig 5), four within about an hour of lowering the CSFP to zero, and six animals were killed because they showed no sign of collapse for about two hours or so.

The correlation coefficient between changes in the SSP and the JVP with the fall of the CSFP was significant ($P = < 0.01$). A correlated t test of the difference between the normal SSP level and that of its level after lowering the CSFP was found to be significant ($P = < 0.01$). It was discovered that the

fall of the CSFP usually caused a rise in the SSP when its pre-lowering level was < 7.5 mm Hg and a fall when the level was at or above 7.5 mm Hg level. A chi-square test (with Yates correction for continuity) of these changes established that the changes are significant ($P = < 0.02$).

DISCUSSION

SYSTEMIC ARTERIAL BLOOD PRESSURE RESPONSES Cushing (1901) enunciated a law which stated that 'an increase of intracranial tension occasions a rise of blood pressure which tends to find a level slightly above that of the pressure exerted against the medulla.' Similar views have been expressed by Janeway (1904), Eyster, Burrows, and Essick (1909), Howe (1927), Munro (1927) and others. The level of CSFP which stimulates a rise of the BP has been described variously by the different authors. The

TABLE 5

SPEARMAN'S RANK CORRELATION COEFFICIENT (r) BETWEEN JUGULAR VEIN PRESSURE AND CEREBROSPINAL FLUID PRESSURE

r	0.99	0.98	0.97	0.95	0.94	0.93	0.92	0.89	0.83	0.79	0.75	0.74	0.68	0.58	0.56	0.50	0.37	0.12	-0.55
No. of animals	1	1	4	1	1	2	1	2	2	2	1	1	1	1	1	2	1	1	1
Significance	at 0.01 level						at 0.05 level						None						

TABLE 6

EFFECTS OF LOWERING OF CEREBROSPINAL FLUID PRESSURE ON BLOOD PRESSURE, PULSE RATE, SUPERIOR SAGITTAL SINUS PRESSURE, AND JUGULAR VEIN PRESSURE AND THEIR SIGNIFICANCE

	Blood pressure (mm Hg)		Pulse rate (per min)	SSP (mm Hg)	JVP (mm Hg)
	Systolic	Diastolic			
Post-lowering level	95.8 ± 32.2	39.1 ± 19.9	234 ± 43	6.3 ± 2.3	2.1 ± 2.3
Difference in levels between pre- and post- lowering of CSFP*	-36.9 ± 42.7	-21.2 ± 22.2	-22.6 ± 44.4	-2.6 ± 4.1	-0.7 ± 2.4
Correlated 't' test for significance of values in Column II	Significant at 0.01 level	Significant at 0.01 level	Not significant	Significant at 0.05 level	Not significant

*Minus sign = a fall of pressure.

BP may be affected when the CSFP reaches the level of (a) *the diastolic BP* (Cannon, 1901; Eyster, 1906; Eyster *et al.*, 1909; Howe, 1927; Munro, 1927; Weed, 1929; Wolff and Forbes, 1929; Wilson, 1932; Fremont-Smith and Merritt, 1933; Masserman, 1934; and others), (b) *the systolic BP* (Cushing, 1901; Wright, 1938; Weinstein, Langfitt, and Kassell, 1964; and others), or (c) *the mean BP* (Eyster *et al.*, 1909; Howe, 1927; Munro, 1927; Browder and Meyers, 1938; and others). On raising the CSFP to about 40 mm Hg experimentally, no response in the BP was detected by Weed and Flexner (1933), Bedford (1942), and Hedges (1963).

Cushing (1903) and Janeway (1904) regarded the extent of the rise of BP as an indication of the degree of compression of the brain. According to Schurmann (1965), the more rapid the increase of intracranial pressure in craniocerebral injury in man, the more marked is the hypertensive reaction. He considered the hypertensive reaction an important diagnostic and prognostic sign in the early stages of head injury. Eichbaum and Bissetti (1965) recorded in dogs with head injury and acute intracranial hypertension an initial short-lasting hypertension, followed by a late hypotension, often reaching shock levels. Other authors, however, consider the BP of little value as an index of the raised intracranial pressure (Stewart, 1921; Jackson, 1922; Bower, 1923; Holbrook, 1924; Adson and Lillie, 1927; McCreery and Berry, 1928; Fremont-Smith and Kubie, 1929; Howe, 1927; Dandy, 1933; Gurdjian, 1933; Browder *et al.*, 1936, 1938; and others). McClure and Crawford (1928) regarded pulse pressure as an important indication.

The findings of the present study, summarized in Table 1 and shown in Figs. 2, 3, 4, 5, 6, and 7, are in sharp contrast with most of the above-mentioned views from the literature. During the initial phase of the raised CSFP the BP showed a response in almost all the animals; the systolic and diastolic BP showed a fall in 52% and 41% respectively; the fall in the systolic BP was statistically significant ($P = < 0.01$).

During the middle phase systolic and diastolic BP rose in 93% and 85% respectively ($P = < 0.01$). During the final phase (40 mm Hg CSFP) a fall in systolic and diastolic BP was seen in 66% and 82% respectively, which was significant when compared with the changes in the BP during the middle phase. In about two-thirds of the animals the BP reached its highest level when the CSFP was about 30 to 40 mm Hg, and further elevations of the CSFP usually led to a fall in the BP. These observations reveal that an acute elevation of the CSFP even to 10 to 15 mm Hg induces BP changes and a decompensation may start when the CSFP goes over 30 to 40 mm Hg. These findings are contradictory to previously-held views that the CSFP must rise to the level of the diastolic or mean BP to produce any such response. Similar views were expressed by Kety, Shenkin, and Schmidt (1948). The views of Meyers (1942) that the diastolic BP does not necessarily or regularly maintain itself above the intracranial pressure, were also confirmed by the present study.

We consider that the animals in group B, with a systolic BP of 74.8 ± 20.4 mm Hg and diastolic BP of 45.0 ± 11.6 mm Hg might be compared with patients suffering from shock resulting from multiple injuries. The response to the raised CSFP in this group of animals was not significantly different from that seen in normal (unshocked) animals, except for the systolic BP response during the initial phase, which showed a significant drop in normal animals only.

With regard to the pathogenesis of the rise of BP accompanying an acutely raised CSFP, there are the following three postulates in the literature:

a. *Primary vasoconstriction of neurogenic origin* from the medullary centres (Cushing, 1901; Eyster *et al.*, 1909; Grimson, Wilson, and Plemister, 1937; Forster, 1943; Brown, 1956; Langfitt, Weinstein, and Kassell, 1965; and others), and probably from the midbrain (Langfitt, Kassell, and Weinstein, 1965)

which, in turn, is due to local ischaemia. Anrep and Starling (1925) and Tsubura (1924) considered the stimulating factors to be the anoxia and fall in the BP of the medullary centres. According to Taylor and Page (1951) the rise of arterial BP caused by increased intracranial pressure is the result of a combination of ischaemia and mechanical compression. Rodbard and Saiki (1952), Rodbard and Stone (1955) postulated the existence of an intracranial baroreceptor similar to the carotid sinus. Thompson and Malina (1959) considered distortion of nervous tissue or brain-stem ischaemia to be responsible for a fall in the vasopressor threshold. Weinstein *et al.* (1964) have suggested that local compression or ischaemia of many parts of the central nervous system may cause arterial hypertension which shows little relationship to the level of intracranial pressure.

b. *Cardiac stimulation* (Freeman, 1940; Freeman and Jeffers, 1940).

c. *Humoral mechanism* (Rodbard, Reyes, Mininni, and Sakai, 1954; Rodbard and Stone, 1954).

Our observations that levels of the CSFP as low as 10 to 15 mm Hg are capable of inducing BP responses contradict some of the views which attribute the BP responses to medullary compression caused by the high CSFP. These low levels of the CSFP are unlikely to interfere to any significant extent with the blood supply of the medullary centres, apart from their effect on the venous drainage of the brain, resulting in a venous congestion. It is thought that congestion of the brain is associated with stimulation and ischaemia with paralysis. The fact that there was a significant drop in systolic BP during the initial phase cannot be accounted for on this basis.

The CSFP of over 35 to 40 mm Hg, producing decompensation in two-thirds of the animals in our series, is not high enough to produce ischaemia of the medullary centres. This contradicts the views of Cushing (1901) that the vasomotor centre shows signs of giving way when the CSFP reaches a high level, producing medullary anaemia. The only alternative to this view is that the vessels in the vasomotor centre could be selectively susceptible to obliteration by the raised CSFP.

Cardiac stimulation could well be a factor responsible for changes in BP, since, in our study, the changes in pulse rate and CSFP were found to be statistically significant. However, the correlation between the changes in the pulse rate and the BP was significant ($P = <0.05$) only during the initial phase.

To explain the BP responses to the raised CSFP one has to consider seriously the possibility of direct

compression of the neurones in the medulla, or the existence of some sort of baroreceptor mechanism intracranially (similar to that seen in the carotid sinus); the whole mechanism cannot be explained purely by the vascular interference with the vasomotor centre caused by the raised CSFP.

A significant fall in the diastolic BP during the final phase may possibly be due to reduced vasomotor tone of the arterioles, which leads to a fall of peripheral resistance, resulting in a fall of the diastolic BP.

The findings of the present series conclusively indicate that recording of the BP (both systolic and diastolic) is an important investigation in cases of suspected acutely rising intracranial pressure (Fig. 2). A small fall of the systolic BP followed by rising systolic and diastolic BP would indicate a transition from the initial to the subsequent middle phase. A fall of BP, especially of diastolic BP, would suggest the transition from middle to final (or decompensating) phase. This would indicate that diastolic BP is a better index of decompensation than systolic BP. Based on these findings we could designate the middle phase as the 'arterial stimulating phase' and the final phase as the 'arterial decompensating phase'.

The prognosis after surgical decompression, once the final phase has started, is unfavourable in the majority of the cases (*vide infra*).

CEREBRAL CIRCULATION AND RAISED INTRACRANIAL PRESSURE According to Wolff and Forkes (1928) at least three important physiological mechanisms seem to be involved in the maintenance of the cerebral circulation during increased intracranial pressure:

1. The raised intracranial pressure causes the intracranial venous pressure to rise. This produces an increase in capillary and arteriolar pressure and leads to an increased intracranial arterial pressure, without any rise in BP (Fleming and Naffziger, 1927). Berens, Smith, and Cornwall (1928) also recorded by ophthalmodynamometry a raised pressure in the central artery of the retina in patients with raised intracranial pressure who showed no increase in BP. However, ophthalmodynamometry is a very unreliable and erratic means of determining the central retinal artery pressure.

2. If this increase in intracranial arterial pressure is not enough to overcome the effects of the cerebral compression, the BP rises. The typical 'Cushing phenomena' occur clinically only when the intracranial pressure rise is sudden and marked.

3. Asphyxia causes a reduction in vascular tone or relaxation of the vessel walls. This allows a greater volume of the blood to flow through the cerebral vessels with less resistance than before. According to them, the brain circulation is not regulated wholly

from a distance by the vasomotor control. Langfitt, Tannanbaum, Kassell, and Zaren (1966) described an inverse relationship between cerebral blood flow and intracranial pressure.

In the present study the correlation between ophthalmic artery pressure (OAP) and BP was found to be significant ($P = <0.01$) in the normal animals and with the raised CSFP (Hayreh and Edwards, 1971). If the OAP is taken as an index of the internal carotid artery pressure (Hayreh and Edwards, 1971), it would indicate a close correlation between the systemic and internal carotid artery pressure. No selective rise in the OAP, as postulated by Berens *et al.* (1928), is seen in these cases. Thus, the cerebral circulation during the raised intracranial pressure is controlled by the systemic BP and indirectly by the various unknown factors controlling the systemic BP responses.

EFFECTS ON PULSE RATE The significant correlation between pulse rate and CSFP seen in this study is contradictory to the views of Cooper (1824), von Bergmann (1880) and many others who regarded bradycardia as an important index of the raised intracranial pressure. Others, however, did not consider this to be so (Vance, 1927; Gurdjian, 1933; Browder and Meyers, 1936, 1938; and others). According to Wright (1938), the bradycardia happened only after the CSFP reached the level of the systolic BP. Meyers (1942), on raising the CSFP to 10 to 60 mm Hg, found little alteration in the pulse rate during the first hour, but it diminished later on. Suzuki (1957), on raising the intraventricular pressure in patients, found an increase in pulse rate, but he commented that 'it may be due to psychic anxiety caused by headache or the like' because, by similar experiments in cats, he noticed bradycardia in some of them.

In the present study, no relationship was found between the BP (both systolic and diastolic) and the pulse rate, all along the course of the raised CSFP. Similarly, Browder and Meyers (1936, 1938) and Meyers (1942) considered that the pulse rate and the BP did not necessarily or regularly bear a close reciprocal relationship. The findings of the present series indicate that a rising pulse rate is a sign of rising CSFP.

EFFECTS ON SUPERIOR SAGITTAL SINUS PRESSURE (SSP) In the present study the SSP is taken as an index of the intracranial venous sinuses. The normal SSP of about 4 mm Hg as seen in the present series and by Hedges (1963), is slightly lower than the normal CSFP (Weed and Hughson, 1921).

On raising the CSFP in steps to 30 to 40 mm Hg in dogs, Weed *et al.* (1933) found no effect on the

SSP. Lamach, Claude, and Targowler (cited by Lauber, 1935) showed that the pressure in the intracranial venous sinuses was partly independent of the intracranial pressure. Bedford (1942), on raising the CSFP rapidly to 40 mm Hg in dogs, found a slight but persistent fall in the SSP, the extent of the fall being roughly proportional to the rate at which the CSFP was increased. The fall in the SSP averaged 20 mm water for a rapid rise to 500 mm water CSFP. For a slow rise of 100 mm water per three minutes, the fall averaged 10 mm water. The fall in the SSP persisted as long as the raised CSFP was maintained. Ryder, Espey, Kristoff, and Evans (1951), on suddenly raising the CSFP in rhesus monkeys, also found a fall of pressure in the sigmoid sinus and considered the latter to be dependent upon the cardiac output. Hedges (1963), on raising the CSFP to 200 to 400 mm water in five experiments on rhesus monkeys, recorded no change in the SSP in two, a rise in one; no mention is made of the response in the remaining two.

The effects of the raised CSFP on the SSP seen in the 26 rhesus monkeys of the present series are shown in Fig. 9. A statistically significant correlation was discovered between the SSP and the CSFP all along the rise of the CSFP (Table 4), which is in sharp contrast with all the previous reports. The SSP was always lower than the CSFP, which was also noticed by Hill (1894) and Becht (1920).

This rise in the SSP associated with this raised CSFP cannot be due, to any significant extent, to the direct pressure on the walls of the sinus because of the anatomical construction of the sinus. Taking the OAP as an index of the internal carotid artery pressure, no significant correlation was seen between the OAP and the SSP as the CSFP was raised to levels higher than 10 mm Hg; this would indicate that the arterial pressure in the brain does not influence the SSP significantly. According to Langfitt *et al.* (1965 a, b), the raised intracranial pressure causes cerebral vasodilatation and an increase in brain volume. The vasodilatation may be one of the factors responsible for the raised SSP. We are of the opinion that the important factor responsible for this is the increased venous pressure in the cerebral veins, the latter being a compensatory mechanism to counteract the venous compression by the raised CSFP.

Hedges (1963) stated that the SSP responses to the raised CSFP were unrelated to those of the ophthalmic vein pressure (OVP). In sharp contrast with that, in our series a significant correlation was seen between the SSP and the OVP in normal animals and with the raised CSFP (Hayreh and Edwards, 1971).

EFFECTS ON INTERNAL JUGULAR VEIN PRESSURE (JVP) Kornder (1919) and Hayashi (1955), from their

experimental intracranial hypertension studies in dogs, concluded that the raised intracranial pressure caused a generalized rise of venous pressure; on giving atropine before the rise of the intracranial pressure no such rise of the venous pressure was seen. Meyers (1942), on raising the intraventricular pressure to 10 to 60 mm Hg in dogs, described a remarkable stability of the systemic venous pressure. A passive reflection in rise of the venous pressure was seen only with an extreme degree of arterial hypertension. Hedges (1963), on raising the CSFP to arterial blood pressure level in rhesus monkeys, found that the JVP was similar to the SSP.

In the present study a significant correlation was seen between the SSP and JVP. This may be due to the fact that the SSP and other intracranial venous sinuses drain into the internal jugular vein, so that a rise in the SSP and other intracranial venous sinuses would lead to a rise in the JVP and not *vice versa*. This may also explain the correlation seen between the JVP and the CSFP, which may in turn indicate that the raised CSFP influences the JVP via the changes in the intracranial venous sinuses.

Figures 4 and 5 suggest the possibility that the JVP changes in these cases are independent of the pressure changes seen in the intracranial venous sinuses (as represented by the SSP changes). A rise in systemic venous pressure in raised CSFP could possibly be caused by the following two factors:

1. Respiratory embarrassment caused by the raised CSFP could interfere with the venous return to the chest and could produce an elevated systemic venous pressure. This, however, could only happen during the late stages of the raised CSFP because respiration is not seriously affected during the early stages.

2. Depression of the vasomotor centre during the arterial decompensation phase of the raised CSFP, associated with a generalized dilatation of the arterioles in the body, could let the blood flow into the venous side at a comparatively higher pressure than that during the normal or arterial-stimulating stages. Such a mechanism would be possible only towards the last stages of the raised CSFP.

If this were the case, the main rise in the JVP would have occurred only during the late phases of the raised CSFP. Statistical analysis of the JVP responses in the present study showed no difference in the rate of change in the JVP during the various stages of the rise of the CSFP from normal to 50 mm Hg CSFP. In view of this, it can be assumed that the JVP is, to a significant extent, dependent upon the pressure in the various intracranial venous sinuses and does not represent a rise in the systemic venous pressure.

CRANIAL PRESSURE We have not been able to find any significant information on this manoeuvre in the literature.

1. *Effects on BP* There was a significant fall in the systolic and diastolic BP (Table 6; Fig. 2). No correlation was seen between the pre- and post-lowering blood pressure, on the drop of the CSFP. Similarly, the level of the raised CSFP just before its dropping to zero had no relationship with the size of the BP changes.

2. *Effects on pulse rate* There was no significant response of the pulse rate (Table 6; Fig. 8).

3. *Effects on SSP* (a) There was a significant drop in the SSP (Table 6, Fig. 9). (b) The post-lowering SSP was significantly higher as compared with the normal SSP (before the start of the raised intracranial pressure). This is most probably due to cerebral vasodilatation produced by the raised intracranial pressure. (c) The SSP rose when its pre-lowering level was less than 7.5 mm Hg and fell when it was at or above 7.5 mm Hg level. This relationship was significant. It is not possible to give an explanation for this phenomenon.

4. *Effects on JVP* A drop in the JVP was seen in half of the animals which was not statistically significant (Table 6). There was, however, a significant correlation between the changes produced in the SSP and the JVP with the fall of the CSFP. The factors responsible for the correlation between the SSP and JVP changes are discussed above.

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