THE EFFECTS OF INCREASED INTRACRANIAL PRESSURE ON CEREBRAL CIRCULATORY FUNCTIONS IN MAN[1]

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The effect of increased intracranial pressure on cerebral blood flow has been the object of very few clinical studies. In accordance with the Monroe-Kellie-Cushing Doctrine, it would be presumed that increased intracranial pressure would increase cerebrovascular resistance and thereby decrease cerebral blood flow. However, Williams and Lennox (1) in 1939 concluded on the basis of cerebral arteriovenous oxygen differences that cerebral blood flow was practically unaffected by a rise in cerebrospinal fluid pressure. Courtice (2) also working with humans and using a similar technique came to a different conclusion: that there was a slowing of blood flow through the brain in certain types of brain tumor associated with increased intracranial pressure. More recently Ferris (3), using a plethysmographic measurement of relative intracranial blood flow, reported a diminution in cerebral blood flow in two subjects when intracranial pressure was artificially raised above 350 mm. of water.

The development of a technique which appears capable of yielding quantitative information on cerebral blood flow in man (4, 5) makes available more definitive information on the effects of increased intracranial pressure on this important function.

METHODS

The patients studied were 13 in number; all but one were suffering from brain tumors. Cerebrospinal fluid pressures were determined in millimeters of water above the horizontal cerebrospinal axis through a needle inserted into the lateral ventricle or lumbar subarachnoid space. Mean arterial pressure was measured from the femoral artery by a damped mercury manometer attached directly to the arterial needle. Cerebral blood flow (CBF) was determined by the nitrous oxide technique previously described (5), using 21% O_2, 64% N_2 and 15% N_2O as the inhalation mixture. From this value and the cerebral arteriovenous oxygen difference or the mean arterial blood pressure, cerebral oxygen utilization

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TABLE I

Patient	Age	Sex	Mental state*	Arterial				Int. jugular				Mean art. B. P.	CSF pressure
				CO_2 content	CO_2 tension	O_2 content	pH	CO_2 content	CO_2 tension	O_2 content	pH		
				vol. %	*mm. Hg*	*vol. %*		*vol. %*	*mm. Hg*	*vol. %*		*mm. Hg*	*mm. H_2O*
Gre.	50	M	C	50.0	38	18.7	7.49	56.9	45	11.6	7.43	95	430
Fri.	40	M	C	52.0	37	11.0	7.45	56.5	41	6.7	7.43	85	100
Ger.	38	M	C	48.9	37	15.6	7.44	54.3	46	9.2	7.39	97	415
Her.	40	M	C	38.2	34	18.3	7.38	43.8	45	12.3	7.31	160†	295
Smi.	43	F	C	45.7	36	14.0	7.42	52.4	45	7.3	7.37	111	170
Ant.	38	F	C	45.1		16.6		49.5		12.5		85	130
Woo.	52	F	U	44.8	38	16.6	7.40	51.2	45	9.4	7.36	130	840
Woo.	52	F	U	50.1	39	17.3	7.43	57.0	50	9.8	7.38	125	820
Fos.	52	M	U	44.9	32	17.8	7.50	53.2	42	8.0	7.42	122	620
Bur.	49	M	U	43.7	34	16.6	7.43	49.3	39	12.2	7.42	97	350
Haw.	48	M	C	48.9	40	18.1	7.42	55.2		10.9		95	460
Pet.	33	M	U	45.6	41	22.5	7.39	55.0	57	13.4	7.32	117	545
Bal.	48	M	C	46.0	29	13.0	7.53	50.7	36	7.2	7.50	95	325
Roo.	41	M	C	48.5	40	13.6	7.40	52.6	46	8.8	7.36	105	410
Mean Normal Values				49	41	18	7.40	55	51	12	7.34	86	150

* C = Conscious. U = Unconscious.

TABLE I—*Continued*

Patient	Cerebral					Resp. min. vol.	Diagnosis	Localization
	CBF	CMR O_2	CVR	A-V O_2	R.Q.			
	cc./100 g./min.	*cc./100 g./min.*	*mm. Hg / cc./100 g./min.*	*vol. %*		*l/min.*		
Gre.	55	3.9	1.7	7.1	0.97	8.9	Metastatic carcinoma	Supratentorial
Fri.	61	2.8	1.4	4.4	1.03	9.1	Cystic oligodendroglioma	Left frontal
Ger.	53	3.4	1.8	6.4	0.84	12.0	Glioma	Left temporo-parietal
Her.	47	2.9	3.4†	6.1	0.93	8.6	Astrocytoma	Right parieto-occipital
Smi.	47	3.1	2.4	6.7	1.00	17.0	Glioma	Left fronto-parietal
Ant.	52	2.2	1.6	4.2	1.05	4.5	Suspected brain tumor—(multiple sclerosis)	
Woo.	31	2.2	4.2	7.2	0.90		Tuberculoma	Posterior fossa
Woo.	33	2.5	3.8	7.6	0.92		Tuberculoma	Posterior fossa
Fos.	33	3.2	3.7	9.8	0.85		Glioblastoma multiforme	Left fronto-parietal
Bur.	39	1.7	2.5	4.4	1.27	9.6	Metastatic carcinoma	Posterior fossa
Haw.	40	2.9	2.4	7.2	0.87		Glioblastoma multiforme	Right temporo-parietal
Pet.	33	3.0	3.5	9.2	1.03	7.1	Astrocytoma	Cerebellar
Bal.	45	2.6	2.1	5.8	0.81		Glioma	Left fronto-parietal
Roo.	64	3.1	1.6	4.8	0.86		Meningioma	Left parieto-occipital
Mean Normal Values	54	3.3	1.6	6.3	0.99	8.1		

† This patient was known to have essential hypertension over a period of many years. These figures have been excluded from the correlations.

(CMR_{O_2}) and cerebrovascular resistance (CVR) were calculated (5). Respiratory minute volume was measured by means of a tightly fitting mask and a Tissot spirometer.

RESULTS

The pertinent data obtained in these studies are presented in Table I. Some of the relationships among the data are indicated by the scatter diagrams (Figures 1–4). There are good correlations between cerebrospinal fluid pressure and mean arterial blood pressure, cerebrovascular resistance, and cerebral blood flow, as well as a satisfactory correlation between cerebral blood flow and mean arterial blood pressure. Some of these correlations could have been deduced from

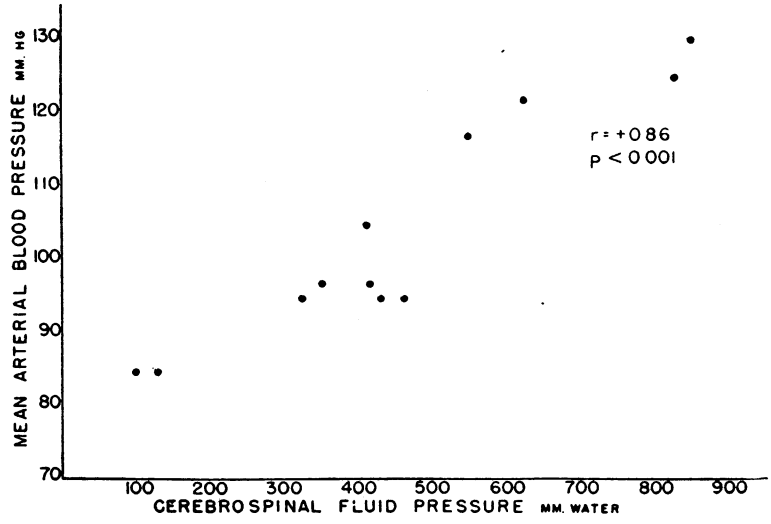

FIG. 1. THE RELATIONSHIP BETWEEN INTRACRANIAL PRESSURE AND MEAN ARTERIAL BLOOD PRESSURE

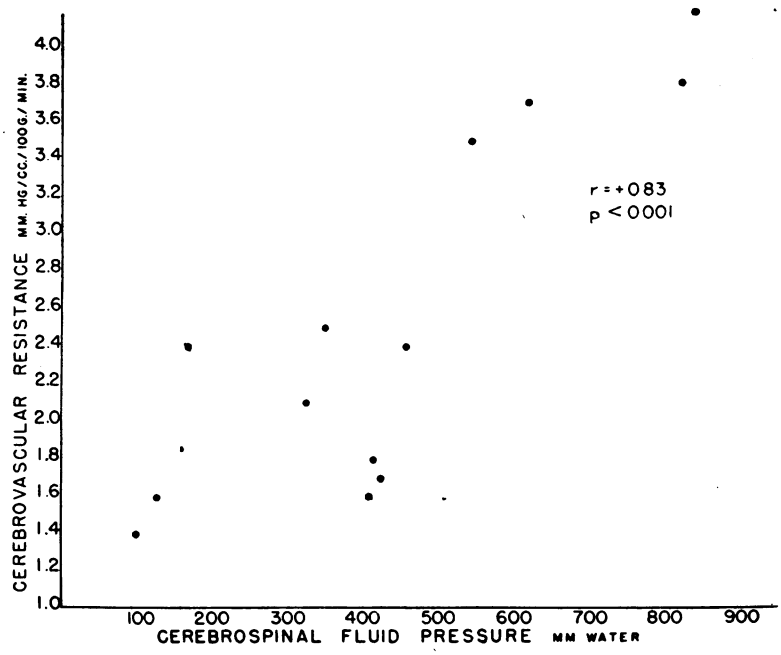

FIG. 2. THE RELATIONSHIP BETWEEN INTRACRANIAL PRESSURE AND CEREBROVASCULAR RESISTANCE

the others; their inclusion is simply for the sake of clarity. In corroboration of Ferris' findings (3), there appears to be a critical level which intracranial pressure must attain before significant cerebral circulatory embarrassment occurs. In our studies this level is close to 450 mm. of water (33 mm. Hg); pressures below that value in nine patients were associated with an insignificant re-

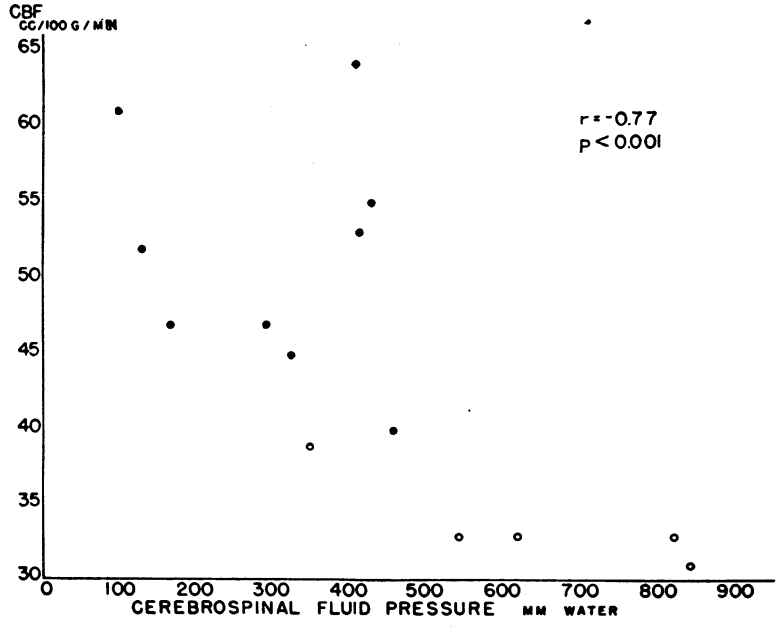

FIG. 3. THE RELATIONSHIP BETWEEN INTRACRANIAL PRESSURE AND CEREBRAL BLOOD FLOW

Open circles represent comatose patients.

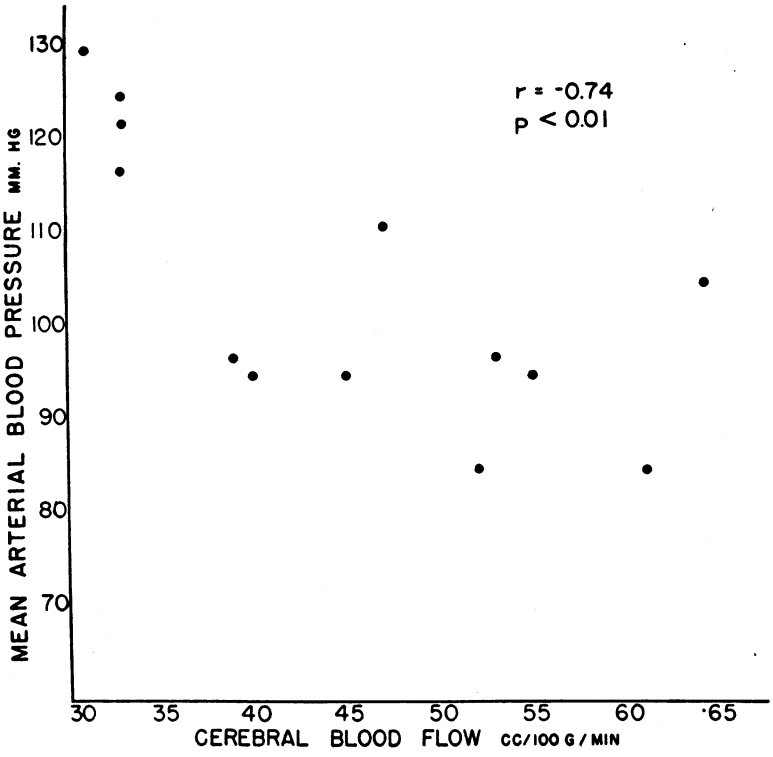

FIG. 4. THE RELATIONSHIP BETWEEN CEREBRAL BLOOD FLOW AND MEAN ARTERIAL BLOOD PRESSURE

duction in cerebral blood flow (51 as compared with a normal value of 54 cc./100 g./min.) while there was a marked diminution in this function in the five cases where cerebrospinal fluid pressures were above 450 mm. (34 cc./100 g./min.). This difference between the two groups is statistically highly significant ($p < 0.001$). There was a distinctly lower average cerebral blood flow in the four observations on patients with posterior fossa tumors (35 cc./100 g./min.) than for the nine with cerebral hemispheric lesions (49 cc./100 g./min.). While this could be due to interference with venous drainage, as Courtice suggests (2), it appears more likely to be related to the greater pressure associated with posterior fossa lesions, since these showed no variation from the general correlation of cerebral blood flow versus cerebrospinal fluid pressure. Although those patients in whom such measurements were made exhibited an increase in respiratory minute volume, and the patients as a whole showed some depression of arterial pCO_2 indicative of respiratory stimulation, these showed no correlation with intracranial pressure.

The patients were classified into two groups, conscious and comatose, on the basis of obvious objective indications such as response to questions and other stimuli. There was a good correlation between mental state and cerebral oxygen consumption as is found in other clinical conditions (6, 7). The conscious group yielded a mean value for CMR_{O_2} of 3.1 cc./100 g./min. while the comatose group averaged 2.5 cc./100 g./min., a difference which is statistically significant ($p = 0.05$). The mean value for this function in normal young men is 3.3 cc./100 g./min. (5).

The effects produced on cerebral blood flow, metabolism and vascular resistance by acutely reducing the intracranial pressure is the subject of another report (8).

DISCUSSION

At the turn of the present century Harvey Cushing reported some observations on a phenomenon which has since been closely associated with his

name (9, 10). By several precise experiments he demonstrated that an increase in intracranial pressure, acutely induced, was associated with a rise in blood pressure to a level somewhat above that in the cerebrospinal system. He showed further that this hypertension was the result of a peripheral vasoconstriction, mediated through tracts in the cervical cord arising in a medullary vasomotor center. He postulated that stimulation of the vasomotor center was the result of medullary ischemia rather than the activation of a sensory reflex. Not much has been added to our knowledge of this phenomenon in the intervening 47 years.

The present study reveals in man those phenomena which Cushing induced in animals and corroborates in many respects the hypothesis by which he explained them. Figure 1 shows the excellent correlation ($r = 0.86$) which is found between intracranial pressure and mean arterial blood pressure, an observation which is now commonplace. There is one difference, however, between this relationship in patients chronically exposed to an increased cerebrospinal fluid pressure and the acute Cushing phenomenon, in that the patients exhibit a progressive increase in blood pressure as intracranial pressure rises, whereas in the experimental counterpart blood pressure does not begin to rise until the cerebrospinal fluid pressure closely approaches it. The acuteness of the animal experiments and the depressant effect of anesthesia on the mechanisms involved may possibly explain this difference.

It is of interest to seek, in these studies on man, evidence for the mechanism whereby blood pressure rises *pari passu* with an increase in intracranial pressure. Quantitative measurement of cerebral blood flow permits an evaluation of cerebrovascular resistance (CVR) in terms of the pressure head necessary to achieve a unit of cerebral blood flow. In the correlation shown in Figure 2 it is seen that this function increases in fairly exact proportion to the increase in cerebrospinal fluid pressure ($r = 0.83$). This is entirely in accord with expectation; the capillaries of the brain, being freely collapsible, transmit any external pressure in opposition to the pressure head of the flowing blood. An exact analogy to this phenomenon is seen in the familiar variable resistance employed in the heart-lung preparation. It is very likely that this increase in cerebrovascular resistance represents the primary effect of high intracranial pressure. Were no compensatory mechanisms operating, this should result in a progressive restriction of cerebral blood flow. That this does occur is evident from Figure 3 showing a fairly good correlation ($r = -0.77$) between intracranial pressure and cerebral blood flow. The relationship, however, is more complex than appears to be the case in this single correlation. More careful scrutiny reveals the fact that up to a cerebrospinal pressure of 450 mm. of water this correlation is poor, indicating possibly, that in this region the compensatory rise in arterial pressure is sufficient to overcome the increased resistance whereas this adjustment falls short in the regions of higher pressure. These findings agree with those of Ferris (3) who found an intracranial pressure of similar magnitude necessary before relative intracranial blood flow was measurably restricted. They also demonstrate in man the implication of experiments on animals in which, by a study of circulation times (11) or pial vessel diameters (12), it was concluded that increased intracranial pressure caused a restriction in cerebral blood flow. The patients who failed to compensate and exhibited a reduction of cerebral blood flow below 40 cc./100 g./min. were all comatose. Whether consciousness failed because of the severe restriction in blood flow, or whether the compensation failed because of the generalized neuronal depression manifested in unconsciousness cannot be decided from these data. Our demonstration of a reduced cerebral blood flow in these comatose patients, although reasonable, is quite at variance with Williams and Lennox (1) who concluded that there was an increased cerebral blood flow in four deeply comatose patients in their series on raised intracranial pressure. They based this conclusion on their finding of a reduced cerebral arteriovenous oxygen difference in these individuals, neglecting the more likely alternative that deeply comatose patients might be expected to have a decreased cerebral metabolism.

Williams and Lennox found in their complete series of seven patients a mean arteriovenous oxygen difference of 6.6 vol. %; Courtice's 24 patients (2) yield a mean value of 6.7 vol. %, as do our pa-

tients. All of these averages are above the normal mean of 6.3 vol. %, which simply means that in this condition there is a slightly decreased supply of oxygen with respect to its utilization. Since the latter is not likely to be increased in this condition this suggests, but by no means demonstrates, a decrease in cerebral blood flow. The arteriovenous oxygen difference, being a function of both blood flow and oxygen consumption is in itself a measure of neither.

Cushing further postulated that this compensatory rise in arterial pressure is the result of medullary ischemia; our findings are compatible with this idea. Figure 4, showing a fairly good correlation between mean arterial blood pressure and cerebral blood flow ($r = -0.74$), suggests that cerebral ischemia plays some role in the hypertension. Certainly, the possibility that the high blood pressure could cause the reduced blood flow is hardly tenable. The manner in which medullary ischemia might effect a rise in blood pressure is quite possibly by way of a relative asphyxia of the vasomotor center. There is at hand no means of studying directly the internal environment of the human medulla. The closest approach possible at present is an examination of the composition of cerebral venous blood which may be expected to reflect but by no means to define general changes in the *milieu interne* of cerebral cells. Where the changes were brought about by alteration in blood flow rather than by a changed internal metabolism this parallelism might be especially valid. An examination of the relationship of the arterial blood pressure to cerebral venous pCO_2, hydrogen ion concentration, and oxygen saturation shows a fair correlation in each case ($r = +0.50, +0.58$ and -0.58, respectively) in such a direction as to imply a rise in arterial blood pressure concomitant with progressive central asphyxia.

It thus appears that increasing intracranial pressure in these patients is associated with an increase in cerebrovascular resistance, a tendency towards restricted cerebral blood flow and progressive cerebral asphyxia. There occurs *pari passu* a rise in arterial blood pressure correlated with the increasing intracranial tension, the restricted circulation and the available indications of central asphyxia.

These findings in man are entirely in accord with Cushing's hypothesis of medullary ischemia and complement hitherto available knowledge with quantitative data on cerebral blood flow, metabolism and cerebrovascular resistance.

SUMMARY

1. The relationships between intracranial pressure and cerebral blood flow, oxygen consumption and cerebrovascular resistance were studied in 13 patients.

2. The rise in cerebrospinal fluid pressure produced by brain tumor is associated with a progressive increase in cerebrovascular resistance, in mean arterial blood pressure, and above a certain level, with a definite decrease in cerebral blood flow.

3. These findings substantiate in man the hypothesis of medullary ischemia elaborated by Cushing on the basis of animal experiments.

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