PAPERS AND ORIGINALS

Autoregulation of Brain Circulation in Severe Arterial Hypertension

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Summary

Cerebral blood flow was studied by the arteriovenous oxygen difference method in patients with severe hypertension and in normotensive controls. The blood pressure was lowered to study the lower limit of autoregulation (the pressure below which cerebral blood flow decreases) and the pressure limit of brain hypoxia. Both limits were shifted upwards in the hypertensive patients, probably as a consequence of hypertrophy of the arteriolar walls. These findings have practical implications for antihypertensive therapy.

When the blood pressure was raised some patients showed an upper limit of autoregulation beyond which an increase of cerebral blood flow above the resting value was seen without clinical symptoms. No evidence of vasospasm was found in any patient at high blood pressure. These observations may be of importance for the understanding of the pathogenesis of hypertensive encephalopathy.

Introduction

Autoregulation of the cerebral circulation is a mechanism at arteriolar level that ensures a constant cerebral blood flow during changes in blood pressure. This is achieved by constriction of the vessels as the blood pressure rises and by dilatation as the pressure falls.

In a normotensive person with a resting mean arterial blood pressure of, for example, 90 mm Hg the lower limit of autoregulation is 60-70 mm Hg (Lassen, 1959; Olesen, 1972 a) Below this level autoregulation is inadequate and blood flow decreases. The brain compensates by increasing its extraction of oxygen, but when the pressure falls to 35-40 mm Hg even this mechanism fails, and symptoms of brain hypoxia develop—dizziness and sleepiness and eventually loss of consciousness. In patients with untreated arterial hypertension the blood pressure limit of brain hypoxia is higher than in normotensive controls (Finnerty *et al.*, 1954; Lassen, 1959). In such patients it might be supposed that the lower limit of the autoregulation mechanism is also raised.

When the blood pressure is increased the cerebral blood flow is kept constant by autoregulatory arteriolar constriction. Failure of autoregulation beyond an upper pressure limit would be expected in acute hypertensive encephalopathy. The traditional concept is that a state of spasm is provoked in the arterioles at a very high blood pressure, resulting in critical hypoperfusion with ischaemia of the brain tissue (Byrom, 1954; Fazekas, 1966; Finnerty, 1972). Alternatively failure of the autoregulation mechanism with forced vasodilatation has been suggested as the initial pathogenetic event leading to this disorder (Byrom, 1969; Lassen and Agnoli, 1972).

The aim of the present study was to test the hypotheses outlined above concerning the lower and upper limits of brain autoregulation in patients with arterial hypertension and in normotensive controls.

Patients

Ten patients with severe arterial hypertension were studied (table I). Their blood pressure levels ranged from 160/110 to 250/145 mm Hg. One patient (case 3) had hypertension possibly due to a renal artery stenosis, while the others were considered to have essential hypertension. All the patients had optic fundi changes of Keith-Wagener grade II, III, or IV, and most had raised serum creatinine levels and slight proteinuria. Changes in the electrocardiogram were noted in all cases, and most showed some radiographical evidence of heart enlargement. Patients with overt cardiac failure were not studied. One patient (case 2) had chronic pulmonary insufficiency after lung resection

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TABLE I—*Clinical Data on Patients With Severe Hypertension*

Case No.	Sex and Age	B.P. (mm Hg)	Grade of Fundal Change	Serum Creatinine (mg/100 ml)	Known Duration of Hypertension	Therapy
1	M. 48	180/130	III	1·6	1 month	Methyldopa, hydroflumethiazide
2	M. 58	220/140	III	1·7	2 years	Methyldopa, hydroflumethiazide, bethanidine
3	M. 57	205/125	III	1·0	1 year	None
4	M. 52	160/110	II	1·1	1 year	Methyldopa, hydroflumethiazide
5	M. 49	235/135	IV	2·0	Newly discovered	Methyldopa, chlorthalidone, dihydrallazine
6	M. 59	220/140	IV	1·0	Newly discovered	None
7	M. 63	220/140	III	2·0	6 months	Clonidine, hydroflumethiazide
8	M. 44	180/130	II	1·3	3 years	Methyldopa, hydroflumethiazide
9	M. 56	190/120	III	1·4	Newly discovered	Frusemide
10	M. 55	250/145	III	1·2	Newly discovered	None

for cancer 13 years previously. This patient was studied one week and another (case 5) one day after recovery from severe hypertensive encephalopathy. Three patients were untreated, while the rest had been on inadequate antihypertensive therapy for varying periods. In four patients (cases 5, 6, 9, and 10) the hypertension was newly discovered, and two of these (cases 5 and 9) had been treated for only one week at the time of study. The results of the studies were useful as a guideline in the antihypertensive treatment initiated or intensified after the study.

In addition we had the opportunity to study three normotensive patients (cases 11-13; table II), one with presenile dementia, one with chronic vertigo of uncertain origin, and one with chronic alcoholism without definite involvement of the nervous system. In cases 11 and 12 the tests were part of their clinical investigation; the third patient gave full informed consent.

TABLE II—*Clinical Data on the Normotensive Patients*

Case No.	Sex	Age	B.P. (mm Hg)	Diagnosis
11 ..	F.	62	130/90	Presenile dementia
12 ..	F.	81	120/80	Vertigo
13 .	M.	66	170/105	Chronic alcoholism

Methods

Cerebral blood flow was measured by the arteriovenous oxygen difference method (Lennox and Gibbs, 1932). If the cerebral metabolic rate of oxygen ($CMRO_2$) is assumed to be constant the cerebral blood flow can be calculated from the cerebral arteriovenous oxygen difference (AVO_2) by means of the Fick principle:

$$\text{Cerebral blood flow} = \frac{CMRO_2}{AVO_2}$$

$1/AVO_2$ gives a relative measure of cerebral blood flow, which is expressed as a percentage of the resting $1/AVO_2$. This method allows for multiple estimations during a short period, while direct methods such as the Kety method or the intra-arterial isotope injection method will permit only a few measurements in one session. $CMRO_2$ has repeatedly been shown to be constant in conscious man (Lassen, 1959). Thus Finnerty *et al.* (1954) found with the Kety method an unchanged $CMRO_2$ at rest and during hypotension with signs of brain hypoxia.

In the present study a catheter was placed in the jugular bulb either from an arm vein under fluoroscopy control or by Seldinger puncture of the internal jugular vein at the level of the carotid bifurcation. Another catheter was placed in the brachial artery using Seldinger's technique, and an intravenous drip into an arm vein was set up. Arterial and jugular pressure was measured with transducers (EMT-34 Elema Schönander). Oxygen content in arterial and jugular venous blood was determined by spectrophotometric measurement of the oxygen saturation of the haemoglobin (Holmgren and Pernow, 1959). $PaCO_2$ was measured with a Severinghaus electrode. Blood pressure was raised by intravenous infusion of angiotensin amide (Hypertensin-Ciba) and reduced by intravenous infusion of trimetaphan camsylate (Arfonad) combined with head-up tilting. Neither of these drugs has any direct effect on the cerebral circulation (Olesen, 1972a, 1972b), and consequently changes in the cerebral blood flow during their administration are secondary to the changes in systemic blood pressure. Blood samples were taken for determination of arterial and jugular venous oxygen content and arterial PCO_2 at various blood pressure levels. Before each sampling a steady state in blood pressure was obtained for two to five minutes.

Results

The average resting mean arterial blood pressures in the hypertensive and control patients were 146 and 112 mm Hg respectively. The corresponding figures for resting cerebral AVO_2 were 6·89 and 6·37 volumes per cent., and for resting $PaCO_2$ 40·3 and 38·0 mm Hg.

In all patients autoregulation was shown by a practically constant cerebral AVO_2 in the face of moderate blood pressure variations around the resting pressure level. This is shown in fig. 1. In each case a typical curve of autoregulation was obtained by visual interpolation of the points. Within a certain pressure range the curve is horizontal. At low pressure autoregulation is inadequate and the curve declines.

An estimate of the lower limit of autoregulation could be derived from the curves in all cases except case 3, where no blood samples were obtained at low pressure. In the hypertensive group the average value for the lower limit was 120 mm Hg, and in the controls 70 mm Hg. There was a good correlation in all the patients between the lower limit pressure values and the estimated habitual mean arterial blood pressure at the time of study, as measured by independent observers in the ward (fig. 2).

Brain hypoxia was elicited in all patients. The symptoms were a feeling of discomfort or dizziness, sleepiness, and nausea, almost invariably accompanied by hyperventilation with a decrease in $PaCO_2$. In the hypertensive group the blood pressure limit of brain hypoxia was on average 68 mm Hg and the calculated average cerebral blood flow during hypoxia was 73% of the resting level. The average $PaCO_2$ was 35·8 mm Hg. The corresponding figures for the controls were brain hypoxia limit 40 mm Hg, cerebral blood flow 66% of the resting level, and $PaCO_2$ 34·5 mm Hg. In the patients as a whole there was a correlation between the brain hypoxia limit of the mean arterial blood pressure and the estimated habitual mean arterial blood pressure (fig. 2).

In three hypertensive patients (cases 1-3) a decrease in

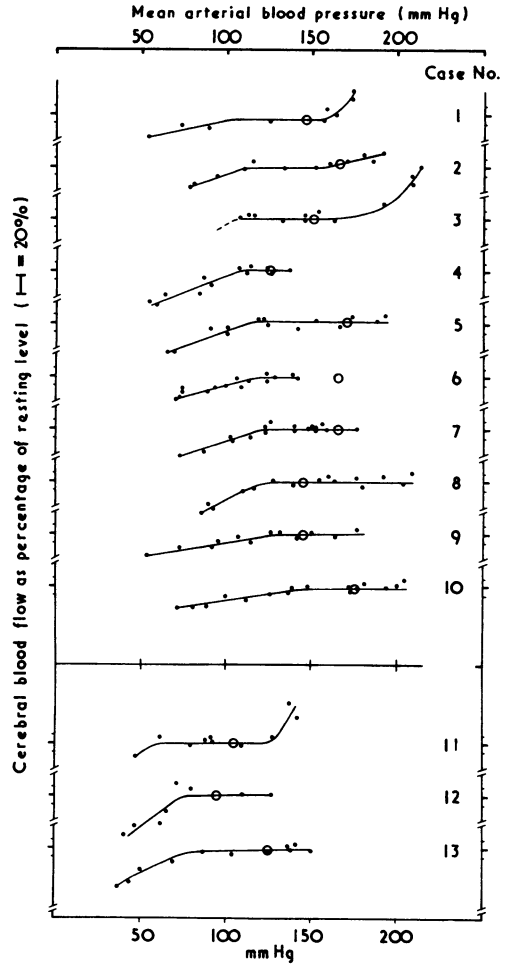

FIG. 1—Autoregulation of brain circulation in the 13 subjects. The ordinate shows cerebral blood flow as a percentage of the resting level. For each curve cerebral blood flow ± 10% is marked. The curves were drawn by simple visual interpolation of the points. An estimate of the patients' habitual mean arterial pressure is indicated by an open circle. It is clearly seen how the autoregulation curves of the hypertensive patients (cases 1-10) are shifted upwards when compared with the controls (cases 11-13). In addition some of the patients show an upper limit of autoregulation beyond which cerebral blood flow increases.

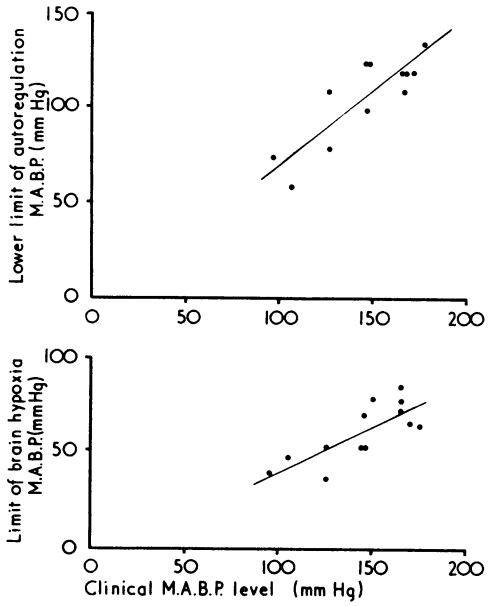

FIG. 2—Above: Correlation between estimate of habitual mean arterial blood pressure level (M.A.B.P.) and lower limit of autoregulation ($r = 0{\cdot}8470$, $P < 0{\cdot}001$). Below: Correlation between estimate of habitual mean arterial blood pressure and mean arterial blood pressure at which brain hypoxia was elicited ($r = 0{\cdot}7759$, $P < 0{\cdot}01$).

cerebral AVO_2 was observed at a mean arterial blood pressure above 160 mm Hg, corresponding to a rise in cerebral blood flow ranging from 17 to 60%. The patients felt no discomfort, especially no headache, at the high blood pressures, which were maintained for 5 to 10 minutes. In five other hypertensive patients an increase in blood pressure to above 160 mm Hg produced no change in blood flow. An increase of 39% in cerebral blood flow was seen in one normotensive patient (case 11) at a mean arterial blood pressure above 120 mm Hg. One of the patients with high flow was chronically hypercapnic, but the others had $Paco_2$ values not differing from those of the rest of the patients, and in none of the patients was the high flow caused by an acute increase in $Paco_2$. No clinical distinction could be drawn between those with high flow and those without. Of the two patients with recent encephalopathy one (case 2) showed a high flow at high pressure and the other (case 5) did not. In no case was even a suggestion of low flow seen at high blood pressure.

No cerebral, cardiovascular, or other complications occurred during or after study in the patients.

Discussion

The lower blood pressure limit of brain autoregulation in the hypertensive patients in the present study was on average 120 mm Hg. This is much above estimates of the limit in normal subjects reported previously as 60 to 70 mm Hg (Lassen, 1959; Olesen, 1972a), and also above the average limit of 70 mm Hg in our own few normotensive cases. We found a fairly good correlation between the lower limit of autoregulation and the habitual blood pressure. The pressures associated with brain hypoxia were in the hypertensive patients on average 68 mm Hg and in the normotensive subjects 40 mm Hg. This limit was previously known to be raised in hypertension (Lassen, 1959).

The calculated cerebral blood flow during brain hypoxia in the hypertensive patients was 73% and in the controls 66% of the resting value. These figures are in accordance with measurements made with the Kety method (Finnerty *et al.*, 1954). The hyperventilation associated with hypoperfusion of the brain is probably a reaction to brain-stem acidosis caused by CO_2 accumulation. It seems unlikely that the resulting hypocapnia adds to the decrease in cerebral blood flow, since Harper and Glass (1965) found in dogs that with a decrease in blood pressure there was also a marked decrease or complete abolition of the CO_2 reactivity of the brain vessels.

The demonstrated shift to a higher blood pressure level of the brain autoregulation curve with hypertension may be caused by hypertrophy of the arteriolar walls (Folkow, 1971). These adaptive changes probably explain the clinical experience that such patients are not able to tolerate too rapid lowering of the blood pressure to normal. This should not be taken as an argument against effective antihypertensive therapy: indeed it might be expected that with a decrease in blood pressure over weeks and months the cerebral circulation would readapt to the lower blood pressure. If a normotensive state is finally achieved a shift of the autoregulation curve back to normal would be expected. The finding of a pronounced shift upwards of the curve in a hypertensive patient signifies that blood pressure reduction must be gradual and very careful, though it should still be achieved if possible. A test like the present one with controlled hypotension will also disclose the exceptional hypertensive patient who develops focal symptoms on blood pressure reduction because of stenosis of a larger cerebral artery. No such patients were found in the present series. With these considerations the results in the present study were useful as an individual guideline of antihypertensive treatment in the patients.

Our observations during induced hypertension may contribute to the current discussion on the pathogenesis of acute hypertensive encephalopathy (Byrom, 1969; Lassen and Agnoli, 1972). It has recently been shown in dogs that during acute

hypercapnia there is an upper blood pressure limit beyond which autoregulation fails and cerebral blood flow increases (Ekström-Jodal *et al.*, 1971). Such an upper limit of autoregulation was found in four of our patients but seemed unrelated to their $PaCO_2$. No evidence of arteriolar spasm at high pressure was found in any of the patients studied. The 5 to 10 minutes of steady state maximum blood pressure should be ample time for autoregulation to operate, since this mechanism is known to be fully effective within 1 minute after blood pressure changes (Symon *et al.*, 1971). The fact that a similar increase in cerebral blood flow was found in one normotensive patient with a mean arterial blood pressure above 120 mm Hg suggests that the phenomenon is not caused by hypertensive vascular disease per se; it seems more likely that an upper limit of autoregulation is present in all persons and that even this upper limit is raised in hypertension.

None of our patients had symptoms during the short period of increased blood pressure. A sustained increase in blood pressure with hyperperfusion of the brain would be expected to cause exudation of plasma through the walls of arterioles and capillaries, this in turn giving rise to focal cerebral oedema, compression of capillaries, a decrease in cerebral blood flow, and the clinical picture of acute hypertensive encephalopathy (Byrom, 1969; Lassen and Agnoli, 1972). The initial event in this pathogenetic chain has been termed a "break-through of autoregulation" (Lassen and Agnoli, 1972). On a smaller scale similar phenomena may occur during sleep hypercapnia, causing the well known morning headache of the hypertensive patient.

Further investigations on the pathogenesis of hypertensive encephalopathy probably must rely on animal experiments with repeated measurements of cerebral blood flow with direct methods at very high blood pressure.

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Use of 4% Chlorhexidine Detergent Solution (Hibiscrub) and Other Methods of Skin Disinfection

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Summary

In a comparison of three antiseptic detergent preparations for hand washing, Hibiscrub, a 4% chlorhexidine detergent solution, caused a significantly greater estimated immediate reduction of skin flora (86·7% ± 3·0) than was obtained with Dermofax, a 0·75% chlorhexidine detergent solution (55·5% ± 5·1), or with Disadine scrub, a povidone iodine detergent preparation (68% ± 6·8). After six applications the mean estimated reductions of skin flora were 99·2% ± 0·2 for Hibiscrub, 97·7% ± 0·7 for povidone iodine, and 91·8% ± 1·6 for Dermofax.

After a series of hand washings with Hibiscrub, as with a hexachlorophane detergent preparation, a further large reduction of skin flora, shown by bacterial counts of hand sampling, was obtained by a second phase of disinfection consisting of two minutes' application on gauze swabs of 0·5% chlorhexidine digluconate in 70% ethanol; a further wash with Hibiscrub, in place of alcoholic chlorhexidine, for the second phase of disinfection caused an increase rather than a reduction in the yield of bacteria on skin sampling. Unlike this "two-phase" disinfection, the application for 30 minutes of compresses soaked in 10% aqueous povidone iodine or in 0·5% aqueous chlorhexidine digluconate did not cause a greater reduction in skin flora than that obtained by the conventional two minutes' application on gauze of 0·5% chlorhexidine in 70% ethanol.

Chlorocresol (0·3%) liquid soap (the base used for Ster-Zac liquid hexachlorophane soap) caused a mean reduction of skin flora when used for hand washing of 29% after one application and 72% after six applications spread over two days. This formulation, though less active and more variable as a detergent skin antiseptic than chlorhexidine, hexachlorophane, or povidone iodine detergent preparations, is an inexpensive disinfectant soap which could be useful in catering establishments. Alcoholic cetrimide applied as for disinfection of an operation site caused a reduction of skin flora greater than that shown by aqueous cetrimide but comparable to that shown by 70% ethyl alcohol in previous experiments.

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Introduction

Several developments in the technique of skin disinfection, including the use of a 0·75% chlorhexidine detergent solution for the hands, were recently reported from this unit (Lilly and Lowbury, 1971). Since then a more concentrated chlorhexidine preparation, Hibiscrub, has been introduced. In this paper we