

# Autoregulation of Cerebral Blood Flow in Hypertensive Patients

## The Modifying Influence of Prolonged Antihypertensive Treatment on the Tolerance to Acute, Drug-induced Hypotension

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**SUMMARY** Autoregulation of cerebral blood flow (CBF) was studied by the arteriovenous oxygen difference method in 13 patients with untreated or ineffectively treated severe hypertension, nine patients with effectively treated, formerly severe hypertension, and ten normotensive controls. Resting mean blood pressure in these three groups was  $145 \pm 17$  (1 SD) mm Hg,  $116 \pm 18$  mm Hg, and  $98 \pm 10$  mm Hg, respectively. Blood pressure was decreased by trimethaphan infusion combined with head-up tilt. The lower limit of CBF autoregulation in the three groups was  $113 \pm 17$  mm Hg,  $96 \pm 17$  mm Hg, and  $73 \pm 9$  mm Hg, and the lowest tolerated blood pressure

where mild symptoms of brain hypoperfusion were encountered was  $65 \pm 10$  mm Hg,  $53 \pm 18$  mm Hg, and  $43 \pm 8$  mm Hg. These pressures were all significantly higher ( $P < 0.01$ ) in the group of untreated or ineffectively treated hypertensive patients than in the normotensive group, demonstrating a shift of CBF autoregulation in the former. The observations in effectively treated hypertensive patients strongly suggested a readaptation of CBF autoregulation toward normal in some cases. In four hypertensive patients studied twice it was found that 8–12 months of antihypertensive treatment on average did not influence the lower limit of CBF autoregulation.

IN HYPERTENSIVE PATIENTS without neurological deficits, the absolute value for resting cerebral blood flow (CBF) is the same as in healthy normotensive individuals.<sup>1</sup> In both hypertensive and normotensive man, CBF is effectively autoregulated, i.e., the brain maintains a constant blood flow despite changes in perfusion pressure. When arterial blood pressure rises, the cerebral arterioles constrict, and when blood pressure falls or intracranial pressure rises, they dilate, keeping CBF constant. The lower limit of CBF autoregulation is the blood pressure below which autoregulatory vasodilatation becomes inadequate, and CBF decreases.<sup>2</sup> This is compensated for by an increased oxygen extraction from the blood, and an even lower blood pressure is required before symptoms of brain ischemia are encountered. This lowest tolerated blood pressure at which symptoms develop is higher in hypertensive than in normotensive man.<sup>3</sup> In a previous study, it was shown that this is due to an adaptation of CBF autoregulation to the chronically elevated blood pressure: the lower limit of CBF autoregulation is shifted to the right on the blood pressure axis.<sup>4</sup>

Studies in hypertensive rats have shown that adaptive changes in hemodynamic parameters may revert to normal when hypertension is treated effectively.<sup>5, 6</sup> The aim of the present study was to investigate whether a similar normalization might occur in CBF autoregulation in hypertensive man during treatment.

### Methods

Autoregulation was tested by measuring the cerebral arteriovenous oxygen difference ( $AVO_2$ ) during induced blood pressure changes. Estimating CBF from  $AVO_2$  was introduced by Lennox and Gibbs in 1932.<sup>7</sup> It has been shown

in many studies that cerebral oxygen uptake ( $CMRO_2$ , cerebral metabolic rate of oxygen) is constant in awake man during controlled hypotension.<sup>2</sup> In both hypertensive and normotensive patients an unchanged  $CMRO_2$  was found during controlled hypotension when mild symptoms of brain ischemia were present.<sup>3</sup> Accordingly, in autoregulation studies, a relative estimate of CBF can be obtained from the reciprocal value of  $AVO_2$ , using the Fick principle:

$$CBF = \frac{CMRO_2}{AVO_2} = \text{constant} \times \frac{1}{AVO_2}$$

In the present study, CBF was calculated as  $1/AVO_2$  and expressed in percent of resting  $1/AVO_2$ .

A catheter was placed in the internal jugular vein from an arm vein under fluoroscopic control, with the tip of the catheter above the base of the skull.<sup>8</sup> Flushing of the catheter with saline caused a murmur at the patient's ear, insuring that the catheter remained in place throughout the study. On a few occasions where no adequate arm veins were present, the internal jugular vein was instead cannulated at the level of the carotid bifurcation with the Seldinger technique. Another catheter was placed in the brachial or femoral artery with the Seldinger technique, and an intravenous drip was established in an arm vein. Arterial and jugular venous pressure was measured with transducers (EMT-34 Elema Schönder) placed at the level of the external auditory meatus. Oxygen content in arterial and jugular venous blood was determined by spectrophotometric measurement of the oxygen saturation of the hemoglobin.<sup>9</sup> Arterial carbon dioxide tension ( $PaCO_2$ ) was measured by a Severinghaus electrode. Blood pressure was raised by intravenous infusion of angiotensin II amide (Hypertensin CIBA) and subsequently reduced by intravenous infusion of trimethaphan camsylate (Arfonad ROCHE) combined with 20–25° head-up tilt. Neither of these drugs has any direct effect on the cerebral circulation, and consequently changes in CBF during their administration are secondary to the effect they induce in systemic blood pressure.<sup>10, 11</sup> The drugs were administered by an infusion pump, and blood pressure changes were induced gradually. At various blood pressure levels, a

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steady state was maintained for 2–5 min. Then blood samples were drawn for determination of arterial and jugular venous oxygen content and  $\text{PaCO}_2$ . When the lowest tolerated blood pressure was reached and the patient developed symptoms of slight brain hypoperfusion in the form of yawning, hyperventilation, or nausea, blood samples were drawn without delay, and immediately thereafter trimethaphan infusion was stopped and the table tilted back into the horizontal position. Within a few minutes, blood pressure then rose to preinfusion levels, and the patient again felt comfortable.

From the measured values of the cerebral  $\text{AVO}_2$  at various blood pressure levels, the relative CBF was calculated and an individual autoregulation curve was drawn by simple visual interpolation of the points. The lower blood pressure limit of CBF autoregulation was read from this curve.<sup>4</sup>

No cerebral, cardiovascular, or other complications were encountered during or after the study.

### Material

Cerebral blood flow autoregulation was studied in four groups of patients, pertinent data of which are given in tables 1–4. All patients received a careful and detailed description of the procedure to be undertaken before they gave their consent to participate. In the individual hypertensive patient, the study provided information useful in clinical management about the cerebral circulation and its tolerance to hypotension. In two normotensive patients with moderate dementia and vertigo or postural hypotension

(table 3) the study was part of the clinical investigation. These patients were fully able to understand the nature of the study.

#### Group 1

Thirteen patients with severe hypertension, often of recent discovery, either untreated or uncontrolled by anti-hypertensive treatment comprised group 1 (table 1). Six of these patients were included in a previous publication.<sup>4</sup>

#### Group 2

Nine patients with a formerly severe hypertension, now well-controlled by pharmacological treatment formed group 2 (table 2). Patients were included in this group when they had had a clinical diastolic pressure of 105 mm Hg or less for at least six months before the study, and when their pretreatment blood pressure level was known to have been considerably higher. Some of the patients had been in effective antihypertensive treatment for one or more years.

#### Group 3

Ten patients with various diseases, all clinically normotensive, were in group 3 (table 3). Two of these patients were included in a previous publication.<sup>4</sup>

#### Group 4

The four patients in group 4 were studied twice with an interval of 8–12 months (table 4). At the first study, which has

TABLE 1. *Clinical Data in 13 Patients with Severe Hypertension, either Untreated or Uncontrolled by Antihypertensive Treatment*

Case/sex/age	BP (mm Hg)	FH	Creat. (mg/100 ml)	Known duration of Ht	Therapy	History/presenting symptoms
H1 /F /55	240/130	0	0.7	4 months	0	
H2 /M/59	220/140	IV	1.0	Newly disc.	0	
H3 /M/50	190/125	0	0.9	Newly disc.	0	
H4 /F /49	180/130	0	0.9	7 years	0	7 years: 160/100; TIA for 3 years
H5 /M/55	250/145	III	1.2	Newly disc.	0	10 months: 160/85
H6 /M/49	235/135	IV	2.0	Newly disc.	Methyldopa, dihydralazine, chlorthalidone for 1 week	Encephalopathy 1 week before study
H7 /F /53	240/130	0	1.0	4 years	Methyldopa, hydroflu- methiazide for 10 days	6 months: 170/100; stopped medication. 10 days before study: minor stroke
H8 /M/44	180/130	II	1.3	4 years	Methyldopa, hydroflu- methiazide	3 years: 180/100; slight diabetes (diet-controlled)
H9 /M/48	180/130	III	1.0	1 month	Methyldopa, hydroflu- methiazide	1 month: 230/170; FH IV
H10/M/64	220/130	III	3.5	3 months	Methyldopa, hydroflu- methiazide	3 months: 260/155; FH IV, TIA
H11/M/44	200/115	IV	2.0	3 years	Methyldopa, hydralazine, hydroflumethiazide	2 months: encephalo- pathy, 180/120, FH IV; severe sclerosis of right internal carotid artery
H12/M/52	160/110	II	1.1	1 year	Methyldopa, hydroflu- methiazide for 3 weeks	Recent retinal thrombosis
H13/M/52	200/125	II	1.1	1 year	Methyldopa, betanidine, pindolol, chlorthalidone	1 year: encephalopathy 250/190; FH IV

Abbreviations: BP = blood pressure; FH = fundus hypertonicus (Keith - Wagner); Creat. = serum creatinine; Ht = hypertension; TIA = transient ischemic attacks; disc. = discovered.

TABLE 2. *Clinical Data in Nine Patients with Formerly Severe Hypertension Effectively Controlled at the Time of Study*

Case/sex/age	BP (mm Hg)	FH	Creat. (mg/100 ml)	Known duration of Ht	Therapy	History/presenting symptoms
H14/M/42	145/105	II	0.9	20 years	Propranolol, hydralazine	11 years: 195/130; FH II
H15/M/59	180/90	II	1.4	1 year	Methyldopa, propranolol, hydrochlorothiazide	1 year: 210/110; FH II
H16/F/59	140/90	I	0.9	6 years	Methyldopa, hydro- chlorothiazide	5 years: 190/120; FH II
H17/M/61	135/100	II	1.3	5 years	Methyldopa, hydrochloro- thiazide, furosemide	5 years: 240/145; FH III
H18/M/58	150/105	II	1.6	7 years	Propranolol, hydralazine	7 years: 205/125; FH II
H19/M/65	145/85	II	1.1	12 years	Propranolol	10 years: 175/125; FH II
H20/F/66	170/90	II	1.3	7 years	Methyldopa chlorthalidone	8 months: 200/120; FH IV; stroke with complete recovery
H21/M/60	140/85	II	1.0	1 year	Propranolol, hydralazine, hydrochlorothiazide	1 year: 200/120; FH III stroke with partial recovery
H22/M/60	160/90	II	1.5	4 years	Hydrochlorothiazide, triamterene	4 years: 180/110

See table 1 for abbreviations.

been previously published,<sup>4</sup> these patients had severe uncontrolled hypertension. The second study was done after an attempt had been made to reduce clinical blood pressure by drug treatment and in one case by removal of a severely arteriosclerotic kidney.

With the exception of this last case, all patients in groups 1, 2, and 4 were classified as having essential hypertension after standard examination procedures. Most had hypertensive fundoscopic changes, and an elevated serum creatinine and proteinuria. Hypertensive changes in the electrocardiogram were common, but patients with heart insufficiency were not studied. In each of the four groups, some patients had a history of cerebral arteriosclerosis, e.g., a previous stroke. Patients with recent strokes (one to two months before the study) were frequently found to have impaired autoregulation and if so were excluded from the present material. Patients with gross neurological deficits were not studied.

Patients with labile hypertension, becoming normotensive during hospital admission without specific treatment, were not included in the present study.

TABLE 3. *Clinical Data in Ten Normotensive Patients*

Case	Sex	Age	BP (mm Hg)	Creat. (mg/100 ml)	Clinical diagnosis
N 1	M	49	130/80	1.0	Chronic alcoholism
N 2	M	41	120/50	0.9	Chronic alcoholism
N 3	M	59	150/70	0.7	Chronic alcoholism
N 4	F	81	120/80	0.9	Vertigo
N 5	F	58	130/90	0.9	Presenile dementia, vertigo
N 6	M	61	120/80	0.9	Epilepsy
N 7	F	69	150/90	0.7	Diabetes mellitus, foot gangrene
N 8	M	53	150/80	0.9	Diabetes mellitus (no vascular complication)
N 9	M	62	130/85	1.2	Postural hypotension dementia
N10	M	65	150/90	1.0	Recent stroke in recovery

For abbreviations see table 1.

## Results

Resting mean arterial blood pressure (MABP) in the uncontrolled hypertensive patients was  $145 \pm 17$  (1 sd) mm Hg; in the well-controlled hypertensive patients,  $116 \pm 18$  mm Hg; and in the normotensive patients,  $98 \pm 10$  mm Hg. The difference in resting MABP between the uncontrolled hypertensive patients and each of the two other groups was statistically significant ( $P < 0.01$ , Mann-Whitney test), while the difference in resting MABP between the well-controlled hypertensive and the normotensive patients was not significant. Resting values of jugular venous pressure,  $\text{PaCO}_2$ , and  $\text{AVO}_2$  did not show any significant differences among the three groups (table 5). Mean values of the lower limit of CBF autoregulation in groups 1, 2, and 3 were  $113 \pm 17$  mm Hg,  $96 \pm 17$  mm Hg, and  $73 \pm 9$  mm Hg, respectively. For this parameter, the difference between uncontrolled and well-controlled hypertensive patients was significant ( $P < 0.01$ , Mann-Whitney test) as it was between uncontrolled hypertensive and normotensive patients ( $P < 0.01$ ), whereas the difference was not significant between the well-controlled hypertensive and the normotensive patients. The lowest tolerated blood pressure in groups 1, 2, and 3 were  $65 \pm 10$  mm Hg,  $53 \pm 18$  mm Hg, and  $43 \pm 8$  mm Hg, respectively. Here, with the Mann-Whitney test, the difference between the uncontrolled hypertensive and normotensive groups was statistically significant ( $P < 0.01$ ), while the well-controlled hypertensive patients, having an intermediate position between the two other groups, showed no significant difference from any of them. The values for jugular venous pressure,  $\text{PaCO}_2$ , and  $\text{AVO}_2$  at the lowest tolerated blood pressure did not show any significant differences among the groups. The calculated CBF at the lowest tolerated blood pressure was about 70% of the resting value in all groups.

The MABP of the lower limit of autoregulation was  $79 \pm 10\%$  of the resting MABP in the uncontrolled hypertensive patients, as compared with  $72 \pm 29\%$  in the well-controlled group, and  $74 \pm 12\%$  in the normotensive group. The corresponding figures for the lowest tolerated MABP in groups 1, 2, and 3 were  $45 \pm 6\%$ ;  $46 \pm 16\%$ ; and  $45 \pm 12\%$

TABLE 4. *Clinical Data in Four Hypertensive Patients Studied in an Uncontrolled Phase and after 8-12 Months of Antihypertensive Treatment*

Case/sex/age	Study	Months between study 1 and 2	BP (mm Hg)	FH	Creat. (mg/100 ml)	Known duration of Ht	Therapy	Remarks
H 23/M/63	1		220/140	III	2.0	6 months	Clonidine Hydroflumethiazide Pindolol	
	2	12	140/100	II	1.8		Hydroflumethiazide Methyldopa Hydroflumethiazide Bethanidine Methyldopa Hydroflumethiazide	Unilateral nephrectomy between study 1 and 2
H 24/M/58	1		220/140	III	1.7	2 years		
	2	12	160/100	0	1.2			
H 25/M/56	1		190/120	III	1.4	Newly dis.	Furosemide, diazepam for 1 week	
	2	8	170/110	II	1.1		Methyldopa, hydrochlorothiazide	Progressive dementia
H 26/M/57	1		205/125	III	1.0	Newly dis.	None	
	2	11	195/135	II	1.1		Methyldopa, hydrochlorothiazide	

See table 1 for abbreviations.

of the resting MABP, respectively. In other words, a reduction in MABP of about 25% was required in each group to reach the lower limit of CBF autoregulation. A further reduction in the resting MABP of about 55% was required to reach the blood pressure level at which mild symptoms of brain hypoperfusion developed. The comparatively greater scatter in the values reflecting tolerance to hypotension in group 2, the well-controlled hypertensive patients, is described in detail below.

The  $P_{aCO_2}$  was rather constant at the autoregulatory plateau. When MABP had been reduced below the lower limit of autoregulation, and CBF had been reduced by 10-15%, most patients began to show a slight but progressive hyperventilation, and when this was the case,  $P_{aCO_2}$  reached a minimum at the lowest tolerated MABP. The reduction in  $P_{aCO_2}$  at this blood pressure level was 4-5 mm Hg in all groups when compared with the resting  $P_{aCO_2}$  level. If the decrease in CBF was tentatively corrected for the concomitant  $P_{aCO_2}$  decrease, the former was modified, and in some cases altogether abolished (table 5). The justification of this correction procedure is evaluated in the discussion.

Figure 1 summarizes the findings: the mean autoregulation curve of the uncontrolled hypertensive patients is shifted to the right on the blood pressure axis when compared with the curve from the normotensive patients. The mean curve from the well-controlled hypertensive patients falls between the two others. In figure 2, the individual autoregulation curves from the nine well-controlled hypertensive patients in group 2 are shown. Their tolerance to the hypotension procedure is highly variable: some curves appear normal, while others are shifted as much to the right as in untreated hypertensive patients, despite a long period of clinical normotension.

Two of the patients in the effectively treated group showed a focal neurological symptom during controlled hypotension, whereas this was not observed in any of the other groups. One patient (case H 21) developed transient

## CEREBRAL BLOOD FLOW percent of rest

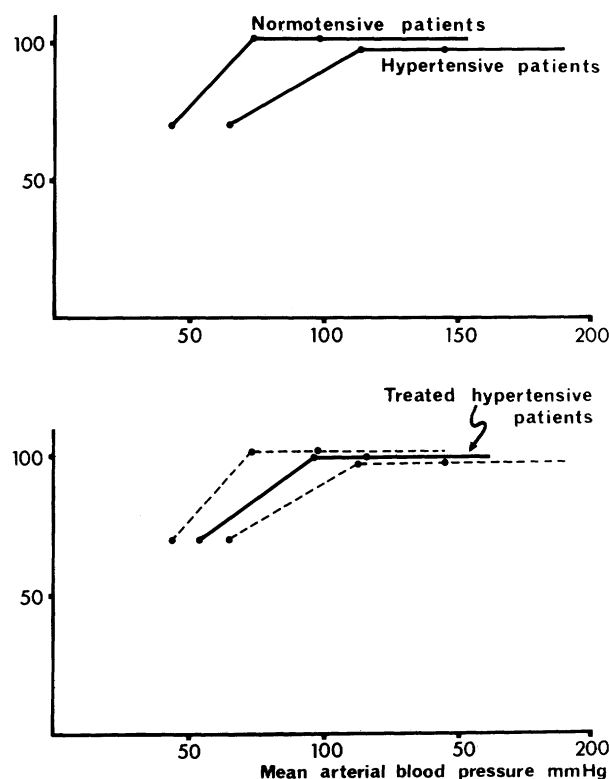


FIGURE 1. Top panel) Mean curves of autoregulation of cerebral blood flow (CBF) in normotensive and severely hypertensive human subjects. Each curve is defined by the mean values of resting blood pressure, the lower limit of CBF autoregulation, and the lowest tolerated blood pressure. The curve from the hypertensive patients is shifted to the right on the blood pressure axis. Bottom panel) Mean curve of CBF autoregulation in patients with a formerly severe hypertension which at the time of the study was effectively controlled by antihypertensive treatment. The curve falls between the two curves above, which are shown by dotted lines.



TABLE 5. Results of Study of Autoregulation of Cerebral Blood Flow (CBF) in Uncontrolled Hypertensives (Group 1), Well-controlled Hypertensives (Group 2), and Normotensives (Group 3)

	Rest				Lower limit of autoregulation				Lowest tolerated blood pressure					
	MABP (mm Hg)	JVP (mm Hg)	AVO <sub>2</sub> (vol. %)	PaCO <sub>2</sub> (mm Hg)	MABP (mm Hg)	JVP (mm Hg)	AVO <sub>2</sub> (vol. %)	PaCO <sub>2</sub> (mm Hg)	CBF (%)	CBF <sub>e</sub> (%)	Hb. (g/100 ml)			
Group 1	145 ± 17 (13)	7 ± 4 (12)	6.50 ± 1.46 (13)	40.8 ± 2.7 (13)	113 ± 17 (12)	2 ± 2 (9)	8.78 ± 1.29 (11)	35.4 ± 4.1 (11)	70 ± 9 (11)	85 ± 18 (11)	13.5 ± 1.4 (13)			
Group 2	116 ± 18 (9)	8 ± 4 (8)	7.51 ± 1.50 (9)	39.3 ± 3.8 (9)	96 ± 17 (9)	2 ± 2 (5)	11.10 ± 0.90 (7*)	35.6 ± 4.3 (7*)	70 ± 12 (7*)	81 ± 14 (7*)	13.8 ± 1.7 (9)			
Group 3	98 ± 10 (10)	6 ± 4 (10)	6.71 ± 1.40 (10)	39.3 ± 2.6 (10)	73 ± 9 (10)	2 ± 5 (6)	9.67 ± 2.15 (8)	35.3 ± 1.6 (8)	71 ± 9 (8)	82 ± 11 (8)	13.1 ± 1.2 (10)			
1 vs 2		P < 0.01	NS		P < 0.01	NS								
1 vs 3		P < 0.01	NS		P < 0.01	NS								
2 vs 3		NS	NS		NS	NS								

Values given as mean ± standard deviation. Number of patients given in parentheses below.

Statistics analyzed by the Mann-Whitney test.

\*Data from case H21, who had only focal symptoms, not included.  
Abbreviations: MABP = mean arterial blood pressure; JVP = jugular venous pressure; AVO<sub>2</sub> = arterial arteriovenous oxygen difference; PaCO<sub>2</sub> = arterial carbon dioxide tension in the resting state and at the lowest tolerated blood pressure; CBF and CBF<sub>e</sub> = the calculated values for CBF at the lowest tolerated blood pressure, without and with a 4% correction per mm Hg decrease in PaCO<sub>2</sub>; Hb = hemoglobin concentration of the blood at the study.

numbness of the left hand, of a type he had frequently experienced since a stroke two years previously.

The other (case H 19) was a 63-year-old man, who had had essential hypertension for at least 20 years and had been clinically normotensive under drug treatment for at least 10 years. He complained of attacks of dizziness. The study (fig. 2) showed that he had a lower limit of autoregulation (around 100 mm Hg) which was also his clinical blood pressure level. At MABP 80 mm Hg, he developed this dizziness, along with yawning and slight hyperventilation, which disappeared when blood pressure rose with withdrawal of trimethaphan and return to the horizontal position. One month after the study he had a transient stroke. His antihypertensive treatment was adjusted to allow somewhat higher blood pressure level, and he improved.

The results from the patients studied twice are shown in table 6. Overall, 8–12 months of antihypertensive treatment

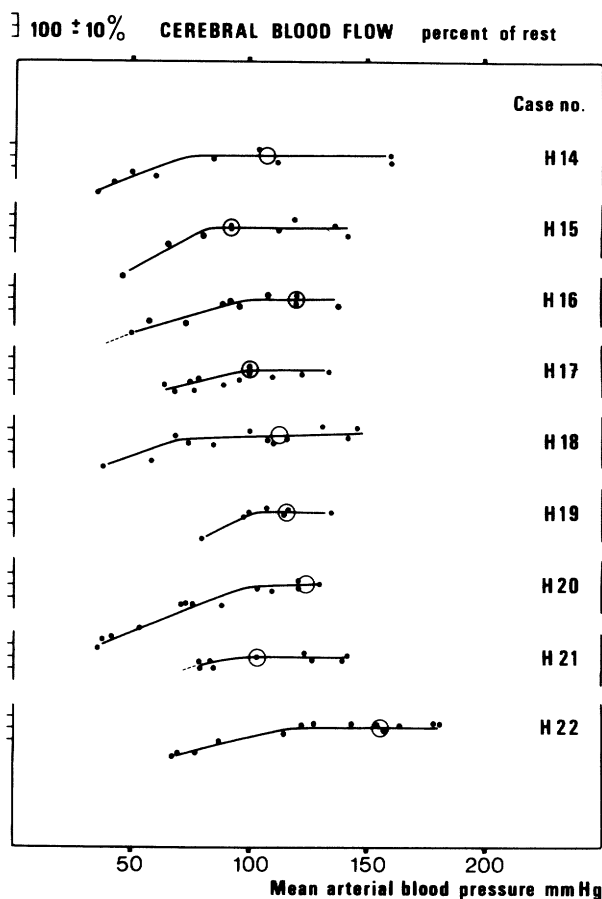


FIGURE 2. Individual curves of autoregulation of cerebral blood flow (CBF) from nine patients with a formerly severe hypertension, which at the time of the study was effectively controlled by antihypertensive treatment. CBF is expressed in percent of the resting value which is marked as 100 percent on each ordinate. The curves have been drawn by simple visual interpolation of the points. Resting mean blood pressure is marked by an open circle on each curve. In case H 16, the lowest tolerated blood pressure was not reached. Case H 19 had both focal and general symptoms during hypotension, while case H 21 had only focal symptoms. While some of the curves are similar to those of normotensive subjects, others are shifted as much to the right as in untreated severe hypertension.

did not cause any change in the lower limit of CBF autoregulation and the lowest tolerated blood pressure. One of the four patients however appeared to have shifted his autoregulation curve toward normal during treatment.

Among all normotensive and hypertensive patients, there was a good correlation between resting MABP and the lower limit of autoregulation MABP ( $r = 0.8004$ ), and between resting MABP and the lowest tolerated MABP ( $r = 0.6589$ ) (fig. 3). In the normotensive group, the few cases with a history of cerebral arteriosclerosis tended to have relatively high values for lowest tolerated blood pressures. This was not observed among the hypertensive patients. In the group of patients with severe uncontrolled hypertension, no difference was found in any of the parameters studied between those patients who were untreated and those who received drug treatment, albeit ineffective.

### Discussion

#### The Method

The use of the AVO<sub>2</sub> method for estimation of CBF in the present study is based on the constancy of the brain oxygen

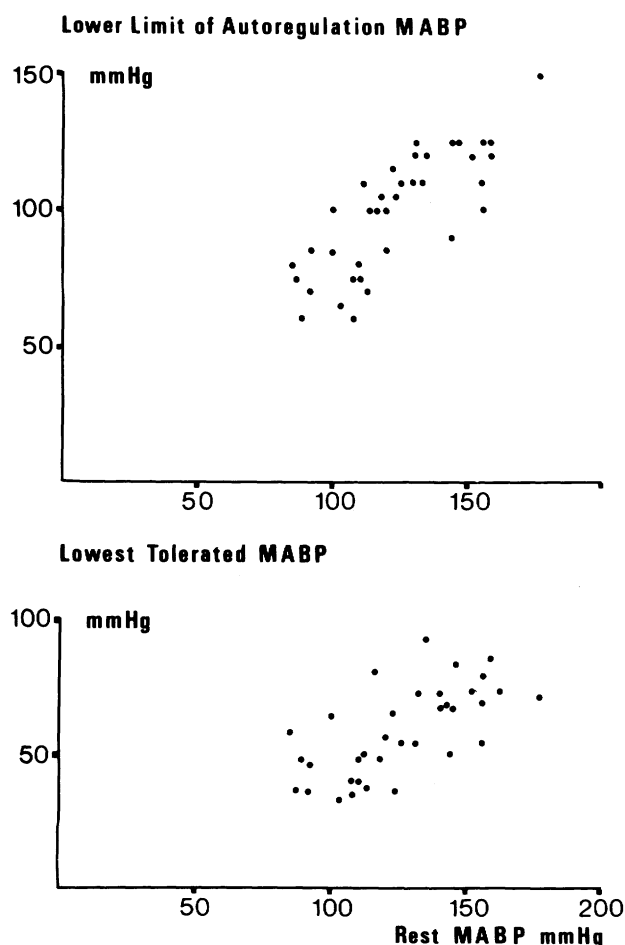


FIGURE 3. Correlations between resting mean blood pressure and the lower limit of autoregulation ( $r = 0.8004$ ) and the lowest tolerated blood pressure ( $r = 0.6589$ ) in all patients in the present study.

TABLE 6. Results of Sequential Studies of Autoregulation of Cerebral Blood Flow (CBF) in Four Hypertensive Patients

	Rest				Lower limit of autoregulation				Lowest tolerated blood pressure				Hb. (g/100 ml)
	MABP (mm Hg)	JVP (mm Hg)	AVO <sub>2</sub> (vol. %)	PaCO <sub>2</sub> (mm Hg)	MABP (mm Hg)	PaCO <sub>2</sub> (mm Hg)	AVO <sub>2</sub> (vol. %)	JVP (mm Hg)	MABP (mm Hg)	JVP (mm Hg)	PaCO <sub>2</sub> (mm Hg)	CBF (%)	
First study	146 ± 11 (4)	9 ± 3 (4)	8.50 ± 1.28 (4)	44.7 ± 7.3 (4)	118 ± 8 (3)	44.7 ± 7.3 (4)	11.37 ± 2.71 (3)	3 ± 2 (4)	72 ± 13 (4)	3 ± 2 (4)	38.8 ± 7.6 (3)	74 ± 6 (3)	14.4 ± 2.0 (4)
Second study	124 ± 11 (4)	7 ± 3 (4)	7.92 ± 1.65 (4)	44.4 ± 10.3 (4)	115 ± 9 (4)	44.4 ± 10.3 (4)	10.85 ± 1.73 (4)	4 ± 2 (4)	66 ± 21 (4)	4 ± 2 (4)	38.2 ± 11.8 (4)	73 ± 6 (4)	15.0 ± 0.9 (4)

Values given are means ± standard deviation. Numbers in study are given in parentheses.  
First study: in uncontrolled phase of severe hypertension.  
Second study: following 8-12 months of antihypertensive treatment.  
See table 5 for abbreviations.

consumption during controlled hypotension in man. It has been demonstrated in both normotensive and hypertensive subjects, that even when symptoms of hypotensive brain ischemia develop, global brain oxygen consumption is not measurably decreased,<sup>3</sup> and the electroencephalogram is unaffected.<sup>12</sup> Presumably, the areas of the brain responsible for early signs of ischemia during hypotension are too small to influence global oxygen consumption.

The AVO<sub>2</sub> method is relatively atraumatic and allows for a great number of measurements in a short span of time. In man, only about 3% of the blood in the jugular bulb is derived from extracerebral structures,<sup>13</sup> and for practical purposes the jugular bulb is free of blood of extracerebral origin. Further, the shift of the lower limit of CBF autoregulation observed with the AVO<sub>2</sub> method in the present study has recently been confirmed in baboons with experimental renovascular hypertension, where the intracarotid <sup>133</sup>Xe method was used for CBF measurement and blood pressure was decreased by controlled bleeding (Jones, Strandgaard et al., unpublished observations).

Below the lower limit of autoregulation, when CBF had been reduced by 10–15%, most patients started to hyperventilate, a reaction presumably caused by CO<sub>2</sub> accumulation in the underperfused brainstem.<sup>14</sup> At the lowest tolerated blood pressure, PaCO<sub>2</sub> reached a minimum at an average of 4–5 mm Hg below the resting level, with no difference among the various groups of patients. In each group, some patients failed to show this reaction during the flow decrease. Hypocapnia causes cerebral vasoconstriction, and might add to the flow decrease observed in our patients. Olesen et al.<sup>15</sup> found a mean CO<sub>2</sub> reactivity in awake man of 4% change in CBF per mm Hg change in PaCO<sub>2</sub>. This they proposed as a correction factor for PaCO<sub>2</sub> differences when the effect of a function test or a pharmacologic substance on CBF is to be assessed. Such a correction is shown in table 5 for the calculated CBF at the lowest tolerated blood pressure. The usefulness of this correction factor in measurements at pronounced hypotension, where the effect of PaCO<sub>2</sub> changes on CBF has been shown to be impaired or even altogether abolished, is doubtful.<sup>16</sup> In figures 1 and 2, the uncorrected figures have been used.

When mild symptoms of cerebral hypoperfusion developed in our patients, CBF was approximately 70% of the resting value in each group. In studies where a state of mental confusion or even loss of consciousness was achieved during controlled hypotension, CBF was reduced to 50–60%.<sup>3, 17</sup> This is still somewhat above the "critical flow level" of about 18 ml/100 g/min in which failure of neuronal function can be detected by EEG slowing in man undergoing carotid surgery.<sup>18</sup>

### The Results

The adaptation of CBF autoregulation in individual patients with arterial hypertension was recently reported by the present author.<sup>4</sup> It was predicted in Lassen's review from 1959,<sup>2</sup> where the concept of CBF autoregulation in man was finally established. It explains the observation made in many studies that during controlled hypotension patients with arterial hypertension develop symptoms of cerebral ischemia at a blood pressure which is well tolerated by normotensive individuals.

In severe, nonlabile hypertension the arterioles are structurally narrowed with thickened walls, and this probably explains why their capacity for autoregulatory vasodilatation is less than normal. In the present study, the lower limit of CBF autoregulation as well as the lowest tolerated blood pressure was found to be correlated with the resting blood pressure, and in a previous study<sup>4</sup> a similar correlation with an estimate of the clinical blood pressure was found. This suggests that the degree of adaptation of CBF autoregulation is correlated to the severity of the hypertension. It may be noted that the hypertrophied cerebral arterioles in hypertensive patients are able to maintain CBF autoregulation at clinical blood pressure levels which would precipitate a hypertensive cerebral crisis in a normotensive subject.

Whether the adaptation or shift to the right of CBF autoregulation is reversible with long-term antihypertensive treatment would be expected to depend on the reversibility of the structural changes in hypertensive arterioles. Adaptation of hemodynamic parameters to high blood pressure has recently been reported in the peripheral circulation of rats with spontaneous or renovascular hypertension.<sup>5, 6, 19</sup> A decreased ability to dilate maximally was observed, signifying a fixed increase in the basic vascular resistance in hypertensive animals. This was found to revert to normal in young animals when hypertension was abolished by drug treatment<sup>5</sup> or by removal of a renal clip.<sup>6</sup> Elderly animals with long standing hypertension showed only a partial normalization of hemodynamic parameters, and their blood pressure could not be returned to normal.<sup>19</sup>

In the present study, the hypertensive patients were classified as having a good blood pressure control when their clinical diastolic blood pressure was 105 mm Hg or less. This was a considerable reduction from pretreatment levels, but not a complete normalization in every case. The average CBF autoregulation curve in these patients had an intermediate position between the curves from the uncontrolled hypertensive and the normotensive patients (fig. 1), suggesting a partial readaptation of autoregulation during treatment. The individual results obtained in the well-controlled group, however, are highly variable: some have an autoregulation curve similar to the curves of normotensive subjects, while in others the curve is shifted as much to the right as in patients with uncontrolled severe hypertension (fig. 2). The response to long-term antihypertensive treatment was studied directly in four patients. Following a rather effective blood pressure lowering for 8–12 months, one of these patients seemingly had shifted his CBF autoregulation toward normal, while the other three showed no definite changes (table 6).

These observations may be reasonably explained in terms of hypertensive arteriolar changes: those patients who have readapted their CBF autoregulation toward normal may be those with predominantly reversible changes in their arterioles, such as muscular hypertrophy. And those who maintain an abnormal autoregulation despite blood pressure reduction may have predominantly degenerative changes and connective tissue proliferation in the arteriolar walls, along with arteriosclerosis of the larger cerebral resistance vessels. These latter features would be expected to dominate in elderly patients and in patients with long standing hyper-

tension. However, most of the patients studied were middle aged, and no relation was found between the outcome of the autoregulation study and the known duration of hypertension. A history of cerebral arteriosclerosis seemed not to influence the result of the study, with the exception that in the normotensive group such patients tended to have relatively high values for the lowest tolerated blood pressure. Observations in a previous study from this center<sup>12</sup> have suggested that in elderly hypertensive arteriosclerotic patients the lowest tolerated blood pressure is not altered during long-term antihypertensive treatment.

#### Clinical Comments

As the period of hypotension in the present and similar studies<sup>3, 4, 12, 17</sup> is only a few minutes, the "lowest tolerated blood pressure" should be understood as a minimum value and not a safety limit to be applied uncritically in the management of hypertensive patients. However, some conclusions pertinent to the clinical situation may be drawn from the differences observed among the groups and within the group of effectively treated hypertensive patients.

First, it should be noted that in all our patients with severe uncontrolled hypertension, the clinical blood pressure level is well above the lower limit of CBF autoregulation and well above the lowest tolerated blood pressure. During controlled hypotension, an average reduction in blood pressure of about 55% was required to induce mild symptoms of brain ischemia. Thus, the fact that CBF autoregulation is adapted to high blood pressure should not be taken as a warning against antihypertensive treatment. Rather it means that initial treatment of severely hypertensive patients should aim at some reduction but not a complete normalization of the blood pressure.

Second, some patients may during antihypertensive treatment readapt their CBF autoregulation curve toward normal. This will allow for a gradual normalization of blood pressure from the point of view of the cerebral circulation. The time factor is not known, but recent work in the baboon has shown that the lower limit of CBF autoregulation may shift to a higher blood pressure level within two months following the onset of renovascular hypertension (Jones, Strandgaard et al., unpublished observations). In a presumably comparable way, blood pressure lowering in patients with malignant hypertension and azotemia only transiently leads to a decrease in kidney function, followed by improvement beyond the initial level.<sup>20</sup>

Third, some patients do not readapt their CBF autoregulation during treatment with antihypertensive drugs.

These patients may do better with a clinical blood pressure somewhat above normal, as exemplified in one case in the present study. A special risk may be present in such patients during hypotensive anesthesia, when the reaction of the brain to further reduction in blood pressure cannot be adequately followed.

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