Changes in CO₂ responsiveness and in autoregulation of the cerebral circulation during and after halothane-induced hypotension

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SYNOPSIS CO₂ responsiveness of the cerebral circulation has been measured in baboons before, during, and after halothane-induced hypotension. At a systolic blood pressure (BP) of 60 mmHg, CO₂ responsiveness was abolished, but was maintained at higher levels of BP. After hypotension, CO₂ responsiveness returned to control values. Autoregulation to BP increases induced by intravenous noradrenaline was impaired when cerebral perfusion pressure during the hypotensive period had been below 30–40 mmHg. It is concluded that at levels of halothane-induced hypotension commonly employed clinically, CO₂ responsiveness of the cerebral circulation may be absent. The return of CO₂ responsiveness in the post-hypotensive phase argues in favour of controlled hyperventilation after neurosurgery which has involved induced hypotension.

Harper and Glass (1965) reported loss of cerebrovascular responsiveness to Pa_{CO₂} changes during haemorrhagic hypotension, while Häggendal and Johansson (1965) reported that some degree of response was retained in these circumstances. Recent evidence (Fitch *et al.*, 1973) shows that the cerebral circulation responds differently during drug-induced hypotension compared with hypotension produced by haemorrhage.

It seemed important, therefore, to establish whether changes in cerebrovascular responsiveness to Pa_{CO₂} occurred during drug-induced hypotension, since the combination of hypotension and hyperventilation could, by a combined action on cerebral perfusion, be clinically undesirable. Consequently, we decided to investigate cerebrovascular responses to changes in Pa_{CO₂} during hypotension induced with halothane at a level of systolic blood pressure commonly employed clinically.

METHODS

Five baboons weighing between 7.2 and 13.8 kg were premedicated with phencyclidine (0.8–1.0 mg/kg) intramuscularly and anaesthesia was induced and

maintained with halothane, N₂O, and O₂. After intramuscular injection of suxamethonium (50 mg), the animals were intubated and ventilated by intermittent positive pressure (Starling ventilator). Muscle relaxation was obtained by injecting pancuronium (1 mg) intramuscularly at 30 min intervals. Oesophageal temperature was held at 37°C by automatically controlled heating lamps.

Catheters were inserted into one femoral artery and into the sagittal sinus. These catheters were connected to Statham strain gauges and a multi-channel heated stylus recorder (Devices) for continuous monitoring of arterial pressure and cerebral venous pressure throughout the experiment. Arterial P_{O₂}, P_{CO₂}, and pH were measured with Radiometer blood gas equipment, and the halothane concentration in cerebral venous blood was measured by gas chromatography (Pye-Unicam). One femoral vein was catheterized for the continuous infusion of replacement fluid (30 ml/h Hartmann's solution) and for the infusion of noradrenaline during autoregulation testing.

Cerebral blood flow (CBF) was measured by two methods: (1) by the Xenon clearance technique; and (2) by electromagnetic flowmeter (Statham) on one carotid artery. The common carotid artery and its branches were exposed in the neck, a catheter for ¹³³Xenon injection was inserted into a branch of the external carotid artery and directed centrally to

wards the carotid bifurcation, and all other branches of the external carotid artery were tied off. An electromagnetic flow probe, placed around the common carotid artery, measured internal carotid blood flow (CarBF) continuously, since the external carotid circulation had been ligated. The scalp and temporalis muscle were reflected and a collimated gamma radiation detector was placed over the lateral aspect of the parietal bone mounted in a coronal plane. Xenon 0.5 ml, dissolved in saline, was injected within 2 s and a clearance curve recorded on a chart recorder and stored on magnetic tape in digital form. The bi-exponential equation of the clearance curve was calculated from the digital data by a small computer (WANG 720) using a programme of the best fitting line, based on the least squares method. Mean cerebral blood flow (CBF) was estimated by the infinite integration of this equation.

When the surgical preparation was complete, control measurements of CBF were made during light halothane anaesthesia and arterial P_{CO_2} was altered both by varying the ventilation volume and by adding CO_2 to the inspired gases. Blood pressure was then reduced by increasing the inspired halothane concentration and CO_2 responsiveness again tested. Finally, all measurements were repeated after discontinuance of halothane and recovery of blood pressure.

Autoregulation in the cerebral circulation to a rise of blood pressure (BP) was tested by infusing nor-adrenaline (NA) intravenously before and after halothane-induced hypotension. Mean blood pressure was calculated as diastolic + one-third pulse pressure and mean cerebral venous pressure as diastolic + one-half pulse pressure measured during the expiratory pause. Mean cerebral perfusion pressure was calculated as the difference between these two values.

RESULTS

FREQUENCY HISTOGRAMS OF MEAN ARTERIAL BLOOD PRESSURE AND CEREBRAL PERFUSION PRESSURE During each experiment, the values for mean arterial blood pressure and cerebral perfusion pressure were stored in a computer (Wang 720) at two minute intervals and frequency histograms were printed out. In Fig. 1, the histogram of each experiment is shown. As can be seen, the histograms of Expts 134, 135, 136, and 138 have two peaks clearly separated, but the peaks of Expt 140 were not distinct because of the lesser degree of hypotension studied in this experiment. Figure 2 is a

FIG. 1 Histogram of mean arterial blood pressure for each experiment individually during both normotensive and hypotensive phases. The frequency scale is in units of 2 min of observation.

similar presentation of cerebral perfusion pressure, but during the hypotension stage only.

The numerical data on systolic blood pressure, mean arterial BP, and cerebral perfusion pressure, together with the results of blood gas analysis and of cerebral venous halothane concentration during the stages of normotension, hypotension, and post-hypotension, are presented in Table 1a. Table 1b is a similar presentation of the numerical data on Expt 140, in which moderate hypotension was studied.

RESPONSIVENESS OF CEREBRAL CIRCULATION TO Pa_{CO_2} CHANGE CO_2 responsiveness of the cerebral circulation was observed during light N_2O/O_2 /halothane anaesthesia before the induction of hypotension. Each CBF result was expressed as a percentage of the CBF at Pa_{CO_2} of 40 mmHg, as estimated from individual tests.

FIG. 2 Frequency histograms of cerebral perfusion pressure for each experiment individually during the hypotensive phase only. The frequency scale is in units of 2 min.

The percentage values were calculated by the equation shown below:

$$\%F_1 = \frac{F_1}{F_{st}} \times 100$$

$$\%F_2 = \frac{F_2}{F_{st}} \times 100$$

$$F_{st} = F_1 + \frac{(F_2 - F_1) \times [40 - (Pa_{CO_2})_1]}{(Pa_{CO_2})_2 - (Pa_{CO_2})_1}$$

F_1 : CBF at $(Pa_{CO_2})_1$.

F_2 : CBF at $(Pa_{CO_2})_2$.

F_{st} : standard CBF at $Pa_{CO_2} = 40$ mmHg.

Table 2a lists the individual values of Pa_{CO_2} , mean BP, cerebral perfusion pressure, CBF by Xe clearance, CarBF by electromagnetic flowmeter, and cerebral venous halothane concentration during the normotensive stage. Tables 2b and 2c give the same values for the hypotensive and post-hypotensive stages respectively. CBF

TABLE 1a

BLOOD PRESSURE AND CEREBRAL PERFUSION PRESSURE (MEANS $\pm$ S.Ds) WITH RESULTS OF BLOOD GAS ANALYSIS AND OF CEREBRAL VENOUS HALOTHANE CONCENTRATION, AT EACH STAGE OF EXPERIMENTS

	Normotension	Hypotension	After hypotension
SBP (mmHg)	113 $\pm$ 14	59 $\pm$ 12	124 $\pm$ 17
mBP (mmHg)	89 $\pm$ 12	44 $\pm$ 9	101 $\pm$ 10
CPP (mmHg)	77 $\pm$ 10	33 $\pm$ 7	81 $\pm$ 15
PaO_2 (mmHg)	176 $\pm$ 23	194 $\pm$ 45	193 $\pm$ 54
$PaCO_2$ (mmHg)	25 $\sim$ 70	24 $\sim$ 74	28 $\sim$ 51
pHa	7.27 $\sim$ 7.53	7.17 $\sim$ 7.57	7.21 $\sim$ 7.40
Cerebral venous halothane concentration (mg/dl)	6.5 $\pm$ 2.3	24.1 $\pm$ 6.7	7.7 $\pm$ 3.2

Experiment 140 is excluded from the columns of hypotension and after hypotension.

TABLE 1b

BLOOD PRESSURE AND CEREBRAL PERFUSION PRESSURE (MEANS $\pm$ S.Ds), WITH RESULTS OF BLOOD GAS ANALYSIS AND CEREBRAL VENOUS HALOTHANE CONCENTRATION DURING HYPOTENSION AND AFTER HYPOTENSION IN EXPT 140

	Moderate hypotension	After moderate hypotension
SBP (mmHg)	81 $\pm$ 5	129 $\pm$ 6
mBP (mmHg)	59 $\pm$ 4	95 $\pm$ 5
CPP (mmHg)	51 $\pm$ 5	86 $\pm$ 2
PaO_2 (mmHg)	161	—
$PaCO_2$ (mmHg)	30 $\sim$ 53	31 $\sim$ 52
pHa	7.35 $\sim$ 7.56	7.33 $\sim$ 7.52
Cerebral venous halothane concentration (mg/dl)	10.0 $\pm$ 2.0	2.9 $\pm$ 0.3

This experiment was deliberately performed at a higher level of blood pressure than the others.

measurement by Xe clearance was not performed after hypotension.

Percentage changes of mean CBF by Xe clearance and Pa_{CO_2} from all the experiments during the normotensive stage have been plotted in Fig. 3a. The plots for each animal are shown with different symbols. There was no statistically significant difference in CO₂ responsiveness between the individual animals, since the F-value of one-way analysis of variance was less than 5% of the critical values [F-value = 3.95 < 6.59 = F(0.95) d.f.(3,4)]. The linear regression equation of these plots was $y = 3.9x - 53.6$ and the correlation

TABLE 2a
CO₂ RESPONSIVENESS BEFORE HYPOTENSION

Experiment no.	PaCO ₂ (mmHg)	mBP (mmHg)	CPP (mmHg)	Xe clearance (ml/100 g/min)					CarBF (ml/min)	% CarBF ₄₀	Halothane in CV blood (mg/dl)
				FI	FG	FW	FM	% FM ₄₀			
134	34	84	73	—	—	—	—	—	53	89	} 6.8
	45	89	71	—	—	—	—	—	65	109	
	33	77	70	—	—	—	—	—	44	71	} 4.8
	43	85	66	—	—	—	—	—	70	113	
135	25	81	72	58	88	25	52	75	45	70	} 9
	42	93	82	88	128	34	72	103	67	104	
	30	81	76	52	72	18	38	72	48	76	} 8.0
	53	123	104	111	139	20	72	136	83	131	
136	27	82	68	36	53	10	27	52	40	56	} 10.2
	67	107	91	145	185	24	103	199	138	192	
	35	77	61	27	45	22	30	74	35	76	} 7.9
	70	104	89	139	185	31	103	255	112	243	
138	32	89	81	53	74	17	42	65	40	75	} 5.1
	52	97	81	111	151	43	99	153	74	138	
	30	88	79	28	54	28	35	61	40	73	} 4.7
	50	90	75	95	123	34	80	139	69	132	
140	33	80	74	44	71	24	41	73	47	79	} 3.9
	52	82	73	90	104	44	82	146	81	136	
	31	80	74	38	51	18	32	69	46	96	} 4.2
	44	88	82	57	81	28	53	114	49	102	

%FM₄₀ = percentage relationship of mean CBF to the calculated mean CBF at PaCO₂ = 40 mmHg. Similarly, %CarBF₄₀ = percentage relationship of carBF to the calculated carBF at PaCO₂ = 40 mmHg. The details of the calculations are given in the text. FI = flow based on initial slope of clearance curve. FG = flow grey matter. FW = flow white matter. FM = mean flow.

TABLE 2b
CO₂ RESPONSIVENESS DURING HYPOTENSION

Experiment no.	PaCO ₂ (mmHg)	mBP (mmHg)	CPP (mmHg)	Xe clearance (ml/100 g/min)					CarBF (ml/min)	% CarBF ₄₀	Halothane in CV blood (mg/dl)
				FI	FG	FW	FM	% FM ₄₀			
134	31	37	26	—	—	—	—	—	40	100	} 20.0
	48	39	26	—	—	—	—	—	40	100	
	30	34	24	—	—	—	—	—	34	87	} 29.5
	49	35	24	—	—	—	—	—	44	112	
	24	49	41	—	—	—	—	—	47	113	} —
	45	42	35	—	—	—	—	—	40	96	
135	28	34	31	23	25	22	23	103	30	100	} 22.4
	44	34	31	19	31	15	22	99	30	100	
	31	39	35	25	43	17	24	100	29	101	} 39.2
	62	35	32	19	43	19	24	100	28	98	
136	31	41	23	43	56	30	40	93	19	96	} 20.8
	43	51	31	51	67	23	44	102	20	101	
	32	51	32	51	74	16	37	97	34	105	} —
	74	55	33	40	58	28	42	111	26	80	
138	28	49	39	57	83	23	51	101	48	95	} 18.9
	53	56	45	61	69	28	50	99	53	105	
	27	54	44	45	69	29	50	99	39	104	} 20.9
	45	58	45	53	67	30	51	101	37	99	
140	34	54	47	43	53	20	36	78	31	80	} 9.0
	52	58	46	95	118	21	74	160	54	140	
	30	63	56	33	49	22	33	71	37	82	} 12.3
	53	61	47	83	98	24	63	136	56	124	

%FM₄₀ and %CarBF₄₀ have the same meanings as in Table 2a.

TABLE 2c
CO₂ RESPONSIVENESS AFTER HYPOTENSION

Experiment no.	P _a CO ₂ (mmHg)	mBP (mmHg)	CPP (mmHg)	CarBF (ml/min)	% CarBF ₄₀	Halothane in CV blood (mg/dl)
134	28	101	84	60	86	11.2
	40	82	66	70	100	
	31	103	85	59	92	5.5
	46	97	49	84	131	
136	38	114	98	38	85	11.1
	50	110	86	79	176	
138	40	100	85	91	100	9.3
	51	112	94	99	109	
	38	104	92	71	95	4.3
	47	88	71	88	118	
140	32	91	84	35	72	3.1
	43	97	88	54	111	
	31	92	85	41	70	2.7
	52	101	85	82	140	

%CarBF₄₀ has the same meaning as in Table 2a.

(a) Normotension

FIG. 3 Plots of percentage change in mean cerebral blood flow, plotted against arterial P_{CO}₂ (in the upper panel in normotension, and in the lower during hypotension).

(b) Hypotension

FIG. 4 Plots of percentage change in carotid blood flow, plotted against arterial P_{CO_2} (in the upper panel in normotension, and in the lower during hypotension).

coefficient $r = 0.9698$. The mean arterial BP of this stage was $89 \pm SD 12$ mmHg. Figure 4a is a similar presentation of the values for CarBF, the regression equation for which is given in Table 3.

During the hypotensive stage, tests of CO_2 responsiveness were repeated in each animal. In Fig. 3b the plots for mean CBF by Xe clearance are shown, again with separate symbols for each

animal. In the four animals (Expts 134, 135, 136, and 138) in which the mean arterial BP was $44 \pm SD 9$ mmHg, neither raising nor lowering the P_{aCO_2} had any effect on the cerebral circulation at this hypotensive stage. Figure 4b shows the CarBF during hypotension, and clearly also indicates the absence of CO_2 responsiveness. The slopes of the regression line for CO_2 responsive-

TABLE 3
REGRESSION EQUATIONS FOR CO_2 RESPONSIVENESS

	Regression equations	Correlation coefficients	No. of measurements
Normotension	CarBF $y = 3.4x - 33.1$ meanCBF $y = 3.9x - 53.6$	$r = 0.9563$ $r = 0.9698$	16 16
Hypotension	CarBF $y = -0.21x + 107.9$ meanCBF $y = 0.16x + 93.6$	$r = -0.3670$ $r = 0.5892$	18 12
After hypotension	CarBF $y = 2.6x + 3.8$	$r = 0.7198$	10

Regression equations for CO_2 responsiveness during normotension (mean BP = $89 \pm SD 12$ mmHg); during hypotension (mean BP = $44 \pm SD 9$ mmHg) and after hypotension (mean BP = $101 \pm SD 10$ mmHg). $x = P_{aCO_2}$ in mmHg. CarBF in ml/min. Mean CBF in ml/100 g/min.

FIG. 5 Plot of percentage change in cerebral blood flow, either mean flow or carotid flow as indicated, against arterial P_{CO_2} in experiment 140, in which only moderate hypotension was studied. $\blacksquare$ Carotid blood flow by electromagnetic flowmeter. $\bullet$ Mean CBF based on ^{133}Xe clearance.

ness during hypotension do not differ significantly from zero response (Table 3).

In Expt 140, in which moderate hypotension (mean BP = $59 \pm \text{SD } 4$ mmHg) was maintained, CO₂ responsiveness was maintained at a level similar to that in the normotensive stage (Fig. 5) [$y = 3.0x - 16.4$; $r = 0.9422$; $n = 8$].

In Fig. 6, CO₂ responsiveness after hypotension is presented as plots of individual animals using the same symbols as in Fig. 3. All the results are based on CarBF measurements. Recovery of CO₂ responsiveness was observed at this stage when mean arterial BP was $101 \pm \text{SD } 10$ mmHg (see also Table 3).

RESULTS OF AUTOREGULATION TESTS Autoregulation was tested by noradrenaline infusion into a central vein before and after hypotension at P_{aCO_2} of 37–44 mmHg. The level of autoregulation was expressed in terms of the percentage autoregulation index calculated from the equation below:

Percentage autoregulation index

$$= \left\{ \left(\frac{P_{NA}}{F_{NA}} - \frac{P_{cont.}}{F_{cont.}} \right) / (P_{NA} - P_{cont.}) \right\} \times F_{cont.} \times 100\%$$

$F_{cont.}$: CBF at control.

F_{NA} : CBF during noradrenaline infusion.

$P_{cont.}$: perfusion pressure at control.

P_{NA} : perfusion pressure during noradrenaline infusion.

FIG. 6 Plot of percentage change in carotid blood flow against arterial P_{CO_2} during the recovery phase after the end of hypotension.

Table 4a gives the individual results of each autoregulation test, CBF being measured by carotid flow probe. The range of percentage autoregulation index before hypotension was between 61–80%, thereby showing a partially autoregulated condition during the control stage. In Table 4b, percentage autoregulation indices before and after hypotension, duration of hypotension, and the level of cerebral perfusion pressure during hypotension on each experiment are summarized. The duration of hypotension was estimated from the total frequency of mean BP under 60 mmHg multiplied by two minutes. Experiments 134 and 136, in which cerebral perfusion pressure was lower than 30 mmHg, had no autoregulation in the post-hypotensive period but Expts 138 and 140, in which cerebral perfusion pressure during hypotension was higher than 40 mmHg, exhibited maintained autoregulation after hypotension at values similar to control.

DISCUSSION

The primary objective of this study was to determine the responsiveness of the cerebral circulation to changes in arterial P_{CO_2} during hypotension similar in degree to that used clinically and produced by a clinical technique—that is, halothane anaesthesia. The main conclusion is that, in the baboon, at a mean BP of 45 mmHg and a systolic pressure of 60 mmHg during halothane anaesthesia, there is no detectable cerebro-

TABLE 4a
RESULTS OF AUTOREGULATION TESTING

Expt no.	Before hypotension									After hypotension								
		CarBF (ml/min)	mBP (mmHg)	CPP (mmHg)	CVR	A/R index	Halothane in CV blood (mg/dl)		Paco ₂ (mmHg)		CarBF (ml/min)	mBP (mmHg)	CPP (mmHg)	CVR	A/R index	Halothane in CV blood (mg/dl)	Paco ₂ (mmHg)	
134	C	47	70	64	1.36	}	75	4.8	37		63	87	70	1.10	}	-2	5.5	40
	NA	52	113	105	2.02						94	137	102	1.09				
135	C	49	82	79	1.61	}	64	9.6	40		—	—	—	—	}	—	—	—
	NA	54	113	108	2.00						—	—	—	—				
136	C	68	105	88	1.29	}	61	10.2	38		72	120	100	1.38	}	-14	4.7	39
	NA	74	130	112	1.51						93	148	124	1.33				
138	C	47	90	80	1.70	}	80	5.1	40		91	102	88	0.95	}	67	4.3	40
	NA	50	123	110	2.22						100	130	115	1.15				
140	C	56	85	79	1.41	}	73	3.9	44		50	98	90	1.80	}	70	2.7	40
	NA	62	120	115	1.85						55	132	130	2.36				

C: control.

TABLE 4b
CHANGES IN AUTOREGULATION IN RELATION TO DURATION AND SEVERITY OF HYPOTENSION

Expt no.	% Autoregulation index		Duration of hypotension (h min)	Cerebral perfusion pressure				CVP mean $\pm$ SD (mmHg)
	Before hypotension	After hypotension		mean $\pm$ SD (mmHg)	25%	50%	75%	
134	75	-2	3 14	27 $\pm$ 6	24	26	28	12 $\pm$ 5
135	64	—	2 58	33 $\pm$ 4	31	33	35	3 $\pm$ 1
136	61	-14	3 08	29 $\pm$ 5	27	30	32	19 $\pm$ 2
138	80	67	2 48	41 $\pm$ 7	39	40	45	11 $\pm$ 1
140	73	70	0 54	51 $\pm$ 5	48	53	56	10 $\pm$ 3

The cerebral perfusion pressure values during hypotension are given both as means $\pm$ SDs and as 25, 50, and 75 percentiles.

vascular response to changes in arterial P_{CO₂} in the range 24–74 mmHg.

This conclusion is in agreement with the findings of Harper and Glass (1965) in the dog, which demonstrated the absence of CO₂ responsiveness at a mean BP of 50 mmHg produced by haemorrhage and with those of Russell (1971) which showed absence of change in the diameter of pial arteries in response to hypercapnia in the rabbit during haemorrhagic hypotension to 30–40 mmHg.

Häggendal and Johansson (1965) however, found some residual response to CO₂ in the dog at a mean BP of 60 mmHg. The higher BP employed in these experiments could well account for the observed maintenance of CO₂ responsiveness, since in the one experiment of the present study, carried out at moderate hypotension (systolic BP=81 mmHg; mean BP=59

mmHg), maintenance of CO₂ response was observed. The study of Hamer *et al.* (1973), in which increased CBF was observed in response to the inhalation of 5% CO₂ in dogs rendered hypotensive by trimetaphan, was conducted at values of hypotension—that is, mean cerebral perfusion pressure=40 mmHg—equivalent to those in two of the experiments of the present study, but below those employed by Häggendal and Johansson (1965). This difference in findings may be due to species variation, or to the agent used for producing hypotension (halothane in our study, and trimetaphan in that of Hamer *et al.*, 1973). However, the methodology employed by the latter for CBF measurement involved sampling of sagittal sinus blood in the dog, a method which may introduce errors due to contamination of the sampled venous blood with blood from non-cerebral sources. Such extra-

cranial contamination could have been altered by the induced P_{CO₂} changes, as a result of changes in skin and muscle blood flow.

Changes in cerebrovascular control mechanisms during hypotension, such as have been demonstrated here, are usually ascribed to maximum vascular dilatation, produced either by the low intravascular pressure ('Bayliss' effect) or by tissue acidosis ('metabolic' effect); the latter mechanism appears very unlikely in view of our earlier finding (Keaney *et al.*, 1973) that even more extreme halothane-induced hypotension produces no CSF acidosis over a two hour period. The tissue metabolite measurements of Eklof *et al.* (1972) also support this conclusion. Using halothane to induce hypotension, it is however impossible to exclude the possibility that the loss of CO₂ responsiveness is secondary to a halothane-induced effect on the vasculature.

After the restoration of normal BP, CO₂ responsiveness was not different from the prehypotensive control values, indicating that, whatever mechanism was involved in blocking CO₂ responses at low BP, it was rapidly corrected after restoration of normotension. This observation does not help to differentiate between a halothane effect and a hypotensive effect *per se* in the mechanism of CO₂ response impairment.

CHANGES IN AUTOREGULATION AFTER HYPOTENSION The results of autoregulation testing before and after hypotension in the present studies have been expressed in terms of percentage autoregulation index, which shows the level of autoregulation as the ratio between the percentage difference in CVR, as compared with control CVR, and the percentage difference in perfusion pressure compared with control perfusion pressure. The value for this index during normotension ranged between 61 and 80% in the present experiments, so that good, though not complete, autoregulation was present during light N₂O/O₂/halothane anaesthesia in agreement with the observations of Waltz (1968) in the cat.

After hypotension, the autoregulation index varied between -14 and +70%, with a mean value of 30%, whereas in the study of Keaney *et al.* (1973) the mean value was 13%. The greater

disturbance of autoregulation in the earlier study can be ascribed to the more severe hypotension employed—that is, mean BP 33 mmHg as compared with 44 mmHg in the present study. Furthermore, as can be seen from Table 4b there was, in the present experiments, a clear relationship between the change in percentage autoregulation after hypotension and the severity of hypotension in terms of cerebral perfusion pressure. Thus, in the two animals subjected to the most severe reduction in cerebral perfusion pressure (Expts 134 and 136) there was a total loss of autoregulation after hypotension, whereas in the animals subjected to lesser BP reduction (Expts 138 and 140) there was little change in autoregulation index. Furthermore, when these results are viewed together with those reported by Keaney *et al.* (1973) it becomes clear that the critical cerebral perfusion pressure below which loss of autoregulation occurs in the post-hypotensive period lies between 30 and 40 mmHg. These results emphasize the value of a quantitative index of autoregulatory ability, rather than the use of a simple present or absent schema. The percentage autoregulation index used here is very similar to the vasoreactivity impairment index (V.I.I.) employed by Olesen (1973), except that perfect autoregulation yields an autoregulation index of 100%, and a V.I.I. of zero. The mechanisms involved in the impairment of autoregulation after hypotension have been discussed by Keaney *et al.* (1973).

CONCLUSIONS AND CLINICAL INFERENCES

When the findings of the present study and of the earlier one are considered together (Keaney *et al.*, 1973), it would appear that, in the baboon, halothane-induced hypotension to a systolic BP of 60 mmHg is associated with loss of reactivity to changes in blood Pa_{CO₂}, but that at a systolic BP of 80 mmHg CO₂ responsiveness is still present. Autoregulation after hypotension is lost when cerebral perfusion pressure is reduced below 30–40 mmHg.

From the clinical viewpoint, it would appear that the CBF is not further reduced by combining hyperventilation with halothane-induced hypotension at a systolic BP of 60 mmHg. At blood pressures above this, hyperventilation does have an effect in reducing flow. The CBF reduc-

tion produced by halothane hypotension to 60 mmHg appears to be similar in degree to that produced by hyperventilation at normotension to a PaCO_2 of approximately 30 mmHg (in each of these situations CBF equalled approximately 75% of the normotensive, normocapnic values).

The mechanism of 'inverse steal' can lead to increases in rCBF in ischaemic areas of brain when hypocapnia is induced (Fieschi *et al.*, 1972). Such beneficial effects of hypocapnia in ischaemic areas presumably depend upon normal CO_2 responsiveness in the other areas of cerebral circulation. During halothane hypotension to 60 mmHg such responsiveness is absent, so that the 'inverse steal'—that is, an improvement in regional perfusion of ischaemic areas with hypocapnia—would seem unlikely at this degree of hypotension. A possible advantage of hyperventilation would then be lost at these levels of BP, but not at intermediate higher values.

The finding of absent autoregulation, but maintained CO_2 responsiveness, in the post-hypotensive period supports the clinical employment of passive hyperventilation in the early postoperative period after surgery which has involved induced hypotension. In this way, cerebral blood flow and blood volume can be reduced by hypocapnia, so preventing the cerebral hyperaemia and possible cerebral oedema formation which might otherwise occur because of sudden elevations in BP at this stage when autoregulation is impaired.

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