Effect of carbon dioxide inhalation on the pattern of gaseous metabolism in ischaemic zones of the primate cortex¹

An experimental study of the 'intracerebral steal' phenomenon in baboons

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SUMMARY The cortical circulation of the baboon has been studied during ischaemia produced by middle cerebral occlusion. Evidence of reactive hyperaemia did not occur in hypercapnia. Metabolic studies as a whole present evidence of increased interference with gaseous metabolism during hypercarbic occlusion, despite raised venous pO_2 during hypercarbia. The significance of these findings is discussed.

Attempts to modify the ischaemia resulting from blockage of cerebral blood vessels continue to be of importance in the treatment of occlusive cerebrovascular disease, and, in neurosurgery, particularly in the management of intracranial aneurysms or in the resection of tumours involving major blood vessels. Clinical and experimental analysis has continued to concentrate therefore on endeavours to find methods which, either acutely or in the more chronic situation, might improve the circulation of areas of brain deprived of their normal blood supply.

The most potent cerebral vasodilator has for many years been known to be increased arterial carbon dioxide tension (Gibbs, Gibbs, and Lennox, 1936; Forbes, 1940; Schmidt, Kety, and Pennes, 1945). Not unreasonably, therefore, many authorities have indicated their belief that inhalation of carbon dioxide is of value in the treatment of cerebrovascular disease (Hegedus and Shackelford, 1965; Meyer and Gilroy, 1968). In a study of patients with the chronic stroke syndrome, Meyer and his colleagues (1968) showed that inhalation of CO_2 increased cerebral metabolic rate for oxygen and glucose and inferred from this, therefore, that the metabolism of tissue imperfectly perfused had been increased by inhalation of CO_2 —presumably a beneficial effect. The development of more regional methods for the study of the cerebral circulation, however (Lassen,

Høedt-Rasmussen, Sørensen, Skinhøj, Cronqvist, Bodforss, and Ingvar, 1963; Høedt-Rasmussen, Sveinsdottir, and Lassen, 1966) has produced evidence that the normal increase of cerebral blood flow during hypercapnia is often abolished or even reversed in some patients with acute cerebrovascular disease or brain tumours (Paulson, 1968; Pálvölgyi, 1968). There has been clear haemodynamic evidence for some years (Symon, 1963, 1968, 1970; Brawley, Strandness, and Kelly, 1967) that the induction of hypercapnia reduces the perfusion pressure in ischaemic zones of the cerebral circulation and impairs the reactivity of the ischaemic zone. Such clinical and experimental evidence together has been crystallized in the concept of the intracerebral steal (Lassen and Pálvölgyi, 1968; Symon, 1969).

Other authorities have suggested that, conversely, reduction of arterial pCO_2 —that is, induced hypocapnia—may increase the perfusion of an ischaemic zone (Lassen and Pálvölgyi, 1968; Soloway, Nadel, Albin, and White, 1968; Battistini, Casacchia, Bartolini, Bava, and Fieschi, 1970), although this has been disputed by other authors (Brock, Hadjdimos, and Schürmann, 1970).

The present study forms the second part of an attempt to analyse the effects of hypercapnia on an ischaemic zone produced by acute middle cerebral artery occlusion in baboons, in comparison with findings at normocapnia, to determine whether carbon dioxide improved or made worse the metabolic

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state of the ischaemic cortex. The effects of hypercapnia on arterial and venous pressures within the ischaemic zone and on the phenomenon of reactive hyperaemia have already been reported (Symon, 1970). The present communication reports the effects of hypercapnia on venous oxygen tension and arteriovenous $p\text{CO}_2$ differences in the ischaemic zone of the baboon hemisphere.

METHODS

Methodology has been stated in detail in a previous communication (Symon, 1970). Ten adult baboons, unselected as to age and sex were used, intubated under phencyclidine sedation, supplemented if necessary by light halothane anaesthesia, and anaesthesia continued thereafter by the intravenous administration of chloralose 60 mg/kg. The animals were ventilated after immobilization with intravenous gallamine triethiodide, 1 mg/kg, using a Starling pump (Palmer Instruments Ltd.). The stroke volume of the pump was adjusted to produce a 'normal' arterial $p\text{CO}_2$, between 35 and 45 mm Hg. Where hypercapnia was to be induced, a mixture of 6% CO_2 in air replaced the air at the inlet of the Starling pump and the arterial $p\text{CO}_2$ of the animal was thereby raised to between 60 and 80 mm Hg. Values of over 55 mm Hg were accepted as hypercapnic for the purposes of the study. Arterial blood pressure, end-tidal CO_2 , and pial arterial pressure were continuously monitored, as previously described. Systemic arterial $p\text{O}_2$ was maintained between 95 and 120 mm Hg, if necessary with oxygen supplements in the inspired air.

The middle cerebral artery was exposed by a subtemporal route through the Sylvian fissure, freed of its arachnoid coverings in the medial part of the fissure, and temporarily occluded by a light spring clip (Symon, 1963). Direct sampling of cortical venous blood from the middle cerebral arterial territory on the lateral aspect of the cerebral hemisphere, was achieved by the introduction of a small catheter into either the major middle cerebral vein before its entry into the lateral sinus, or into a convenient branch emanating from the Sylvian region (Fig. 1). Animals were fully heparinized (1,000 i.u./kg intravenously) after the catheters were in place. Small quantities of blood, freely flowing, were collected in Radiometer microcapillaries whose volume was expanded by connection to a small length of polyethylene tubing, to a volume sufficient (0.2 or 0.3 ml.) to obtain immediate analysis of regional cerebral venous blood for $p\text{O}_2$ and $p\text{CO}_2$ in the microelectrodes of an Astrup apparatus (Radiometer, Copenhagen).

The animals were maintained on a heated operating table, and their temperature remained constant at about 38°C throughout the experiments. The right common carotid artery was exposed in the neck, but the carotid sinus was not dissected.

The experimental protocol was similar to that described in the first part of the study (Symon, 1970). A control occlusion in normocapnic circumstances was made first, followed by an occlusion under hypercapnia, and a third occlusion under normocapnia was then made to ensure

FIG. 1. Diagram showing the position of pial arterial catheter for pressure recording, and venous catheter for blood gas tensions and pH.

that differences between normocapnia and hypercapnia were not those of sequential occlusions. This cycle was then repeated at least once, provided that the general condition of the animal remained satisfactory and normal reactivity to the inhalation of 3% CO_2 could be demonstrated. This took the form of a narrowing of the arteriovenous (AV) $p\text{CO}_2$ difference and increase in regional venous oxygen tension. The results in each animal therefore represent the mean of several normocapnic occlusions, compared with at least two occlusions under hypercapnia. A close approximation to control levels of venous $p\text{O}_2$ and arteriovenous $p\text{CO}_2$ differences was awaited before restarting the cycle of observations. The metabolic disturbances of hypercapnia *per se* generally return to normal in about 10 min, but after hypercapnic occlusion, although CO_2 inhalation was discontinued some 5 min after release of the occlusion in the experiments reported here, abnormality of cerebral venous gas tensions persisted for an appreciable time thereafter. Further control readings could not be made before the lapse of at least 30 min.

RESULTS

The data for cerebral venous $p\text{O}_2$ and AV $p\text{CO}_2$ differences are summarized in Tables 1 and 2.

In control circumstances—that is, with the middle cerebral artery intact—there was clear evidence that hypercapnia produced profound vasodilatation in the cortical vasculature under study. This had the characteristics of luxury perfusion described by Lassen (1966). In normocapnia, in the 10 animals the regional venous $p\text{O}_2$ was found to be 36.5 ± 4.5 mm Hg, while with the induction of hypercapnia it rose to a mean value of 54.8 mm Hg ($\text{SD} \pm 5.0$),

TABLE 1

CV PO_2 LEVELS—HYPERCAPNIA AND NORMOCAPNIA + OCCLUSION OF MIDDLE CEREBRAL ARTERY

Expt. no.	Control CV PO_2 (mm Hg)		Occluded levels (mm Hg)		Release levels (mmHg)	
	N/capnia	H/capnia	N/capnia	H/capnia	N/capnia	H/capnia
5	30	52	20	20	49	47
6	35	58	29	48	54	40
7	33	45	16	20	22	22
8	39	56	25	39	55	52
9	47	63	24	24	72	68
10	37	55	20	26	50	48
11	34	57	22	34	56	44
12	38	50	24	24	48	45
13	35	58	20	32	50	48
14	37	54	22	30	47	45
Mean	36.5	54.8	22.2	29.7	50.3	46.0
SD	± 4.5	± 5.0	± 3.6	± 8.9	± 12.3	± 11.3
$\uparrow$ $P < 0.001$ $\uparrow$ $\uparrow$ $P < 0.01$ $\uparrow$ $\uparrow$ $P < 0.01$ $\uparrow$ $\uparrow$ $P < 0.001$ $\uparrow$ $\uparrow$ $P < 0.001$ $\uparrow$ $\uparrow$ $P < 0.01$ $\uparrow$ $\uparrow$ $P < 0.001$ $\uparrow$ $\uparrow$ $P < 0.001$ $\uparrow$ $\uparrow$ $P < 0.01$ $\uparrow$ $\uparrow$ $P < 0.001$ $\uparrow$ $\uparrow$ $P < 0.001$ $\uparrow$ $\uparrow$ $P < 0.01$ $\uparrow$						

($P < 0.001$). There was no significant change in the systemic arterial pO_2 , which was maintained throughout the experiments at between 95 and 120 mm Hg, the animals breathing air supplemented as necessary by oxygen. Similar evidence of regional vasodilatation was given by the changes in arteriovenous pCO_2 differences, the AV pCO_2 difference for the normocapnic animals being 9.3 mm Hg (SD ± 1.5), while, after the induction of hypercapnia, the AV pCO_2 difference fell to 5.3 mm Hg (SD ± 1.9). These figures are significantly different ($P < 0.001$).

When the middle cerebral artery was occluded, both in the normocapnic and in the hypercapnic animals, regional venous oxygen tension fell. In absolute terms, the level of venous oxygen was lower in occlusion in normocapnic circumstances (22.2 mm Hg, SD ± 3.6) than in hypercapnia (29.7 mm Hg, SD ± 8.9 , $P < 0.01$), although the fall from control circumstances to those of occlusion was very much greater in hypercapnia than in normocapnia ($P < 0.001$). By the same token, in both normocapnia and hypercapnia, the arteriovenous pCO_2 difference rose with occlusion of the

TABLE 2

EFFECT OF HYPERCAPNIA ON AV pCO_2 DIFFERENCE IN BABOON MC CORTEX IN RELATION TO OCCLUSION OF MIDDLE CEREBRAL ARTERY

Expt no.		AV pCO ₂ difference (mm Hg)					
		Control value		During occlusion		On release of occlusion	
		N/capnia	H/capnia	N/capnia	H/capnia	N/capnia	H/capnia
CMR*	2	9	6	19	16	12	40
	3	10	3	19	25	11	38
	4	9	7	21	8	8	14
	5	10	7	18	12	0	5
	6	12	6	21	10	13	15
	7	7	4	11	12	14	50
	8	10	2	7	10	No reading	
	9	7	8	25	30	9	18
	10	10	6	18	20	10	26
	11	9	4	16	16	9	28
	Mean	9.3	5.3	17.5	15.9	9.6	26.0
SD	±1.5	±1.9	±5.1	±7.2	±4.0	±14.5	
		↑ <0.001 ↑		↑ NS ↑		↑ <0.001 ↑	
		↑ <0.001 ↑		↑ <0.05 ↑			
				↑ <0.01 ↑			

*Cerebral metabolic rate.

middle cerebral artery. Once more, the change was greatest in the hypercapnic animals, and here AV $p\text{CO}_2$ difference was not significantly higher in the normocapnic (17.5 mm Hg, $\text{SD} \pm 5.1$) than in the hypercapnic (15.9 mm Hg $\text{SD} \pm 7.2$).

After the release of temporary arterial occlusion, considerable reactive hyperaemia occurs in normocapnic circumstances, which is absent or very much reduced in hypercapnia (Symon, 1969, 1970). The impairment of reactive hyperaemia was evident in the results of gas analysis in the present experiments. Thus, on release of the occlusion, regional venous $p\text{O}_2$ levels in the normocapnic animal showed an enormous increase. During this time, the blood in the venous catheter could be seen to be much brighter red than normal (the red veins of Feindel and Perot, 1965; and Waltz, 1969), and a simple test of the presence of hyperaemia could be made by the assessment of drop-rates, which were observably much higher than normal during this phase. Direct electromagnetic flowmeter recordings from such veins have been made in subsequent experiments (Symon and Dorsch, unpublished observations), and have shown that, in normal circumstances, a 40 to 60% increase in flow may occur during reactive hyperaemia. Regional venous $p\text{O}_2$ in the 10 animals in normocapnia was 50.5 mm Hg ($\text{SD} \pm 12.3$), compared with the control value of 36.5 mm Hg ($\text{SD} \pm 4.5$). These differences are significant at the $P < 0.001$ level. In contrast, with release of occlusion in hypercapnia, although the venous $p\text{O}_2$ rose promptly, the levels reached, 46.0 mm Hg, $\text{SD} \pm 11.3$, were significantly lower than the control levels of 54.8 mm Hg, $\text{SD} \pm 5.0$ ($P < 0.01$). In these circumstances also, and only in these circumstances, the regional venous $p\text{O}_2$ in hypercapnia was significantly lower than in normocapnia ($P < 0.01$). The arteriovenous $p\text{CO}_2$ differences on release of occlusion, in the normocapnic group, showed a prompt return to normal levels (9.6 mm Hg, $\text{SD} \pm 4.0$, compared with the control level, 9.3 mm Hg, ± 1.5). In hypercapnia, however, not only did the arteriovenous $p\text{CO}_2$ differences not return to the very low figures of control under hypercapnia, but actually rose to levels above those during occlusion (mean on release, 26.0 mm Hg, $\text{SD} \pm 14.5$), significantly higher than the levels during occlusion ($P < 0.05$) or the control levels ($P < 0.001$) and also significantly higher than the release levels of AV $p\text{CO}_2$ difference in normocapnia ($P < 0.001$).

DISCUSSION

In control circumstances, with the circulation intact, dilatation of the cortical vasculature by CO_2 raised the regional cerebral venous $p\text{O}_2$ and de-

creased the arteriovenous $p\text{CO}_2$ difference, as one might expect. This in effect constituted a situation similar to the luxury perfusion syndrome of Lassen, in which the regional blood flow exceeded the metabolic requirements of the tissue.

During the ischaemic episode, the differences between the normocapnic and hypercapnic condition were considerably reduced. There was a considerably greater fall in venous $p\text{O}_2$ with occlusion in hypercapnia, although the absolute value of venous $p\text{O}_2$ remained significantly higher in hypercapnia than in normocapnia. During occlusion, the contrast in arteriovenous $p\text{CO}_2$ differences between normocapnia and hypercapnia virtually disappeared, there being no significant difference in these data in the normocapnic and hypercapnic. Furthermore, the narrow arteriovenous $p\text{CO}_2$ difference of the hypercapnic in the control circumstance, contrasted sharply with the establishment of virtually the same arteriovenous difference as the normocapnic during occlusion. The differences in gaseous metabolism between the hypercapnic and normocapnic were therefore very much less during the circumstances of occlusion. It would not be possible, however, to say that in these circumstances there was evidence of an adverse effect of hypercapnia compared with normocapnia, since the venous $p\text{CO}_2$ was over 7 mm Hg higher in the effluent from the hypercapnic zone and the arteriovenous $p\text{CO}_2$ differences were the same. In the generalized vasodilatation of hypercapnia, however, possible admixture of blood from non-ischaemic zones has to be considered. It has already been demonstrated that the regional venous pressure in the ischaemic zone in hypercapnia is considerably higher than in normocapnia, and that there is a significantly higher systemic blood pressure in hypercapnia (Symon, 1970). It is possible that the relatively higher venous oxygen tension in the veins draining the hypercapnic ischaemic zone may be due to admixture of blood from brain not ischaemic but still subject to hypercapnic luxury perfusion. This does not however explain why the arteriovenous $p\text{CO}_2$ differences remain the same in ischaemia and hypercapnia, but an examination of Tables 1 and 2 will show that, even in control circumstances, the numerical differences between hypercapnia and normocapnia are vastly greater in terms of arterial $p\text{O}_2$ than in terms of AV $p\text{CO}_2$ difference. It is likely therefore that the admixture of blood from non-ischaemic brain would be detectable more in the venous $p\text{O}_2$ levels than in AV $p\text{CO}_2$ difference. It seems doubtful that significant protective effect on the ischaemic zones could be claimed for hypercapnia on the basis of these findings. The data presented here differ in some respects therefore from

findings in the cat (Halsey and Clark, 1970), in which induction of hypercapnia soon after middle cerebral arterial occlusion caused a qualitative reduction in oxygen availability in the area of the experimental infarct as judged by chronically implanted polarographic electrodes.

The data from the period immediately after the release of occlusion are of great interest. The changes, both in AV $p\text{CO}_2$ difference and in regional venous $p\text{O}_2$ are entirely compatible with the relative absence of hyperaemia after the release of occlusion in circumstances of hypercapnia. In normocapnia, marked increase in venous $p\text{O}_2$ levels far above control occurred at once when the occlusion was released. In the hypercapnic, there was no great overswing in venous $p\text{O}_2$. The contrast might be explained by an assumption that the degree of ischaemia produced under hypercapnia was appreciably less—in other words, that hypercapnia had protected the ischaemic zone. This explanation, however, is not borne out by the remainder of the data either in occlusion, as has been shown, or at release. Presumably, during occlusion, if the cortex continues to metabolize, there will be an accumulation of metabolites in the ischaemic zone. The reaction of the vasculature on the release of occlusion will be to return this mass of accumulated metabolites to the remainder of the circulation and to restore the metabolic situation within the ischaemic zone to normal. Reactive hyperaemia appears to do this almost immediately in the normocapnic, as judged by the prompt return of the arteriovenous $p\text{CO}_2$ difference to normal levels after the release of the occlusion in normocapnia. In hypercapnia, however, there is a considerable increase in the arteriovenous $p\text{CO}_2$ difference after the release of temporary occlusion, so that the AV $p\text{CO}_2$ difference on release is actually higher than during occlusion. Both these circumstances suggest that the accumulation of metabolites has been not less but more in the ischaemic zone during hypercapnia, and that the reactivity of the circulation in hypercapnia is so impaired that a prompt resolution of this abnormal circumstance is not possible on release of temporary occlusion.

The results are probably best explained in conjunction with those previously reported (Symon, 1970), in which it was shown that, in the ischaemic zone during hypercapnia, arterial perfusion pressure was lower and regional venous pressure higher than in the normocapnic zone. These two findings together suggest a greater degree of circulatory stasis in the ischaemic zone during hypercapnia. This would explain the greater accumulation of products of metabolism in the hypercapnic ischaemic zone. After the release of temporary occlusion, the known reduc-

tion of reactive hyperaemia in hypercapnic circumstances would explain why this larger quantity of accumulated metabolites produced greater acid shift in effluent blood, and a vast increase in the arteriovenous $p\text{CO}_2$ difference, both persisting for some time in the absence of any hyperaemic increase in regional cerebral blood flow. Direct recording by electromagnetic flowmeter in such draining veins has confirmed that hyperaemia after middle cerebral arterial occlusion is in large measure absent in hypercapnia (Symon and Dorsch, unpublished observations).

The implications of these effects of hypercapnia on possible therapy of cerebrovascular disease deserve consideration. There is evidence that in the chronic stroke syndrome the inhalation of 5% CO_2 (Meyer, Sawada, Kitamura, and Toyoda, 1968) or the administration of papaverine over a long term (Meyer *et al.*, 1965; Giraud *et al.*, 1965) produced changes which, assessed by the analysis of arterial and jugular venous blood, suggested an increase in the cerebral metabolic rate for oxygen (CMRO_2), and there is some evidence also that the inhalation of 5% CO_2 increased cerebral glucose consumption. These are presumably indications of increased neuronal metabolism and therefore of a beneficial effect of CO_2 . In more acute circumstances, it has been suggested that inhalation of high concentrations of CO_2 during temporary occlusion of the carotid artery in the surgery of carotid stenosis (White *et al.*, 1967) lessens the degree of ischaemia experienced by the hemisphere again as analysed by arterial and jugular venous $p\text{O}_2$ and $p\text{CO}_2$ levels. It is possible that the circumstances of the chronic stroke syndrome are different from those of acute ischaemia, but quite clear that, within the circumstances of the acute stroke, the analysis of total cerebral venous blood from the jugular bulb will not give relevant information about the effect of regional ischaemic zones. The relative venous hyperoxia and reduced AV $p\text{CO}_2$ difference of the generalized luxury perfusion syndrome induced by CO_2 are so considerable as to obscure less dramatic regional changes, which may indeed be in the opposite direction. The evidence of reduced regional blood flow presented by Lassen and Pálvölgyi (1968, 1969) provides evidence that hypercapnia does not invariably produce increase in blood flow in relation to foci of cerebrovascular disease, and may indeed reduce the blood flow in certain abnormal conditions, particularly in the region of brain tumour.

A further factor in relation to the acute stroke is the undoubted occurrence in these circumstances of oedema with, not infrequently, the production of a mass lesion. As a result, the intracranial pressure may become raised. In these circumstances, further

intracranial vasodilatation induced by the inhalation of CO₂ would be likely to produce a much greater rise in intracranial pressure than in the normal patient, or in a patient some time after a cerebrovascular episode where the phase of reactive oedema had settled and any mass lesion had disappeared. This would be in keeping with the findings of Jennett, McDowall, and Barker (1967) in relation to the inhalation of volatile anaesthetics in patients with mass lesions. It would seem probable therefore that the induction of hypercapnia and probably the use of any other vasodilator therapy should be abjured in the acute phase of cerebrovascular occlusion. It seems unlikely that the circumstances of perfusion within the ischaemic zone will be improved; there is good evidence indeed that impairment of ischaemic zone perfusion will result directly, and the effects of the general vasodilatation induced by CO₂ are likely to have a detrimental effect on intracranial pressure as a whole, with secondary adverse effects upon tissue perfusion.

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