The effects of hyperglycaemia on changes during reperfusion following focal cerebral ischaemia in the cat

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SUMMARY The effects of isosmolar loads of glucose and saline after onset of focal cerebral ischaemia (middle cerebral artery occlusion) were compared in cats. In cats given saline cerebral blood flow (CBF) fell and then rose slightly on the marginal gyrus (infarct penumbra). There was a sustained fall in CBF on the suprasylvian and ectosylvian gyri (infarct core). Reperfusion restored blood flow to preocclusion levels with no overall postischaemic hypoperfusion. Below ischaemic flows of 14 ml/100 g/min brain specific gravity was reduced in a smaller proportion of gyri by contrast with non reperfused cortex, suggesting that in some gyri resolution of cerebral oedema had taken place. GABA uptake was normal in the infarct core, but was reduced within the ischaemic penumbra. In animals given glucose after occlusion, CBF fell on the marginal gyrus during reperfusion. The degree of resolution of cerebral oedema was less than in saline infused cats. GABA uptake showed a pattern of abnormality similar to that seen in saline infused cats, except that uptake values were lower in the infarct core. Pial surface potassium activity remained elevated in the penumbra following reperfusion in glucose infused cats, but returned to normal in saline infused cats. Implications for the management of cerebral ischaemia in man are discussed.

Restoration of the blood supply to ischaemic brain following occlusive stroke does not necessarily imply functional viability. In experimental focal cerebral ischaemia, the distribution of which in the cat we have previously described,^{1,2} blood supply is restored in the postischaemic period to a degree which is related to the duration and severity of the ischaemia.³ Some of the biochemical mechanisms thought to operate during ischaemia and reperfusion have recently been reviewed, and include the appearance of free radicals in association with reduced or restored oxygen supply, and the accumulation of lactic acid.⁴ In man *mild* degrees of hyperglycaemia may be seen after the onset of stroke and this study was designed to examine whether hyperglycaemia of this pattern, by increasing lactic acid concentration in the brain, might worsen the effects of the ischaemia, in particular with respect to CBF,

pial surface potassium activity, cerebral water content and *in vitro* neurotransmitter uptake. Core and penumbral territories were examined separately in the expectation that any adverse effects of hyperglycaemia would be more clearly recognisable in an incompletely affected than in a severely affected area. We define the penumbra as a cortical territory subject to reduction of blood flow and suppression of electrophysiological function but in which extracellular potassium ion homeostasis is largely preserved.

Methods

Anaesthetic, operative and experimental techniques have been described previously.^{1,2} Fasting adult mongrel cats (weight range 2.1-4.2 kg) were anaesthetised with halothane and a mixture of oxygen and nitrous oxide, and anaesthesia was then maintained with a single intravenous dose of alpha chloralose (60 mg/kg) supplemented by inhaled halothane (<0.5%) if mean arterial blood pressure rose above 120 mmHg. Animals were paralysed with gallamine triethiodide and ventilated to maintain PaCO₂ at 28-32 mmHg. Arterial pH, pO₂ and pCO₂, plasma glucose and serum osmolality were measured intermittently.

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The right middle cerebral artery was approached by transorbital dissection and, after baseline measurements had been made, was occluded using a miniature Scoville clip. The left marginal and right marginal, suprasylvian and ectosylvian gyri were exposed: recording electrodes were positioned and the brain covered with a pool of warmed mineral oil.

CBF was measured by hydrogen clearance, flows being analysed by the two minute initial slope method.⁵ Pial surface potassium activity was measured using valinomycin membrane electrodes with an adjacent mechanically coupled reference barrel, the combined unit being suspended from a high impedance differential amplifier. Cortical specific gravity was measured by microgravimetry and used as an index of brain water content. *In vitro* synaptosomal GABA uptake was measured using ³H or ¹⁴C GABA and was expressed as nmol/g wet weight/min.²

After occlusion cats were given either 2N saline (Group 1, n = 10) or 10% D-glucose (Group 2, n = 10) at 20 ml/hr. Group 1 and 2 experiments were carried out for the most part in alternation. The clip was removed after 2 hours and the infusion stopped; after reperfusion for 1 hour ribbons of cortex were excised from relevant gyri for microgravimetry and neurochemistry.

As conventional indices of mean value and dispersal the mean $\pm$ SEM is given in the text and tables; however, since the data was not always normally distributed, statistical analysis was performed using the non parametric two tailed Wilcoxon signed rank test or Mann Whitney U test except where otherwise stated.

Results

Physiological variables (table 1)

Mean values for arterial blood pressure, pH, pO₂ and pCO₂ are shown in table 1. The two groups

were comparable and variables did not change significantly during each experiment.

Plasma glucose and osmolality (table 1)

Plasma glucose remained constant throughout in Group 1; in Group 2 preocclusion values were similar to those in Group 1. There was a rise in glucose during occlusion which was sustained during reperfusion (p = 0.001 compared with preocclusion, Students *t* test; p = 0.01 compared with Group 1). There was no significant change in serum osmolality during any experiment and the two groups were statistically similar.

Cerebral blood flow (table 2)

Preocclusion whole hemisphere CBF was 33.2 ± 1.38 ml/100 g/min in Group 1 and 37.3 ± 1.38 ml/100 g/min in Group 2. Flow on the *marginal gyrus* (MG) fell in Group 1 compared with preocclusion CBF (p = 0.01) and did not change during occlusion, but was restored to preocclusion values during reperfusion. In Group 2 the fall in CBF was less though still significant (p = 0.01) and CBF was restored to preocclusion values at the start of reperfusion, during which there was a slight fall in CBF (p < 0.05, comparing terminal with initial reperfusion CBF). On the *suprasylvian gyrus* (SG) there was a significant fall in CBF in both groups compared with preocclusion values (p < 0.01); CBF remained unchanged during occlusion and returned to preocclusion values during reperfusion. On the *ectosylvian gyrus* (EG) both groups showed similar changes in CBF with a fall during occlusion (p = 0.01 com-

Table 1 Systemic arterial blood pressure and blood gases, plasma glucose and osmolality (mean $\pm$ SEM).

	MABP mmHg	pH	PaCO ₂ mmHg	PaO ₂ mmHg	Glucose mmol/l	Osmolality mosmol/kg
GROUP 1						
Preocclusion	137 $\pm$ 9.1	7.29 $\pm$ 0.03	30.5 $\pm$ 0.98	291 $\pm$ 31	9.7 $\pm$ 1.07	321 $\pm$ 11
Occlusion	131 $\pm$ 6.3	7.30 $\pm$ 0.05	30.0 $\pm$ 1.4	300 $\pm$ 20	9.8 $\pm$ 1.23	323 $\pm$ 14
Reperfusion	122 $\pm$ 6.6	7.29 $\pm$ 0.02	31.0 $\pm$ 1.6	326 $\pm$ 18	10.5 $\pm$ 1.1	331 $\pm$ 22
GROUP 2						
Preocclusion	129 $\pm$ 10.1	7.34 $\pm$ 0.01	30.2 $\pm$ 0.7	267 $\pm$ 19	8.4 $\pm$ 0.6	293 $\pm$ 9
Occlusion	117 $\pm$ 4.7	7.30 $\pm$ 0.03	30.9 $\pm$ 0.65	276 $\pm$ 23	20.8 $\pm$ 2.3	295 $\pm$ 6
Reperfusion	116 $\pm$ 8.5	7.31 $\pm$ 0.02	29.7 $\pm$ 1.2	274 $\pm$ 23	18.9 $\pm$ 1.9	289 $\pm$ 9

Table 2 Regional cerebral blood flow ml/100 g/min (mean $\pm$ SEM)

Group	Marginal gyrus		Suprasylvian gyrus		Ectosylvian gyrus	
	1	2	1	2	1	2
Preocclusion	34.5 $\pm$ 4.1	34.2 $\pm$ 5.5	28.0 $\pm$ 2.0	36.8 $\pm$ 7.8	38.0 $\pm$ 3.5	39.3 $\pm$ 2.9
Occlusion						
2 minute	18.5 $\pm$ 2.0	25.3 $\pm$ 5.0	10.9 $\pm$ 1.3	12.6 $\pm$ 1.5	11.5 $\pm$ 1.2	11.6 $\pm$ 1.8
terminal	20.7 $\pm$ 2.4	27.5 $\pm$ 3.6	8.9 $\pm$ 1.1	10.7 $\pm$ 1.4	8.6 $\pm$ 1.2	11.0 $\pm$ 2.4
mean	20.2 $\pm$ 1.9	27.7 $\pm$ 4.4	9.9 $\pm$ 1.1	11.5 $\pm$ 1.4	9.6 $\pm$ 1.3	10.9 $\pm$ 1.9
Reperfusion						
2 minute	39.6 $\pm$ 7.7	30.2 $\pm$ 4.1	44.4 $\pm$ 14.1	36.6 $\pm$ 9.2	40.1 $\pm$ 4.7	61.6 $\pm$ 15.0
terminal	30.9 $\pm$ 4.8	20.6 $\pm$ 3.8	30.9 $\pm$ 5.1	19.1 $\pm$ 3.2	45.1 $\pm$ 7.1	41.8 $\pm$ 10.5

pared with preocclusion CBF) and restoration to preocclusion values during reperfusion. This resembled the situation previously reported in animals subject to occlusion alone. The differences in mean occlusion CBF between MG-SG and MG-EG were significant in both groups ($p < 0.01$). In Group 1 there was no difference between gyri during reperfusion, but in Group 2 CBF was consistently higher on EG than SG ($p < 0.02$). Whole hemisphere CBF and cerebral vascular resistance were similar in each group during reperfusion.

Electrocorticogram (ECoG)

The ECoG was measured on MG. Similar changes were seen in both groups with a greater than 75% reduction in the amplitude of the time compressed voltage envelope during occlusion and no recovery during reperfusion.

Cortical specific gravity (table 3)

A significant reduction in cortical specific gravity occurred in Group 1 in EG ($p < 0.02$), and in Group 2 in both SG and EG ($p < 0.01$), where there were also significant differences between MG and SG ($p < 0.02$) and between MG and EG ($p < 0.01$). The reduction in specific gravity on homologous gyri was similar in Groups 1 and 2. In previous experiments in which animals were not reperfused we have shown that cortical specific gravity only falls when blood flow falls below 14 ml/100 g/min.² In the present experiments there was no fall in specific gravity when occlusion flows lay above 14 ml/100 g/min. Below 14 ml/100 g/min there was a substantially wider range of values for the fall in specific gravity which was of bimodal distribution and independent of infusate (fig 1a), compared with the normal distribution in non-reperfused cats² (fig 1b). The variance of the reduction in specific gravity was significantly greater in reperfused than in non reperfused cortex with occlusion flows below 14 ml/100 g/min, ($F = 6.51$, $p < 0.01$). In one group of reper-

Fig 1 Distribution of reduction in specific gravity from non reperfused cortex² (a) and reperfused cortex (b). Units are in 0.0020 specific gravity unit bins.

fused gyri with occlusion flows below 14 ml/100 g/min and fall in specific gravity above the mean for non reperfused cortex,² the fall in specific gravity was significantly greater ($p < 0.01$) than that in non-reperfused cortex, whereas in a second group, with fall in specific gravity less than the mean for non reperfused cortex, the fall was significantly less ($p < 0.01$). In this latter group the reduction in specific gravity was greater ($p < 0.05$) in cats infused with glucose (mean reduction in specific gravity 0.0037 ± 0.0004) than in those receiving saline (mean reduction 0.0020 ± 0.0006).

In vitro neurotransmitter uptake (table 3)

GABA uptake on MG was less than that in the

Table 3 (a) Cortical Specific Gravity (mean $\pm$ SEM) and (b) In Vitro Synaptosomal GABA uptake nmol/g wet weight/min (mean $\pm$ SEM)

	Ischaemic	Hemisphere		Control	Hemisphere		Mean
	MG	SG	EG	MG	SG	EG	
3(a) Cortical specific gravity							
Group 1	1.0413	1.0390	1.0375	1.0420	1.0431	1.0436	1.0429
SEM n = 10	0.0009	0.0016	0.0017	0.0017	0.0004	0.0005	0.0012
Group 2	1.0419	1.0372	1.0356	1.0430	1.0429	1.0433	1.0430
SEM n = 10	0.0010	0.0015	0.0021	0.0005	0.0006	0.0007	0.0006
b GABA uptake							
Group 1	3.15	4.10	3.88	3.73	3.98	4.78	4.18
SEM n = 7	0.58	0.6	0.76	0.61	0.47	0.63	0.31
Group 2	3.33	2.95	3.28	3.65	4.20	4.12	4.00
SEM n = 10	0.57	0.27	0.42	0.61	0.44	0.61	0.43

homologous control hemisphere gyrus in Group 1 ($p < 0.02$); and on MG and SG ($p < 0.05$) in Group 2. Within each group there was no difference between gyri. Uptake values were lower in Group 2 than Group 1 in SG ($p < 0.02$) and EG ($p < 0.05$). By comparison with non reperfused cats, in which there is a linear relationship between GABA uptake and ischaemic flow,² GABA uptake was higher in the reperfused infarct core, which includes EG in all experiments and SG in some (fig 2), but not significantly different in MG. There was no relationship between uptake values and CBF during reperfusion, except in penumbral gyri in which flow fell during reperfusion where GABA uptake was reduced ($p < 0.01$, Chi squared test) (fig 3).

Fig 2 Relationship between in vitro synaptosomal GABA uptake and mean CBF during occlusion in the infarct core (SG and EG). Gyrus values for GABA uptake are higher than those predicted from non reperfused cortex,² shown ----. Mean $\pm$ SEM for GABA uptake from the non ischaemic hemisphere and preocclusion whole hemisphere CBF is shown - - - - . Saline infused SG Δ , EG $\square$. Glucose infused SG $\blacktriangle$, EG $\blacksquare$.

Fig 3 Relationship between in vitro GABA uptake and mean CBF during occlusion in the infarct penumbra (MG). Values for non reperfused cortex as in fig 2. Saline infused MG $\circ$. Glucose infused MG $\bullet$.

Pial surface potassium activity (Kp) (table 4)

The changes in Kp seen following occlusion have already been reported.¹ Superimposed transcriptions of Kp electrode outputs (mV) are shown in fig 4a, (occlusion) and fig 4b (reperfusion). In one experiment in Group 2 the rise in Kp was due to a fall in mean arterial pressure during ischaemia. Values of Kp on MG were significantly higher in Group 2 at the end of the occlusion and this difference was maintained throughout reperfusion ($p = 0.02$, excluding data from hypotensive animal).

Discussion

Considerable evidence exists to suggest that hyperglycaemia, by increasing brain lactic acidosis, may be harmful during cerebral ischaemia. Most of this evidence is experimental, with induction of ischaemia after hyperglycaemia has been estab-

Table 4 Pial surface potassium activity mmol/l (mean $\pm$ SEM)

	Preocclusion	Occlusion				Reperfusion
		Initial	Terminal	Rise in Kp		Terminal
				transient	sustained	
Group 1 Marginal n = 6	2.88 ± 0.18	7.05 ± 2.0	4.08 ± 0.52	5	0	3.18 ± 0.34
Suprasylvian n = 7	3.30 ± 0.29	33.90 ± 5.49	20.2 ± 3.75	1	6	3.78 ± 0.25
Group 2 Marginal n = 8	3.00 ± 0.12	7.82 ± 1.31	11.7 ± 3.71	5	3	6.68 ± 1.99
Suprasylvian n = 7	2.90 ± 0.20	15.0 ± 4.79	13.6 ± 3.93	1	6	8.0 ± 3.93

Fig 4 Superimposed transcriptions of Kp electrode outputs (mV) from MG in saline infused and glucose infused cats, (a) during occlusion and (b) during reperfusion. The single experiment in which there was a sustained rise in Kp due to hypotension is shown (*). The difference in Kp at the end of reperfusion was significant ($p < 0.02$) regardless of the inclusion of this experiment in the data.

lished, that is after the brain has been preloaded with glucose.⁴⁻¹⁵ In man, however, when hyperglycaemia is seen in the absence of pre existing diabetes, it is presumed to develop *after* onset of stroke. Diabetics,¹⁶ and individuals with mild hyperglycaemia¹⁷ have a greater risk of cerebral vascular disease than normoglycaemic individuals, and Pulsinelli *et al*¹⁸ confirmed in a comparative study that diabetics did worse clinically after ischaemic stroke. In a recent study in Newcastle 95% patients developing neurological deterioration after subarachnoid hemorrhage were found to have an elevated fasting blood sugar on at least one occasion.¹⁹ This study was designed to investigate whether a pattern of hyperglycaemia resembling that in man might worsen the effects of the ischaemia. Since deterioration may follow reperfusion, and Myers' results were obtained in a reperfusion model¹⁰⁻¹² we investigated the effects of reperfusion following both saline and glucose loading after the onset of ischaemia. In the light of recent observations²⁰ suggesting that blood glucose levels above a value of 100 mg% (5.5 mmol/l) may be detrimental in stroke in man the present study should be regarded as a comparison between the effects of moderate and severe hyperglycaemia. Blood glucose levels during preparation and in the "normoglycaemic" group were mildly elevated presumably as a result of stress, but were comparable with those measured in animals subject to occlusion alone.²¹

Local blood flow

The pattern of blood flow during the ischaemia closely resembled that seen in animals subject to occlusion alone.¹ Patterns of CBF were similar in both groups of animals other than on MG where flow fell during reperfusion in glucose-infused cats. The length and depth of the ischaemia are factors thought to influence the pattern of recovery of flow after focal and global ischaemia. Steen *et al*²² found reperfusion CBF after incomplete ischaemia to be slightly higher than after complete ischaemia and related it to the length of the ischaemia. Ginsberg *et al*²³ found that after longer periods of global complete ischaemia inhomogeneities of flow with zones of severe persistent ischaemia appeared suggesting that full functional recovery was unlikely. In focal cerebral ischaemia Traupe *et al*³ found that early postischaemic hypoperfusion was related to the length of the ischaemia, and even when CBF returned to normal hypoperfusion developed after a further hour of recirculation. Such degrees of hypoperfusion were not seen in this study, though diversion of blood into a vasodilated central ischaemic territory may have accounted for the fall in CBF on MG in glucose infused cats.

Cortical specific gravity

Reduction in cortical specific gravity occurred below flows of 14 ml/100 g/min, that is, in the infarct core but not in the penumbra. This apparent CBF

threshold is lower than that seen in the baboon,²⁴ though comparable with that found previously by ourselves² and by Schuier and Hossmann in the cat.²⁵ Reperfusion had no effect on the threshold for oedema formation, but below the threshold there were two distinct groups of gyri, one with more and one with less water than would have been predicted on the basis of results from animals which had not been reperfused. There are at least two possible explanations for this. First, ischaemic cortex is known to contain more albumin,²⁶ and extravasated protein adds to brain solids, so tending to preserve an apparently normal specific gravity despite water accumulation.²⁷ Alternatively, in certain areas reperfusion may allow preserved or at least only partially damaged water clearance mechanisms to operate, whereas in others greater damage may occur. This may be the case in man where, after ischaemic stroke, neurological deterioration occurring after early improvement is not infrequently due to oedema. In these experiments reduction in specific gravity did not appear to relate to flow during reperfusion, integrated reflow, potassium activity or recovery of neurotransmitter uptake.

GABA uptake

Potential errors in the interpretation of GABA uptake values have been reviewed previously.² In cats subject to ischaemia without reperfusion there is a topographical gradient of loss of GABA uptake which may represent an effect of ischaemia on the synaptic compartment, either through changes in synaptosomal glycolysis, or through damage to the uptake site.² In the present study, on reperfusion (as opposed to the *in vitro* reprovision of substrate) there is recovery of uptake mechanisms within areas which form the infarct core, though values from glucose infused cats were lower than those from saline infused cats. In the penumbra, uptake values did not differ significantly from values found in the marginal gyrus in non reperfused cats,² though lower values were obtained from gyri in which flow had fallen during reperfusion.

Pial surface potassium activity

In saline infused cats Kp tended to recover to baseline values during reperfusion. In glucose infused cats Kp values in the penumbra at the end of occlusion were higher than those seen in saline infused cats. This difference persisted during reperfusion, and may have been related to the fall in CBF seen on MG during reperfusion.

Hyperglycaemia and the evolution of a cerebral infarct

The evidence found in these experiments for an

adverse effect of hyperglycaemia on the evolution of a cerebral infarct may be summarised as follows:

- 1 A fall in CBF during reperfusion of the marginal gyrus in glucose-infused cats.
- 2 In cortex subject to core values of blood flow and with an overall fall in specific gravity less than that occurring in non reperfused cortex, reduction in specific gravity was greater in glucose-infused cats.
- 3 GABA uptake in reperfused core territories was less in glucose-infused than in saline-infused cats.
- 4 Recovery of pial surface potassium activity during reperfusion was less complete in glucose-infused than in saline-infused cats. In some instances the differences between groups, although significant, were not great, and in the light of the findings in man it is possible that a comparison of plasma glucose values in the range of 3–4 mmol/l (54–72 mg%) with those in the range recorded in the saline-infused cats in the present studies (8–10 mmol/l, 144–188 mg%) might provide further evidence of an adverse effect of increasing blood sugar.

Acidosis and the penumbra

It is still unclear whether flow reduction in penumbral areas as defined by ECoG suppression reflects ischaemia, or whether it is due to local diaschisis resulting either from damage to a small pool of functionally critical neurones or from loss of collateral functional input from the infarct core. The present findings from the reperfused cortex suggest greater damage in the penumbra in association with marked hyperglycaemia. This apparent vulnerability of penumbra to an elevated blood sugar level suggests that such zones are ischaemic rather than simply the site of diaschisis. This suggestion is supported by our data from surface pH selective electrodes placed on the marginal gyrus, which indicate that acidosis is an early change in progressive ischaemia.²⁸

Conclusion

In conclusion, the present results suggest that changes both in the core and the penumbra of an ischaemic territory may be influenced adversely by marked hyperglycaemia, to a degree which can affect recovery during reperfusion: this is most probably due to increased acidosis. In the context of conditions associated in man with areas of mild to moderate focal ischaemia such as occlusive stroke or vasospasm following aneurysmal subarachnoid haemorrhage, our findings suggest that the effects of a given degree of mild ischaemia may be amplified by hyperglycaemia, and that the relationship of hyperglycaemia with the severity of stroke may represent a cause as well as an effect. A metabolic vicious circle may thus develop in which the hyperglycaemic component of the stress response to

stroke serves in turn to increase the extents both of swelling and of definitive neuronal loss. The implication that restriction of glucose availability might improve the outcome from ischaemic stroke is under investigation; recent findings in this laboratory suggest partial protection of mitochondrial respiration in cerebral ischaemia by induction of mild hypoglycaemia (3–4 mmol/l).²⁹

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References

- Strong AJ, Venables GS, Gibson G. The cortical ischaemic penumbra associated with occlusion of the middle cerebral artery in the cat. 1: Topography of changes in blood flow, potassium ion activity and EEG. *J Cereb Blood Flow Metabol* 1983;3:86–96.
- Strong AJ, Tomlinson BE, Venables GS, Gibson G, Hardy JA. The cortical ischaemic penumbra associated with occlusion of the middle cerebral artery in the cat. 2: Studies of histopathology, water content and in vitro neurotransmitter uptake. *J Cereb Blood Flow Metabol* 1983;3:97–108.
- Traupe H, Kruse E, Heiss WD. Reperfusion of focal ischaemia of varying duration: post ischaemic hyper and hypo perfusion. *Stroke* 1982;13:615–22.
- Siesjö BK. Cerebral circulation and metabolism. *J Neurosurg* 1984;60:883–908.
- Symon L, Pasztor E, Branston NM. The distribution and density of reduced cerebral blood flow following acute middle cerebral artery occlusion: An experimental study by the technique of hydrogen clearance. *Stroke* 1974;5:355–64.
- Rehncrona S, Rosen I, Siesjö BK. Excessive cellular acidosis: an important mechanism of neuronal damage in the brain. *Acta Physiol Scand* 1980;110:435–7.
- Eklöf B, Siesjö BK. The effect of bilateral carotid artery ligation upon acid base parameters and substrate levels in the rat brain. *Acta Physiol Scand* 1972;86:528–38.
- Salford LG, Siesjö BK. The influence of arterial hypoxia and unilateral carotid artery occlusion upon regional blood flow and metabolism in the rat brain. *Acta Physiol Scand* 1974;92:130–41.
- Ljunggren B, Norberg K, Siesjö BK. Influence of tissue acidosis upon restitution of brain energy metabolism following total ischaemia. *Brain Res* 1974;77:173–86.
- Myers RE. Anoxic brain pathology and blood glucose. *Neurology (Minneapolis)* 1976;26:345. (Abstr)
- Myers RE, Yamaguchi S. Nervous system effects of cardiac arrest in monkeys. *Arch Neurol* 1977;34:65–74.
- Myers RE. Lactic acid accumulation as a cause of brain edema and cerebral necrosis resulting from oxygen deprivation. In: Korobkin R, Guilleminault C, eds. *Advances in Perinatal Neurology*. New York: Spectrum Publications, 1979;85–114.
- Hansen AJ. The extracellular potassium concentration in brain cortex following ischaemia in hypo and hyperglycaemic rats. *Acta Physiol Scand* 1978;102:324–9.
- Gjedde A, Siemkowicz E. Effect of glucose pretreatment on cerebral metabolic recovery after ischaemia. *Ann Neurol* 1978;4:166–7.
- Siemkowicz E, Hansen AJ. Brain extracellular ion composition and EEG activity following 10 minutes ischaemia in normo and hyperglycaemic rats. *Stroke* 1981;12:236–40.
- Palumbo PJ, Elveback LR, Whisnant JP. Neurological complications of diabetes mellitus; transient ischaemic attacks, stroke and peripheral neuropathy. In: Schoenberg BS, ed. *Neurological Epidemiology*. New York: Raven Press, 1978;593–9.
- Riddle MC, Hart J. Hyperglycaemia, recognised and unrecognised as a risk factor for stroke and transient ischaemic attacks. *Stroke* 1982;13:356–9.
- Pulsinelli W, Waldman S, Sigsbee B, Rawlinson D, Plum F. Experimental hyperglycaemia and diabetes mellitus worsen stroke outcome. In: Betz E, Grote J, Heuser D, eds. *Pathophysiology and Pharmacology of Cerebrovascular Disease*. Baden Baden: Gerhard Witzstroch, 1980;196–9.
- Sastry-Kolluri KVR. *Haematological and biochemical changes in aneurysmal subarachnoid haemorrhage*. MSc Thesis. University of Newcastle, 1982.
- Mohr JP. Approaches to pathophysiology of stroke through NINCDS data bank. In: Plum F, ed. *14th Princeton Stroke Conference*. New York: Raven Press, 1984. (In Press)
- Venables GS. Experimental focal cerebral ischaemia in the cat. DM. Thesis. University of Oxford, 1983.
- Steen PA, Michenfelder JD, Milde JH. Incomplete versus complete cerebral ischaemia. Improved outcome with a minimal blood flow. *Ann Neurol* 1979;6:389–98.
- Ginsberg MD, Budd WW, Welsh FA. Diffuse cerebral ischaemia in the cat. I Local blood flow during severe ischemia and recirculation. *Ann Neurol* 1978;3:482–92.
- Symon L, Branston NM, Chikovani O. Ischaemic brain edema following middle cerebral artery occlusion in baboons: Relationship between regional cerebral water content and blood flow at 1–2 hours. *Stroke* 1979;10:184–91.
- Schuijer FJ, Hossmann KA. Experimental brain infarcts in cats. II Ischaemic brain edema. *Stroke* 1980;11:593–601.
- Bowen DM, Goodhardt MJ, Strong AJ, et al. Biochemical indices of brain structure, function and 'hypoxia' in cortex from baboons with middle cerebral artery occlusion. *Brain Res* 1976;117:503–7.
- Marmarou A, Tanaka K, Shulman K. An improved gravimetric measure of cerebral oedema. *J Neurosurg* 1982;56:246–53.
- Gibson G, Miller SA, Venables GS, Strong AJ. Evidence of acidosis in the ischaemic penumbra. *J Cereb Blood Flow Metabol* 1983;Suppl 1:S401–S402.
- Strong AJ, Miller SA, West IC. Protection of respiration of a crude mitochondrial fraction in cerebral ischaemia by control of blood glucose. *J Neurol Neurosurg Psychiatry* (In Press).