Effects of cerebral oedema and arterial hypotension on cerebral blood flow in an animal model of hepatic failure

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SUMMARY The effects of arterial hypotension and a raised intracranial pressure on cerebral blood flow (CBF) have been investigated in an animal model of hepatic failure. Arterial hypotension was associated with a fall in CBF in the animals with liver failure but not in the controls. Significant differences in mean CBF between the two groups of animals could be demonstrated when the systolic blood pressure was in the 30-60, 60-90, and 90-120 mmHg range, but not in the 120-150 mmHg range. A raised intracranial pressure also resulted in a fall in CBF in the animals with liver failure, and a significant difference could be demonstrated between the two groups when the intracranial pressure was in the 20-40 mmHg range but not in the 0-20 mmHg range. Furthermore, in the animals with liver failure the cerebral metabolic rate for oxygen (CMRO₂) fell as the CBF fell, there being a highly significant correlation between these two parameters. In the controls no such relation existed. Treatment with neither charcoal haemoperfusion nor high dose corticosteroids affected the fall in cerebral blood flow that occurred during arterial hypotension in the animals with liver failure. Corticosteroids, however, did reduce the fall in cerebral blood flow associated with a high intracranial pressure. These results suggest a disruption of the cerebral circulatory responses in hepatic failure. They also raise the possibility that CMRO₂ and cerebral blood flow may be maintained at normal levels in hepatic encephalopathy if cerebral oedema and arterial hypotension can be prevented.

In healthy subjects cerebral autoregulation can maintain cerebral blood flow and cerebral metabolic rate constant over a wide range of blood pressure (Harper, 1965), but the competence of such autoregulation in patients with hepatic encephalopathy is uncertain. In both fulminant hepatic failure and chronic liver disease hypotension may occur spontaneously or after precipitating events, such as haemorrhage (Ward *et al.*, 1977). Thus, in a recent study in fulminant hepatic failure (Trewby and Williams, 1977), we found that hypotension occurred in 88% of patients during their illness and 16% of their total time in grade IV coma (Trey and Davidson, 1970) was passed with a systolic blood pressure of less than 80 mmHg. Furthermore, cerebral oedema has been described in 38% of such cases examined at necropsy (Gazzard

et al., 1975), and the combination of a raised intracranial pressure with arterial hypotension would certainly be expected to reduce both cerebral blood flow (CBF) and cerebral oxygen delivery and result in a further deterioration in encephalopathy. In this study, we have investigated, in an animal model of hepatic failure, the effects of a raised intracranial pressure as well as a low systolic blood pressure on both CBF and cerebral metabolic rate for oxygen (CMRO₂). The effects of high dose corticosteroids given to prevent cerebral oedema, and charcoal haemoperfusion (Gazzard *et al.*, 1974) used as a method of artificial liver support, on these cerebral circulatory responses have also been investigated.

Methods

The experiments were performed on 18 6-week-old Yorkshire Large White pigs (18-20 kg), in 13 of whom liver failure was induced. The remaining five served as controls. Both groups of animals were

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anaesthetised with intravenous thiopentone (12 mg/kg), and after intubation were placed on a volume cycled ventilator and maintained on halothane, nitrous oxide, and oxygen. Intravenous and intra-arterial lines were established using the common femoral vessels. Antibiotics (streptomycin, 50 mg/kg; penicillin G sodium, 30 mg/kg; and lincomycin, 30 mg/kg) were given intravenously during the operation to prevent anaerobic septicaemia. In the test animals total devascularisation of the liver was carried out according to the technique first described by Rappaport *et al.* (1953) and developed by Opolon *et al.* (1971). The triangular ligaments of the liver, the hepatic arteries, and the common bile duct were divided, skeletonising the portal vein and the supra- and infra-hepatic portions of the inferior vena cava. A side-to-side portocaval shunt was then carried out, and the portion of the portal vein between the anastomosis and the liver was then doubly ligated and divided. In the control animals a laparotomy was performed and the hepatic artery and portal vein dissected but neither hepatic artery ligation nor portocaval shunt was carried out. During the operation the systolic blood pressure was maintained above 80 mmHg by volume expansion where necessary.

In both groups of animals an intracranial (Gaeltec) pressure transducer was inserted into the subdural space through a burr hole over the parietal area. Finally, two catheters were introduced, one through a branch of the external jugular vein and the other through a branch of the external carotid artery, and their tips advanced so as to lie just within the internal carotid artery and internal jugular vein. The position of these catheters was confirmed by injecting methylene blue into the carotid catheter, when, if correctly placed, only the most lateral part of the eye turned blue and dye could be aspirated from the internal jugular catheter.

After the operation the animals were allowed to recover consciousness and breathe spontaneously. Subsequently, as signs of liver failure became apparent, inhalation of anaesthesia (nitrous oxide), and respiratory support with the ventilator were used to maintain the paO_2 between 20 and 40 kPa (mean 27.6 ± 1 SEM 1 kPa in the controls and 37.2 ± 1 SEM 6 kPa in the test animals) and the paCO_2 between 4.5 and 6.0 kPa (mean 5.5 ± 1 SEM 0.7 kPa in the controls and 4.5 ± 0.7 kPa in the test animals). All animals received infusions of 10% dextrose (500 ml/6 h). Plasma glucose concentrations were measured using Dextrostix at four hourly intervals, and the levels were maintained at higher than 5.5 mmol. If the animals became very restless, they were sedated with 25 mg doses of thiopentone. A five lead electroencephalogram was

recorded at 30 minute intervals.

Biochemical evidence of liver failure in the test animals included the finding of a rise in plasma bilirubin and aspartate transaminase and a progressive slowing in the dominant frequency of the electroencephalogram. In all animals in the liver failure group a significant increase in blood ammonia had occurred within two hours of laparotomy (Hanid *et al.*, 1978), and post-mortem histological examinations of the liver showed the presence of massive necrosis in the test animals but not in the controls.

In both groups of animals systolic blood pressure and intracranial pressure were monitored continuously. Systolic rather than mean blood pressure was chosen as the marker of arterial blood pressure, since, in the animals, as in man, this correlated better with the clinical state and with the EEG appearances.

Animals were killed at 12 hours after hepatic artery ligation, or when the electroencephalogram had been isoelectric for 30 minutes, whichever was the sooner.

TREATMENT SCHEDULES

In six of the 13 animals with liver failure, charcoal haemoperfusion was carried out starting four hours after hepatic artery ligation. In these animals a Scribner arteriovenous shunt was inserted between the femoral artery and femoral vein and whole blood was perfused through a column containing 100 g activated charcoal (Becton Dickinson Ltd), at a flow rate of 100-200 ml/min, using a Watson-Marlow roller pump and standard dialysis lines, for a period of four hours. The animals were heparinised throughout the procedure to maintain a Lee-White whole blood clotting time of 10-20 minutes. Another five of the pigs were given methylprednisolone, the regimen consisting of a loading dose of 2 g followed by 500 mg every two hours starting four hours after hepatic artery ligation. The remaining two pigs with liver failure received no specific treatment.

MEASUREMENT OF CEREBRAL BLOOD FLOW AND CMRO₂

In the 13 pigs with liver failure, cerebral blood flow was measured at hourly intervals starting two hours after hepatic artery ligation, at a time when they had received neither charcoal haemoperfusion nor corticosteroids. In five of these animals, flow measurements were obtained when the systolic blood pressure was less than 90 mmHg. In four of these hypotension had occurred spontaneously, in one it was induced by haemorrhage. Measurements of cerebral blood flow were continued in those ani-

imals treated with charcoal haemoperfusion or corticosteroids. Of these 11 animals, nine developed systolic blood pressures of less than 90 mmHg, seven spontaneously and two after haemorrhage. Hourly measurements of cerebral blood flow were also made in the five control animals, four of whom became hypotensive, two spontaneously, and two after haemorrhage. Standard techniques were used for measuring cerebral blood flow (Hoedt-Rasmussen and Veall, 1971). 0.5 mCi of ^{133}Xe were injected into the internal carotid artery and the clearance from the brain monitored with a 3-in collimator, ratemeter, and recorder. The half life of ^{133}Xe in whole brain ($T_{\frac{1}{2}}$) was calculated from the two minute disappearance curve (Hoedt-Rasmussen and Veall, 1971), and the blood/whole brain xenon partition coefficient (λ) was corrected for haematocrit and assumed to have the same value as reported for human brain by Veall and Mallett (1965). Cerebral blood flow was calculated from the equation:

$$\text{CBF (ml/100 g/min)} = 100 \times \lambda t \times 0.693/T_{\frac{1}{2}}$$

The CMRO_2 was determined in four of the control animals and in seven of the animals with liver failure from the product of CBF and the cerebral arteriovenous oxygen content difference. The latter was derived from the arterial and cerebral venous blood gas concentrations (measured using Radiometer electrodes), and the percentage haemoglobin saturation which was derived from the pig oxyhaemoglobin dissociation curves (Bartels and Harms, 1959).

Results

The progressive rise in intracranial pressure that occurred with the development of liver failure in this pig model has been previously described by Hanid *et al.* (1976, 1978). In the present group of animals the mean intracranial pressure was significantly greater within two hours of laparotomy than in the control animals, and thereafter it continued to rise until the animals' death. This rise in intracranial pressure was not significantly affected by charcoal haemoperfusion or corticosteroids when started four hours after hepatic artery ligation. On opening the calvaria at necropsy, all animals with liver failure had obviously swollen and oedematous brains with flattened cortical gyri, but no evidence of intracranial haemorrhage. In the control animals there was no post-mortem evidence of cerebral oedema, and in only one of the five controls did the intracranial pressure rise above 40 mmHg and this was shortly before death, the animal having sustained a subdural haematoma.

Although in the individual animals with liver failure there was no correlation between arterial

blood pressure and cerebral blood flow, taking the group as a whole a highly significant correlation could be demonstrated between these two parameters ($r = 0.52$, $P < 0.001$). In the control animals no such relation could be demonstrated ($r = 0.11$, P NS). Because the difference between the two groups could be due to the higher intracranial pressure in the animals with liver failure, a separate analysis was carried out of the relation between blood pressure and cerebral blood flow in those animals with liver failure whose intracranial pressure was less than 25 mmHg. A significant correlation was still found between the two parameters ($r = 0.48$, $P < 0.05$).

To facilitate further statistical comparison between the animals with liver failure and the controls the values for cerebral blood flow were divided according to whether the systolic blood pressure lay between 30-60, 60-90, 90-120, or 120-150 mmHg (Fig. 1). In the three lower blood pressure ranges (30-60, 60-90, and 90-120 mmHg) the mean cerebral

Fig. 1 Cerebral blood flow (mean $\pm$ 1 SEM) in different blood pressure ranges in the control animals and the animals with liver failure. *Significant difference in mean cerebral blood flow compared to controls.

blood flow was significantly lower in the animals with liver failure than in the controls ($P < 0.02$, $P < 0.01$, $P < 0.005$ respectively for each difference, Fig. 1). In the 120-150 mmHg range there was no difference in mean cerebral blood flow between the two groups of animals. In the animals with liver failure, but not in the controls, values for mean cerebral blood flow were significantly lower in the

90-120 mmHg blood pressure range than in the 120-150 mmHg range ($P < 0.01$, Fig. 1) and also significantly lower in the 60-90 mmHg range than in the 90-120 mmHg range ($P < 0.05$). Raised intracranial pressure could not account for these differences in cerebral blood flow for there was no significant difference in mean intracranial pressure in the four blood pressure ranges.

When the effects of a raised intracranial pressure on cerebral blood flow were analysed a significant correlation was found between these two parameters in the animals with liver failure taken as a whole ($r = -0.32$, $P < 0.01$), those animals with the highest intracranial pressure having the lowest cerebral blood flow. A similar but statistically less significant correlation could also be demonstrated in the control animals ($r = -0.35$, $P < 0.05$). When only those observations associated with a systolic blood pressure of more than 90 mmHg were considered, a significant correlation was still found between intracranial pressure and cerebral blood flow in the animals with liver failure ($r = -0.44$, $P < 0.01$), but no such relation was found in the control animals ($r = -0.22$, P NS). When the values for cerebral blood flow were divided into groups according to the level of intracranial pressure, the mean cerebral blood flow was found to be significantly lower in the animals with liver failure than in the controls when the intracranial pressure was in the 20-40 mmHg range, but in the 0-20 mmHg range there was no difference between the two groups (Fig. 2).

When the combined influence of arterial hypotension and a raised intracranial pressure on cerebral blood flow was analysed using three variable linear regressions, a highly significant correlation was found between cerebral blood flow and the combination of blood pressure and intracranial pressure in the animals with liver failure (line of best fit $CBF = 0.143 \times BP - 0.214 \times ICP + 21.2$, $r = 0.67$, $P < 0.001$). No such correlation could be demonstrated in the control animals (line of best fit: $CBF = 0.22 \times BP - 0.19 \times ICP + 29.3$, $r = 0.34$, P NS), and in neither group of animals was any relation found between blood pressure and intracranial pressure.

EFFECT OF CHARCOAL HAEMOPERFUSION AND CORTICOSTEROIDS

Neither charcoal haemoperfusion nor corticosteroids had any effect on the reduction in cerebral blood flow that occurred at low blood pressures, the mean cerebral blood flow in the blood pressure range 120-150 mmHg, 90-120 mmHg, and 60-90 mmHg not differing significantly from those found in the animals with liver failure before treatment (Table 1).

Fig. 2 Cerebral blood flow (mean $\pm$ 1 SEM) in different intracranial pressure ranges in the control animals with liver failure. *Significant difference in mean cerebral blood flow compared to controls. All observations taken when systolic BP $>$ 90 mmHg.

Table 1 Mean cerebral blood flow (ml/min/100 g) $\pm$ 1 SEM in different blood pressure ranges in controls and in treated and untreated animals with liver failure

Blood pressure (mmHg)	120-150	90-120	60-90	30-60
Controls	41.5 $\pm$ 2.8	40.4 $\pm$ 2.5	35.1 $\pm$ 5.8	37.6 $\pm$ 7.1
Liver failure before treatment	34.8 $\pm$ 7.1	28.7 $\pm$ 2.7	19.5 $\pm$ 1.1	13.8*
Charcoal haemoperfusion	75.6*	31.3 $\pm$ 3.3	25.7 $\pm$ 2.1	23.3 $\pm$ 2.6
Corticosteroids	35.4 $\pm$ 2.6	30.4 $\pm$ 2.0	24.9 $\pm$ 2.2	—

*Mean of two observations only.

When divided according to treatment regime, significant correlations were found between systolic blood pressure and cerebral blood flow in the animals treated by charcoal haemoperfusion ($r = 0.58$, $P < 0.001$), and in the animals treated with corticosteroids ($r = 0.72$, $P < 0.001$) and also in the animals before the start of either charcoal haemoperfusion or corticosteroids ($r = 0.60$, $P < 0.01$).

Similarly, charcoal haemoperfusion had no effect on the reduction in cerebral blood flow that occurred at high intracranial pressures, the mean cerebral blood flow in the 0-20, 20-40, and 40-60 mmHg range not differing significantly from those found in the

animals before treatment.

In those animals treated with corticosteroids, however, the mean cerebral blood flow was not so reduced in the 40-60 mmHg intracranial pressure range as in the untreated animals or the animals treated with charcoal haemoperfusion (Table 2).

Table 2 Mean cerebral blood flow (ml/100 g/min) $\pm$ 1 SEM separated into three groups according to intracranial pressure in control animals and in treated and untreated animals with liver failure

Intracranial pressure (mmHg)	0-20	20-40	40-60
Controls	40.4 $\pm$ 1.5	41.1 $\pm$ 3.4	14*
Liver failure before treatment	36.4 $\pm$ 3.0	25.2 $\pm$ 3.4	20.3 $\pm$ 1.1
Charcoal haemoperfusion	27.2 $\pm$ 1.7†	23.7 $\pm$ 2.9	22.4 $\pm$ 1.2
Corticosteroids	—	31.5 $\pm$ 2.9	29.9 $\pm$ 1.3†

*Mean of two observations only; †cerebral blood flow significantly higher ($P < 0.001$) than in the untreated animals with liver failure; ‡blood pressure significantly lower in this group than in control group so cerebral blood flow cannot be compared.

A significant correlation was also found using three variable linear regressions between cerebral blood flow and the combination of blood pressure and intracranial pressure in animals before treatment ($CBF = 0.23 \times BP - 0.37 \times ICP + 9.4$, $r = 0.80$,

$P < 0.001$), in animals after treatment with charcoal haemoperfusion ($CBF = 0.086 \times BP - 0.15 \times ICP + 16.5$, $r = 0.53$, $P < 0.01$) and in animals after treatment with corticosteroids ($CBF = 0.14 \times BP - 0.087 \times ICP + 16.6$, $r = 0.66$, $P < 0.001$).

RELATION BETWEEN CEREBRAL BLOOD FLOW AND $CMRO_2$

Analysis of the relation between cerebral blood flow and $CMRO_2$ showed a significant correlation in the animals with liver failure (Fig. 3). No such correlation was seen in the control animals, in whom the cerebral A-V O_2 content difference increased as the cerebral blood flow fell, so tending to maintain the $CMRO_2$ constant despite low cerebral blood flows (Fig. 3). At low cerebral blood flows (less than 37.5 ml/min/100 g) the mean $CMRO_2$ was significantly lower in the animals with liver failure than in controls with values of 1.03 ± 0.10 and 1.82 ± 0.20 ml/min/100 g respectively (mean $\pm$ 1 SEM, $P < 0.01$). When the cerebral blood flow was greater than 37.5 ml/min/100 g, however, there was no significant difference between the two groups, with values respectively of 1.60 ± 0.25 and 1.33 ± 0.15 ml/min/100 g (mean $\pm$ 1 SEM, P NS). Numbers were not sufficient to allow separate analysis of the

Fig. 3 Showing a significant correlation between cerebral blood flow and $CMRO_2$ in animals with liver failure ($r = 0.58$, $P < 0.01$) but not in controls ($r = -0.062$, P NS) X: untreated animals, O: measurement made during treatment with charcoal haemoperfusion, ●: measurement made during treatment with corticosteroids.

effect of the high dose corticosteroids or charcoal haemoperfusion on CMRO₂ in the animals with liver failure.

Discussion

These studies suggest that, in this animal model of liver failure, there is a marked derangement of cerebral autoregulation in response to both a low systolic blood pressure and a rise in intracranial pressure. Although the use of the two minute disappearance curve of ¹³³Xe for measuring cerebral blood flow may not give as accurate a measure of absolute flow as analysis of the 10 or 15 minute curves (Van Duyl *et al.*, 1976), it is a method which has been extensively used in man and other primates (Hoedt-Rasmussen and Veall, 1971), and was chosen in this series of experiments because of its usefulness for assessing rapidly changing flow in an unstable clinical situation. Inaccuracies due to extracerebral contamination with ¹³³Xe are unlikely to be significant because injection of methylene blue into the arterial cannula resulted in virtually no extracerebral staining. The advantage of this method over alternative methods for measuring rapidly changing cerebral blood flow, such as the use of electromagnetic flowmeters, is that an extensive dissection of the carotid artery is not necessary, so the accompanying vasomotor nerve fibres, some of which may be important in regulating cerebral blood flow, remain undisturbed.

In the control animals, despite heavy sedation and a recent general anaesthetic, cerebral blood flow was maintained when hypotension occurred. The reduction in cerebral blood flow that occurred in the hypotensive animals with liver failure could not be accounted for on the basis of hypoxaemia or hypercapnia, for the paCO₂ was maintained within narrow limits and the oxygen tension was greater than 100 mmHg. Nor could it be explained on the basis of a higher intracranial pressure in the hypotensive than in the normotensive animals. Likewise the significant fall in cerebral blood flow that occurred when intracranial pressure rose to high levels in the animals with liver failure could not be accounted for on the basis of arterial hypotension.

Combined analysis of the effect of intracranial pressure and blood pressure on cerebral blood flow showed a significant correlation between these parameters in the animals with liver failure, but not in the controls. A further distinction between the two groups of animals was the failure of cerebral oxygen extraction to increase at low cerebral blood flows in the animals with liver failure, this resulting in a decrease in CMRO₂. One explanation

for this would be the opening up of intracerebral arteriovenous shunts (Rowed *et al.*, 1972). Such shunts have been described in the systemic (Tyor and Sieker, 1959) and pulmonary circulation (Robin *et al.*, 1975) in both acute and chronic liver failure. At low flow rates the shunting of blood through such low resistance vessels in the brain would result in tissue hypoxia and a diminished CMRO₂ despite a high arterial and cerebral venous oxygen content. An alternative explanation is that cellular respiration in the animals with liver failure might be more sensitive to the build-up of metabolites that would accompany a low cerebral blood flow. The subsequent reduction in intracellular pH might be sufficient to lower the CMRO₂, especially if combined with a pre-existing intracellular acidosis. The latter is well described in patients with liver disease even in the presence of an extracellular alkalosis (Bittar *et al.*, 1962).

In this series of experiments rather low values for cerebral blood flow and CMRO₂ were found, even in the normotensive controls. However, similar low values have been reported by Van Duyl *et al.* (1976) using ¹³³Xe to measure cerebral blood flow in the pig. In our calculation of CMRO₂, however, an extracerebral component to the oxygen content of the blood in the internal jugular vein could result in a spuriously low value for CMRO₂ being obtained. Also the derivation of blood oxygen content from the oxygen tension may result in inaccuracies in the calculated CMRO₂ if the oxy-haemoglobin dissociation curve were shifted in hepatic failure. However, previous workers have shown that, if a shift does occur, it is a shift to the right (Fritts, 1963), which would have the effect of increasing rather than decreasing the calculated CMRO₂.

Another study carried out in a goat model of hepatic failure on cerebral circulatory responses has shown a marked reduction in the normal cerebral vasodilatation that occurs in response to hypoxaemia (Stanley and Cherniack, 1976) or hypercapnia (Stanley *et al.*, 1975). When taken together with our findings, these studies suggest a failure of many aspects of cerebral homeostatic mechanisms in hepatic failure. Underlying these changes may be the accumulation of toxic intermediates influencing both the neuronal and humoral mechanisms which are thought to be involved in cerebral autoregulation (Harper *et al.*, 1972). The lack of improvement with charcoal haemoperfusion does not exclude a toxic aetiology, for irreversible brain damage might have occurred before it is started. Alternatively, the putative compounds may be ineffectually removed by activated charcoal.

In the present study, corticosteroids given four hours after hepatic artery ligation had no effect

on the low cerebral blood flow that occurred in the animals with liver failure when hypotensive. They did, however, lessen the fall in cerebral blood flow that occurred at high levels of intracranial pressure. The mechanism and clinical significance of this is not clear, for in man high dose corticosteroids given at the onset of coma have affected neither the incidence of cerebral oedema nor the overall survival (Gazzard *et al.*, 1975), and this would be consistent with the observations of Hanid *et al.* (1976) that, in this animal model, high doses of steroids need to be given immediately after hepatic artery ligation if a raised intracranial pressure is to be avoided. The lack of an effective method of treating or preventing cerebral oedema in patients with hepatic failure makes it all the more important to prevent episodes of hypotension if secondary hypoxic brain damage is to be avoided. Of particular importance in this respect are the prevention of gastrointestinal bleeding, the avoidance of hypovolaemia, and the prompt treatment of cardiac arrhythmias, blood gas and electrolyte disturbances, all of which, by resulting in arterial hypotension, may reduce both cerebral blood flow and CMRO₂.

Martin Clarke and Pyra Majumdar provided assistance with the isotope studies. We are also grateful to the Medical Research Council and Smith & Nephew Research Ltd for their support, and to Linda Rimmer for editorial assistance. R. L. Mackenzie was supported by a Roscoe Reid Graham Travelling Fellowship of the University of Toronto.

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