Effect of liver failure on the cerebral circulatory and metabolic responses to hypoxia in the goat

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Summary
1. Six unanaesthetized goats were used to evaluate the effect of liver failure on the hypoxic responsiveness of cerebral blood flow. The animals breathed air and several different hypoxic gas mixtures enriched with sufficient CO₂ to maintain an isocapnic state. The cerebral metabolic rate for O₂ (CMRO₂) was also measured in four of these goats.

2. In baseline studies there was a linear relationship between cerebral blood flow and arterial O₂ saturation (Sa,0₂) measured at different levels of isocapnic hypoxia. The slopes of the cerebral blood flow/Sa,0₂ response lines were used to quantify the response of cerebral blood flow to hypoxia. In the healthy goat, CMRO₂ was not depressed by hypoxia until the O₂ tension (Po₂) in arterial and cerebral venous blood had fallen below critical threshold values of approximately 3.2 and 2.2 kPa (24 and 16 mmHg) respectively.

3. Liver failure was accompanied by a fall in cerebral blood flow and CMRO₂. There was also a depression in the response of cerebral blood flow to hypoxia and a disproportionate reduction of cerebral O₂ delivery in hypoxia. CMRO₂ was further reduced at arterial and cerebral venous Po₂ values, which were much higher than the critical threshold values for producing hypoxic CMRO₂ depression in health.

4. It is concluded that the brain becomes more vulnerable to the adverse effects of hypoxia during liver failure. This may be of practical importance in the management of patients with arterial hypoxaemia or other complications (e.g. anaemia or shock), which may reduce cerebral oxygen delivery.

Key words: anoxaemia, anoxia, brain, liver disease.

Introduction

Normally cerebral blood flow rises in hypercapnia and hypoxia, whereas the cerebral metabolic rate for oxygen remains constant over a wide range of arterial gas tensions (Kety & Schmidt, 1948). In patients with liver cirrhosis there is a reduction in CBF and CMRO₂, which is related to the severity of hepatic encephalopathy (Fazekas, Ticktin, Ehrentraut & Alman, 1956; Posner & Plum, 1960; James, Nashat, Sampson, Williams & Garassini, 1969b). The response of CBF to an increase in arterial CO₂ tension is also depressed in liver failure, and a further reduction in CMRO₂ occurs during hypercapnia (Stanley, Salisbury, McHenry & Cherniack, 1975). Since arterial hypoxaemia is a frequent complication of liver disease (Stanley, Ackrill & Wood, 1972), the present study was undertaken to determine whether there might also be an alteration of CBF responsiveness and the stability of CMRO₂ in hypoxia during liver failure.

(1) Abbreviations: CBF, cerebral blood flow; CMRO₂, cerebral metabolic rate for oxygen; Sa,0₂, arterial oxygen saturation.
Methods

Animals

The experiments utilized six goats (A–F) and were performed in conjunction with a previously reported study of the effects of liver failure on the CO₂ responsiveness of the cerebral circulation and metabolism (Stanley et al., 1975). We chose to study the goat because each internal maxillary artery, a branch of the external carotid artery, provides the total blood flow to each cerebral hemisphere via the rete mirabile (Andersson & Jewell, 1956) and this favourable anatomical arrangement allows the easy measurement of CBF at frequent intervals with a technique described by Edelman, Epstein, Cherniack & Fishman (1972). An indwelling electromagnetic flow meter (Biotronex, BL-5025), which had been calibrated in vivo, was placed in relationship with the internal maxillary after ligating its extracerebral branches and provided a continuous record of unilateral CBF. Zero flow was obtained by means of a balloon-type occluder placed just proximal to the flow transducer. By a retroperitoneal approach an indwelling catheter was placed in the abdominal aorta. In four of the goats (C, D, E and F) another catheter was introduced into the superior sagittal sinus through a burr hole in the midline of the skull just anterior to the horns. These catheters allowed the easy sampling of arterial and cerebral venous blood. All surgical procedures were performed under general anaesthesia, but the actual studies outlined below were performed in the conscious, unanaesthetized state, at least a week being allowed for recovery before the experimental period commenced. During this time the animal was trained to stand quietly in a stock while breathing various gas mixtures through a snugly-fitting mask covering the mouth and nostrils.

Measurements

CBF was measured during normoxia and at different levels of steady-state isocapnic hypoxia in all six goats. CMRO₂ was also evaluated in the four goats (C, D, E and F) equipped with catheters for arterial and cerebral venous sampling. In the usual test procedure the animals spent four separate 8 min periods breathing air and three different hypoxic gas mixtures (11, 9 and 7% O₂ in N₂). Preliminary experiments had established that approximately 5 min was required for the blood gas composition and CBF to reach steady-state conditions after a change in the inspired O₂ concentration. An extended test procedure in one of the goats (D) included two extra periods breathing 15 and 8% O₂ in N₂. The CO₂ concentration in the expired gas was measured continuously by a rapid infrared analyser (Godart Capnograph), and aortic blood pressure by a pressure transducer (Statham P-23 Db). During hypoxic breathing the inspired gas was enriched with sufficient CO₂ to maintain the same end-tidal CO₂ concentration as during air-breathing. In two of the goats (A and F) CBF was also measured during steady-state normoxic hypercapnia and during hypoxia with an equal degree of hypercapnia. Both of the goats spent two extra periods breathing air or 10% O₂ in N₂ (gas mixtures were enriched with sufficient CO₂ to maintain an end-tidal CO₂ concentration of approximately 6.5%). In the eighth minute of breathing each gas mixture, CBF was measured and blood samples were drawn from the aortic and sagittal sinus catheters. The blood samples were analysed for O₂ tension (P0₂), CO₂ tension (Pco₂) and pH, with appropriate electrodes (Radiometer E5046/E5036/PHM71), and for O₂ content and O₂ saturation by using the manometric method of Van Slyke & Neil (1924). Total CBF was assumed to be twice the value measured by the flow probe and was expressed in relation to the brain weight obtained post mortem. CMRO₂ was estimated as the product of CBF and the O₂ content difference between arterial and cerebral venous blood. Cerebral O₂ delivery was calculated by multiplying CBF by the arterial O₂ content.

Experimental procedure

The test procedure outlined above was performed in duplicate on separate days during a control period. Liver failure was then induced by daily intraperitoneal injections of 5–10 ml of carbon tetrachloride diluted by an equal volume of olive oil. Serum samples became overtly jaundiced after 3–7 days of this regimen and the test procedure was repeated on two separate days when severe liver failure was indicated by a serum bilirubin concentration exceeding 6 mg/100 ml and a serum aspartate transaminase concentration exceeding 100 i.u./ml. Transfusions of whole blood were used to correct a slight fall in haemoglobin concentration during the experimental period in two goats (B and C). As a
Cerebral circulation and metabolism

Fig. 1. Relationship between CBF and arterial oxygenation in a healthy goat (D) breathing air and five different hypoxic gas mixtures. The arterial CO₂ tension (kPa) is indicated beside each of the points and was held between 5.6 and 5.9 kPa. Cerebral blood flow has a curvilinear relationship with arterial O₂ tension, but is almost linearly related to arterial O₂ saturation.

result the mean haemoglobin concentration in the six goats was virtually the same during liver failure (10.2 g/100 ml) as in the baseline period (10.3 g/100 ml). Post-mortem histological examination of the liver revealed an acute hepatic necrosis.

Results

After the onset of liver failure there was on average a 30% fall in CBF from 67.4 to 47.2 ml min⁻¹ 100 g⁻¹, and a 22% fall in CMRO₂ from 3.46 to 2.69 ml min⁻¹ 100 g⁻¹, a reduction in arterial Pco₂ (Pa,CO₂) from 5.4 to 4.1 kPa and a rise in arterial pH from 7.407 to 7.443. All these changes were significant when assessed by the paired t-test (P<0.001). The mean arterial blood pressure during liver failure (89.9 mmHg) was not significantly different from that in the baseline period (92.1 mmHg).

Cerebral circulatory response to hypoxia

Fig. 1 shows the relationship of CBF with (a) arterial O₂ tension (Pa,O₂) and (b) arterial O₂ saturation (Sa,O₂) at six levels of oxygenation in a healthy goat (D). Variation in Pa,CO₂ did not exceed 0.3 kPa during five periods of hypoxic breathing and one period of air breathing. CBF increased progressively during hypoxia, but the relationship of CBF with Pa,O₂ was distinctly alinear whereas an almost linear relationship was obtained when CBF
Fig. 3. Effect of liver failure on the CBF response to hypoxia in two goats (A and F) with the $P_{a,CO_2}$ held constant either at its value during air breathing or at a fixed level of hypercapnia. The $P_{a,CO_2}$ value is shown beside each of the points; O, baseline period; ●, liver failure. Note three effects of hypercapnia in the different clinical states: (a) it raises the normoxic and hypoxic CBF values, but (b) does not change the slope of the CBF/Sa,02 relationship; (c) there is less upward displacement of the CBF/Sa,02 response lines in liver failure due to diminished CBF response to hypercapnia (Stanley et al., 1975). As a corollary of (b) the reduced CBF response to hypoxia in liver failure is not mediated by hypocapnia.

was plotted against Sa,02. This linearity of the CBF/Sa,02 relationship was evident in all the goats whether studied in health or in liver failure. The slope of the CBF/Sa,02 relationship was therefore used as an expedient method of measuring the cerebral circulatory response to hypoxia.

The CBF responses to hypoxia before and after the onset of liver failure in the six goats are shown in Fig. 2. The slope of the CBF/Sa,02 relationship declined by an average of 61% from 0.81 (±0.08 SEM) in the baseline studies to 0.31 (±0.04) ml min⁻¹ 100 g⁻¹ %Sa,02⁻¹ after the onset of liver failure ($P<0.01$). Possible trauma or thrombosis associated with the preparation for cerebral venous sampling could not explain the decline in CBF responsive to hypoxia, since this change was equally profound in the two goats without sagittal sinus catheters (A and B) as in the others (C, D, E and F). The mean arterial blood pressure rose in hypoxia by an average during breathing 7% $O_2$ of 7-1 mmHg in the baseline studies, and by 4-8 mmHg in liver failure.

Since the goats became hypocapnic in liver failure, the CBF response to hypoxia was also evaluated in two goats (A and F) when the $P_{a,CO_2}$ was held

Fig. 4. Effect of hypoxia on cerebral $O_2$ delivery in the six goats. Mean (± SEM, $n=12$) values of cerebral $O_2$ delivery and arterial $O_2$ saturation are plotted during the inhalation of air and three different hypoxic gas mixtures; O, baseline period; ●, liver failure. Expressed as a percentage of its normoxic value, cerebral $O_2$ delivery declines more steeply in relation to the fall in arterial $O_2$ saturation when the animals were in liver failure.
TABLE 1. Effects of breathing various hypoxic gas mixtures on the cerebral metabolic rate in four goats (C, D, E and F)

CMRO₂, Cerebral metabolic rate for oxygen; Sa,O₂, arterial O₂ saturation. Sufficient enrichment with CO₂ was given in the inspired gases to maintain same Pa,CO₂ in hypoxia as in normoxia.

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<td>CMRO₂ (ml min⁻¹ 100 g⁻¹)</td>
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at an almost constant level of hypercapnia. As shown in Fig. 3, hypercapnia increased CBF during normoxia and hypoxia alike, but the upward displacement of the CBF/SaO_2 response lines was not associated with any change in their slope. Thus the depression of the cerebral circulatory response to hypoxia was independent of PaCO_2.

Due to the fall in CBF the cerebral O_2 delivery in liver failure was reduced from 8.74 (±0.34) to 6.09 (±0.40) ml min^{-1} 100 g^{-1}. Also, as is evident in Fig. 4, the reduced response of the cerebral circulation led to a disproportionate reduction of cerebral O_2 delivery in hypoxia.

**Effect of hypoxia on cerebral metabolism**

This was assessed in four of the goats (C–F) by comparing CMRO_2 at three different levels of hypoxia with the CMRO_2 in normoxia. The average values of CMRO_2, SaO_2, PaO_2 and PaCO_2 in duplicate studies before and after the onset of liver failure are listed in Table 1. In the baseline studies there was no reduction in CMRO_2 while the goats breathed 9 or 11% O_2; CMRO_2 decreased only when the inspired O_2 concentration had been reduced to 7% and the average SaO_2 had fallen to 47.4%. However, the fall in CMRO_2 during liver failure was accentuated when breathing each of the three hypoxic gas mixtures, even though the arterial hypoxaemia was less profound at each level of inspired O_2 concentration due to alveolar hyper-ventilation and an increased O_2 affinity of haemoglobin in alkalosis. The average PaCO_2 remained constant in hypoxia.

Fig. 5 shows the relationship between CMRO_2 and PaO_2 in the individual hypoxic breathing trials performed on each goat. During the baseline studies a reduction in CMRO_2 by hypoxia was not a consistent feature until the PaO_2 had fallen to less than 3.2 kPa. In twenty-one baseline studies with the PaO_2 ranging from 3.2 to 5.9 kPa the mean CMRO_2 was 3.52 (±0.07) ml min^{-1} 100 g^{-1}, which was almost identical with the normoxic CMRO_2 of 3.46 (±0.10) ml min^{-1} 100 g^{-1}. However, when the PaO_2 fell to less than 3.2 kPa in three baseline trials in different goats (C, E and F) there was a precipitous drop in CMRO_2 to only 72-79% of its normoxic value. The cerebral venous Po2 (Pcv,O_2) during these episodes of hypoxic CMRO_2 depression ranged from 1.9 to 2.2 kPa and was 2.4 kPa or above in the other twenty-one hypoxic breathing periods. A PaO_2 of 3.2 kPa (24 mmHg) and a Pcv,O_2 of 2.2 kPa...
(16 mmHg) were therefore regarded as critical threshold values for producing hypoxic depression of aerobic metabolism in the brain of the healthy goat. Above these threshold Po2 values the CMRO2 did not deviate by more than 12% below its normoxic value in the baseline studies. However, after the onset of liver failure, the CMRO2 fell by more than 12% below its normoxic value in sixteen out of the twenty-four hypoxic breathing periods, with the Pa,o2 ranging from 3-5 to 6-4 kPa. The Pa,o2 – Pcv,o2 was often increased at any given level of hypoxaemia during liver failure, so that sometimes the Pcv,o2 was below the threshold level for producing hypoxic CMRO2 depression although the Pa,o2 was still above its own threshold level. Thus in four of the sixteen instances of hypoxic depression the Pcv,o2 values were only 1-9 to 2-2 kPa even with the Pa,co2 ranging from 3-5 to 4-3 kPa. In the other twelve instances the depression of CMRO2 occurred when both the Pa,o2 and Pcv,o2 values were higher than the threshold values obtained in the baseline studies.

Discussion

Cerebral circulatory response to hypoxia

The respiratory alkalosis in hepatic failure might have altered the measurement of CBF responsiveness for two reasons. First, the Pa,co2 value might conceivably modify the CBF response to hypoxia, just as it alters the ventilatory response to hypoxia. However, a change in Pa,co2 has not been found to influence the CBF response to hypoxia (Shapiro, Wasserman & Patterson, 1966; James, Millar & Purves, 1969a), and this was confirmed by the findings shown in Fig. 3. The second possible effect of a respiratory alkalosis concerns the use of Sa,o2 rather than Pa,o2 differences to quantify the change in the hypoxic stimulus. As discussed in the accompanying paper (Stanley, Kelsen & Cherniack, 1976), a leftright shift in the oxygen-haemoglobin dissociation curve due to alkalosis slightly reduces the decrement in Sa,o2 required to produce a given fall in Pa,o2 in the upper portion of the curve. Therefore measurements of CBF responsiveness to arterial hypoxaemia would have been even lower if related to Pa,o2 rather than Sa,o2 differences when the goats were in liver failure. The arterial pressure measurements were always within the range where CBF is independent of blood pressure (Harper, 1966). Hypoxia also evoked the usual slight rise in blood pressure during the baseline studies and liver failure alike, which eliminated the possibility that the reduction in CBF responsiveness might be linked with the usually less efficient autoregulation of CBF in hypoxia (Haggendal, 1968).

The fall of CMRO2 in liver failure and its further reduction in hypoxia provide a sufficient explanation for the diminished CBF response to hypoxia without invoking other mechanisms, such as changes in the reactivity of the cerebral vessels (Smith & Vane, 1966; Detar & Bohr, 1968) or in the autonomic regulating system (James et al., 1969a). CBF and cerebral oxygen delivery are partly controlled by cerebral metabolic requirements (Schmidt, Kety & Pennes, 1945) and consequently a reduction in cerebral metabolic rate is usually accompanied by decreases in both CBF and its response to hypercapnia (Fujishima, Scheinberg, Busto & Reinmuth, 1971). Allowing for a small contributory effect of hypocapnia, the reduction of CBF produced by liver failure was closely matched by the fall of CMRO2 in normoxic conditions. When comparing measurements in liver failure with those in the baseline period at equivalent degrees of hypoxia (Sa,o2 ≈ 63%), the percentage difference in CBF (42%) was in keeping with the difference in CMRO2 (43%).

The hypoxic CMRO2 depression in liver failure can also account for the disproportionate fall in cerebral oxygen delivery in hypoxia without implying a deficiency in the homeostatic function of the cerebral circulation. Thus, at any given Sa,o2 value, the discrepancy between the cerebral oxygen delivery in liver failure as compared with control studies (see Fig. 4) was no greater than the percentage fall of CMRO2 in liver failure shown in Table 1.

The usual stability of CMRO2 during moderately severe hypoxia is well known (Kety & Schmidt, 1948; Cohen, Alexander, Smith, Reivich & Wollman, 1967). The control studies agreed with these earlier observations, but demonstrated that large falls in CMRO2 occur if the Pa,o2 or Pcv,o2 are reduced below critical threshold levels of approximately 3-2 and 2-2 kPa respectively. In isolated instances the increased liability to hypoxic CMRO2 depression in liver failure seemed to be mediated by cerebral hypoperfusion due to severe hypocapnia. This widened the usual Pa,o2 – Pcv,o2 difference so that the critical Pcv,o2 threshold was crossed when the
was still above its own critical threshold level. In most instances, though, the decline in CMRO₂ became evident when the $PcvO₂$ was also above its normal threshold value. This suggests that aerobic cerebral metabolism may be abnormally sensitive to tissue hypoxia in liver failure. An upward resetting of the threshold $PcvO₂$ for hypoxic CMRO₂ depression has been observed in experimental animals with both respiratory and non-respiratory acidosis (Grote, Kreuscher, Vaupel & Gunther, 1971), and the metabolic sensitivity to hypoxia was potentiated by cerebral oedema. These observations may be relevant in liver disease, which can cause an intracellular acidosis in spite of the extracellular alkalosis (Bittar, Watt, Pateras & Parrish, 1962) and is complicated by generalized fluid retention. Cellular respiration may also be impaired in liver failure, since components of the cellular oxidoreductive system are shifted to a more reduced state in some tissues (Henley & Laughrey, 1970). In addition the proportion of glucose metabolized with oxygen by the brain is reduced in patients with hepatic coma (James et al., 1969b), which suggests a greater reliance on anaerobic metabolism to maintain cerebral oxygen requirements even in the normoxic state. Alternatively the hypoxic depression of CMRO₂ at relatively high $PcvO₂$ values may reflect increased cerebral arteriovenous shunting, or variation in capillary density, so that the $PO₂$ in cerebral venous blood is much higher than in the cerebral capillaries. Cerebral arteriovenous shunts are now thought to exist in healthy animals (Rowed, Stark, Hoffer & Mullan, 1972), and opening of arteriovenous anastomoses seems to be a generalized feature in liver failure (Dal Palu, Donnagio, Dal Zotto & Pessina, 1968). Finally, the abnormal sensitivity of cerebral metabolism to hypoxia may be secondary to the effects of arterial unsaturation on a failing liver. The depression of CMRO₂ in liver disease is presumably due to an accumulation of toxic metabolites, which may be aggravated in hypoxia since hepatic function is sensitive to the $SaO₂$ (Brauer, Leong, Holloway & Krebs, 1963).

Clinical implications

The severity of hepatic encephalopathy is closely correlated with the CMRO₂ and interventions which cause deterioration (Posner & Plum, 1960) or improvement in the clinical state (James et al., 1969b) are accompanied by corresponding changes in the CMRO₂. Therefore when hypoxic CMRO₂ depression occurs in patients with liver disease, relief of hypoxia may be a useful therapeutic adjunct. Arterial hypoxaemia is usually mild in most patients with liver disease who live at sea-level. However, many isolated cases have been reported with $PaO₂$ values less than 6-4 kPa (e.g. Hutchison, Sapru, Sumerling, Donaldson & Richmond, 1968), below which hypoxic CMRO₂ depression was measurable among the goats in liver failure, and severe hypoxia may be more common in patients residing at high altitude. Possibly the use of long-term oxygen therapy or environmental change may provide a marginal benefit in such cases with severe unsaturation. Of greater practical importance may be the patients with gastrointestinal bleeding; shock and anaemia will compound the cerebral hypoxia produced by arterial $O₂$ unsaturation. In such cases the correction of even mild arterial hypoxaemia may be desirable in addition to the restoration of blood volume and the provision of an adequate haemoglobin concentration.

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References


