Effect of liver failure on the response of ventilation and cerebral circulation to carbon dioxide in man and in the goat

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Summary

1. The acid-base state of arterial blood and cerebrospinal fluid, and the ventilatory response to CO₂, were measured in twelve patients with liver disease. The CO₂ response was also measured in eight goats before and after the experimental production of liver failure. Arterial Pco₂ and pH, cerebral blood flow and the cerebral metabolic rate for oxygen were also measured in four of the goats while they breathed air and various CO₂-enriched gas mixtures.

2. Liver failure was accompanied by a respiratory alkalosis in both the patients and in the goats. Decreased Pco₂ and increased pH occurred in the cerebrospinal fluid and in the arterial blood of the patients.

3. The slope of the ventilatory response to CO₂ was reduced when liver failure was severe, in patients and goats alike. In addition there was a reduction in the extrapolated Pco₂ at zero ventilation, even when liver failure was mild.

4. Cerebral blood flow and metabolic rate were consistently reduced in the goats during liver failure. There was also less cerebral vasodilatation and a greater reduction in cerebral metabolism during experimental hypercapnia when these animals were in liver failure.

5. The decreases in the ventilatory and cerebral circulatory responsiveness to CO₂ indicate that the brain is less well defended against hypercapnia in liver failure, and these changes are especially unfavourable as cerebral function deteriorates when the Pco₂ is increased.

Key words: alkalosis, carbon dioxide, cerebral blood flow, cerebrospinal fluid, cerebral metabolism, liver cirrhosis, ventilatory control.

Introduction

Hyperventilation, respiratory alkalosis (Vanamee, Poppell, Glicksman, Randall & Roberts, 1956; Tyor & Sieker, 1959; Reinicke, Friis & Mullertz, 1963) and reduced cerebral blood flow (Fazekas, Ticktin, Ehrentraut & Alman, 1956; Posner & Plum, 1960; James, Nashat, Sampson, Williams & Garassini, 1969) are common features in acute and chronic liver failure. They are possibly interrelated since hypocapnia reduces cerebral blood flow (Kety & Schmidt, 1946) and diminished cerebral perfusion may stimulate ventilation by increasing the brain extracellular Pco₂ (Comroe, 1965). However, the effect of liver failure on the usual interplay between ventilation, CO₂ and the cerebral circulation is still unclear.

In the present study the acid–base state of arterial blood and cerebrospinal fluid, and the ventilatory response to inhaled CO₂, were evaluated in a group of patients with liver disease. The studies were then extended to examine the effect of liver failure in unanaesthetized goats. The animal model allowed a detailed investigation of the CO₂ responsiveness of both ventilation and the cerebral circulation.
Methods

Human studies

These were performed in a group of twelve male patients with liver failure at the Philadelphia General Hospital and the Philadelphia Veterans Administration Hospital. Sanction for the investigations had been obtained from the separate Ethical Committees of these institutions. Ten of the patients consented to the studies after a full explanation of their nature and purpose. Informed consent was given by the next of kin on behalf of two terminal patients with hepatic coma.

Nine of the patients had hepatic cirrhosis due to chronic alcoholism, two had cryptogenic cirrhosis and one had acute hepatic necrosis without cirrhosis due to viral hepatitis. Their clinical and biochemical data are given in Table 1. Encephalopathy was graded according to the clinical severity of neuropsychiatric features using the criteria of Sherlock (1958): grade 0, normal; grade I, minor disorder of consciousness; grade II, gross disorder of consciousness; grade III, coma. None of the patients had clinical or radiographic evidence of cardiopulmonary disease. Except in two patients with hepatic coma, ventilatory function was assessed by measuring the vital capacity and the forced expiratory volume in 1 s (FEV₁) by using a low-resistance spirometer. No patients were admitted to the study if the test results deviated by more than 25% from predicted normal values (Kory, Callahan, Boren & Syner, 1961; Cotes, Rossiter, Higgins & Gilson, 1966).

Acid-base measurements. Samples of arterial blood and lumbar cerebrospinal fluid were drawn into glass syringes while the subjects were lying quietly on their left sides. The syringes were heparinized only when used for blood collection. In sampling cerebrospinal fluid a small quantity of the fluid was drawn into a dry syringe, air then being expelled before the test sample was collected. The pH, Po₂ and PCO₂ in blood and cerebrospinal fluid samples were measured with appropriate electrodes (Radiometer PHM 71/E 5046/E 5036). Arterial and cerebrospinal fluid bicarbonate concentrations were calculated from the measured PCO₂ and pH values by using the Henderson-Hasselbalch equation, the solubility of CO₂ and pK' being obtained from the data of Severinghaus (1965) for blood, and from those of Mitchell, Herbert & Carman (1965) for cerebrospinal fluid. Results in patients were compared with those in ten hospital patients without cardiorespiratory or metabolic disease.

Ventilatory response to CO₂. This was evaluated by a modification of the rebreathing method (Read, 1967). The subjects rebreathed for 3–4 min through a temperature controlled pneumotachygraph (Heisch no. 2, Instrumentation Associates) from a rubber bag containing approximately 6 l of 5–7% CO₂ in oxygen. The pneumotachygraph was warmed

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Spleno- megaly</th>
<th>Spino- megaly</th>
<th>Ascites</th>
<th>Spider naevi</th>
<th>Grade of encephalopathy</th>
<th>Serum bilirubin (mg/100 ml)</th>
<th>Serum glutamic-oxaloacetic transaminase (i.u./100 ml)</th>
<th>Serum albumin (g/100 ml)</th>
<th>Haemoglobin (g/lOO ml)</th>
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<td>111</td>
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<td>84</td>
<td>3-3</td>
<td>12-8</td>
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</table>
to prevent condensation. The initial \( \text{CO}_2 \) concentration in the bag was approximately equal to the subject's mixed venous \( \text{Pco}_2 \), assumed to be 6 mmHg in excess of the arterial \( \text{Pco}_2 \). On average the alveolar \( \text{Pco}_2 \) had risen to 61 mmHg (range 56–69 mmHg) by the end of the rebreathing period. The pressure difference across the pneumotachygraph was measured by a differential pressure transducer (Statham PM-5) to monitor air flow. Gas was continuously sampled at the mouth for the measurement of end-tidal \( \text{CO}_2 \) concentration by an infrared analyser (Godart Capnograph) calibrated by three known \( \text{CO}_2 \) mixtures. Airflow and \( \text{CO}_2 \) concentration were recorded (Electronics for Medicine, model DR-12), and electronic integration of the airflow signal provided a continuous record of tidal volume, with calibration from a 1.5 litre syringe. The \( \text{P} \text{O}_2 \) within the bag did not fall below 200 mmHg during rebreathing. The measurements during the first 30 s of rebreathing were discarded; ventilation was then measured over five breath intervals during the test period and was plotted against the end-tidal \( \text{Pco}_2 \) at the mid-point of each interval. A straight line was drawn through the ventilation \( \text{Pco}_2 \) points and was extrapolated to its intersection with the \( \text{Pco}_2 \) axis. Similar measurements were made in sixteen healthy males aged 23–56 years.

**Animal experiments**

These utilized eight adult goats, which were trained to stand quietly in a stock while breathing various gas mixtures through a tightly fitting mask covering the mouth and nostrils.

**Surgical procedures.** Six of the goats were prepared beforehand for the measurement of unilateral cerebral blood flow (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 artery, a branch of the external carotid artery which in the goat provides the total ipsilateral cerebral blood flow via its anastomotic branch to the rete mirabile (Andersson & Jewell, 1956). To reduce the extracerebral flow through the internal maxillary artery, its branches other than to the rete were ligated. Zero flow was obtained by means of an arterial balloon-type occluder just proximal to the flow transducer. In four of these goats a catheter was placed in the abdominal aorta, by a retroperitoneal approach, and another catheter was introduced into the superior sagittal sinus through a midline burr hole at the anterior margin of the horns. After these surgical procedures at least a week was allowed for recovery before the experimental period commenced.

**Measurements.** In all eight goats the ventilatory response to \( \text{CO}_2 \) was measured during rebreathing in a closed circuit identical with the one used in the human experiments. In the six goats with indwelling flow probes measurements of cerebral blood flow were also made at 30 s intervals during the rebreathing period and were plotted against the corresponding end-tidal \( \text{Pco}_2 \). In the four goats with aortic and sagittal sinus catheters, ventilation, cerebral blood flow, cerebral vascular resistance and cerebral metabolic rate for oxygen were also measured during normocapnia and at several different constant levels of hypercapnia. The animals spent three or four separate periods breathing air or 2–8% \( \text{CO}_2 \) in air in an open circuit. Ventilation was continuously monitored by the pneumotachygraph and aortic blood pressure by a pressure transducer (Statham P-23 Db). Ventilation and cerebral blood flow were measured and samples of arterial and cerebral venous blood were collected after 7 min breathing each different gas mixture. Blood samples were analysed for \( \text{PO}_2 \), \( \text{PCO}_2 \) and pH and also for \( \text{O}_2 \) content, by the manometric Van Slyke method. Total cerebral blood flow was assumed to be twice the value measured by the flow probe and was expressed in relation to the brain weight as obtained at post mortem. Cerebral vascular resistance was calculated as the ratio of mean aortic blood pressure to the cerebral blood flow. Cerebral metabolic rate for \( \text{O}_2 \) was estimated as the product of cerebral blood flow and the \( \text{O}_2 \) content difference between arterial and cerebral venous blood.

**Experimental procedure.** Duplicate test procedures were repeated on successive days during a control period. Liver failure was then induced in the goats by daily intraperitoneal injection of 5–10 ml of carbon tetrachloride diluted by an equal volume of olive oil. Serum samples became overtly jaundiced 3–7 days later and the test procedures were repeated on 2 separate days when severe liver failure was indicated by a serum bilirubin concentration exceeding 6 mg/100 ml and a serum glutamic–oxaloacetic transaminase concentration of over 100 i.u./ml. Post-mortem histological examination of the liver immediately afterwards showed acute hepatic necrosis.
Results

Human experiments

Acid-base measurements (Table 2). The PCO₂ was reduced and pH increased in the arterial blood; plasma bicarbonate concentrations were reduced in keeping with a partially compensated respiratory alkalosis. In the cerebrospinal fluid there was also a reduction in PCO₂, a slight increase in pH and a reduction in bicarbonate concentration. However, the difference in pH of cerebrospinal fluid in the patients and control subjects was only 0.25 unit compared with an arterial pH difference of 0.53 unit. The cerebrospinal fluid–arterial PCO₂ difference was not significantly greater in the patients (1.11 kPa, 8.3 mmHg) than in the control subjects (1.08 kPa, 8.1 mmHg). Hypocapnia was never associated with either an acidosis of the arterial blood or cerebrospinal fluid, or with an arterial PO₂ of less than 65 mmHg.

Ventilatory studies. The measurements of ventilatory capacity and the ventilatory response to CO₂ are given in Table 3. The forced expiratory volume in 1 s and vital capacity in the conscious patients were normal, excluding any major obstructive or restrictive ventilatory defect. In the comatose patients there was no clinical evidence of airway obstruction. No clinical changes were observed in any patient during or immediately after the CO₂ rebreathing period. The comatose patients were in a terminal state and died 2–4 days after the investigations; post-mortem examination revealed no disease of their lungs.

The ventilation–PCO₂ response lines were analysed by measuring their slope (Sco₂) and intercept with the PCO₂ axis (Bco₂). The mean Sco₂ in the patients was only 72% of the mean value in the control subjects, but individual values were widely scattered and the difference between the groups was not significant. However, in the six patients with grade II and III encephalopathy the mean Sco₂ (10.1 1 min⁻¹ kPa⁻¹, 1.35 1 min⁻¹ mmHg⁻¹) was only 42% of the value in the control group and this difference was significant (P < 0.01). Both of the comatose patients and two out of the four patients with grade II encephalopathy had lower Sco₂ values than any of the control subjects. In the other six patients with less severe encephalopathy the average Sco₂ (24.1 1 min⁻¹ kPa⁻¹, 3.32 1 min⁻¹ mmHg⁻¹) was
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Table 3. Ventilatory capacity and response to CO₂ in the patients
FEV₁ = forced expiratory volume in 1 s; VC = vital capacity; SCo₂ and BCo₂ = the slope and horizontal intercept of the ventilation-PCO₂ response lines. Predicted normal values of FEV₁ and VC are given in parentheses beside the measured values.

<table>
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<tr>
<th>Subject no.</th>
<th>FEV₁ (l)</th>
<th>VC (l)</th>
<th>FEV₁/VC (%)</th>
<th>SCo₂ (l min⁻¹ kPa⁻¹)</th>
<th>BCo₂ (kPa)</th>
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<td>—</td>
<td>—</td>
<td>4·5</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>3·7</td>
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<tr>
<td>3</td>
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<td>6·8</td>
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<td>3·9 (5·0)</td>
<td>72</td>
<td>23·2</td>
<td>4·7</td>
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<td>5·4 (5·0)</td>
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</tr>
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<td>4·9 (4·7)</td>
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<td>24·0</td>
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<td>5·3 (4·7)</td>
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<tr>
<td></td>
<td>Range</td>
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<td>4·5–6·1</td>
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</table>

virtually the same as in the control subjects. BCo₂ was reduced in nine out of the twelve patients and this occurred even in those without encephalopathy.

A ventilation-PCO₂ plot in Fig. 1 illustrates the decreases in SCo₂ and BCo₂ in the patients with hepatic coma. It also demonstrates that ventilation was abnormally high at PCO₂ values of less than 6·7 kPa (50 mmHg) as a result of the reduction in BCo₂. However, owing to a reduction in slope (SCo₂) of their ventilation-PCO₂ response lines, the comatose patients were actually ventilating less than the control subjects at the higher PCO₂ levels.

Animal experiments

The investigations during liver failure were performed when the mean serum bilirubin was 9·2 (range 6·1–21·6) mg/100 ml, implying that the biochemical disorder was of similar severity to that in the patients with grade II or III encephalopathy.

Acid-base measurements (Table 4). As in the patients, the four goats developed hypocapnia and a respiratory alkalosis when they were in liver failure. Associated with the changes in arterial blood, there

Fig. 1. Ventilation is plotted against alveolar PCO₂ during progressive hypercapnia produced by rebreathing in two patients in hepatic coma: patient no. 1 (●) and patient no. 2 (○). Broken lines indicate data in two subjects with highest and lowest CO₂ responsiveness in the control group. Note that the ventilation CO₂ response lines in the patients are depressed in slope and are heading for the horizontal axis at a very low or negative PCO₂ value.
TABLE 4. Blood gas partial pressures and acid–base measurements in four goats
Results are given as mean values±SEM, for eight control and eight experimental observations in four goats.

<table>
<thead>
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<th></th>
<th>arterial</th>
<th>cerebral venous</th>
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<tr>
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<td>$\text{PO}_2$ (kPa)</td>
<td>$\text{PCO}_2$ (kPa)</td>
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<td>Control</td>
<td>11.0±0.6</td>
<td>5.4±0.1</td>
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<tr>
<td>Liver failure</td>
<td>11.1±0.3</td>
<td>4.1±0.2</td>
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</tbody>
</table>

Fig. 2. Relationship between ventilation and arterial $\text{PCO}_2$ during air breathing and at two or three different steady-state levels of hypercapnia in four goats. Duplicate experiments before (●) and after (○) the onset of liver failure. The ventilation–$\text{PCO}_2$ response lines are depressed in slope and if extrapolated they intercept the horizontal axis at a lower $\text{PCO}_2$ during liver failure.

was also a reduction in $\text{PCO}_2$ and an increase in pH in cerebral venous blood during liver failure.

Ventilatory response to steady-state hypercapnia. The arterial $\text{PCO}_2$ in these four goats was increased to two or three different steady-state values by giving them various $\text{CO}_2$-enriched gas mixtures to breathe in an open circuit. As shown in Fig. 2, the ventilatory response to $\text{CO}_2$ was approximately linear. However, after the onset of liver failure the ventilation–$\text{PCO}_2$ response lines were consistently depressed in slope ($\text{Sco}_2$) and in intercept with the $\text{PCO}_2$ axis ($\text{Bco}_2$). Regression lines derived by the least squares method indicated that the mean $\text{Sco}_2$ fell from $10.44$ (SEM $1.65$) $1 \text{ min}^{-1} \text{ kPa}^{-1}$ ($1.39$, 1.56) $1 \text{ min}^{-1} \text{ kPa}^{-1}$.
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FIG. 3. Data in Fig. 2 are replotted to show the relationship between ventilation and arterial hydrogen concentration \([H^+]\) before (●) and after (○) liver failure. The ventilation-[H+] response lines are also depressed in slope and if extrapolated they meet the horizontal axis at a reduced \([H^+]\).

Ventilatory response to progressive hypercapnia. Similar findings to the steady-state studies were also observed in all eight goats when the ventilatory response to CO\(_2\) was studied by the rebreathing method. After the onset of liver failure, there was a fall in SCO\(_2\) from 9.75 (SEM 0.45) 1 min\(^{-1}\)kPa (1.39 1 min\(^{-1}\)mmHg\(^{-1}\)) to 5.40 (SEM 0.53) 1 min\(^{-1}\)kPa\(^{-1}\) (0.72 1 min\(^{-1}\)mmHg\(^{-1}\)) and in BCO\(_2\) from 5.53 (SEM 0.13) kPa (41.5 mmHg) to 3.91 (SEM 0.16) kPa (29.3 mmHg). The decrease in SCO\(_2\) and BCO\(_2\) were not due to the surgical procedures, since they also occurred in two goats without catheters or an implanted flow probe.

Cerebral circulation and metabolism (Table 5). The mean cerebral blood flow fell by 30\% after the onset of liver failure as compared with that in the control period, whereas cerebral vascular resistance increased by 40\%. These changes were associated with hypocapnia, the mean arterial P\(_{CO2}\) falling by nearly 10 mmHg. The cerebral metabolic rate for O\(_2\) fell by 22\%. All these changes occurred in each goat.
TABLE 5. Cerebral circulation and metabolism in four goats

Results are given as mean values±SEM, for eight control and eight experimental observations in four goats.

<table>
<thead>
<tr>
<th></th>
<th>Cerebral blood flow (ml min⁻¹100 g⁻¹)</th>
<th>Mean arterial pressure (mmHg)</th>
<th>Cerebral vascular resistance (mmHg min⁻¹ml⁻¹100 g⁻¹)</th>
<th>Arteriovenous O₂ differences (vol. %)</th>
<th>Cerebral metabolic rate for O₂ (ml min⁻¹100 g⁻¹)</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>68.0 ± 2.6</td>
<td>93.3 ± 4.0</td>
<td>1.37 ± 0.09</td>
<td>5.05 ± 0.21</td>
<td>3.46 ± 0.10</td>
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<tr>
<td>Liver failure</td>
<td>47.8 ± 2.8</td>
<td>89.1 ± 4.1</td>
<td>1.92 ± 0.16</td>
<td>5.70 ± 0.28</td>
<td>2.69 ± 0.14</td>
</tr>
</tbody>
</table>

Fig. 4. Cerebral blood flow plotted against arterial Pco₂ in four of the goats during duplicate experiments before (●) and after (○) onset of liver failure. In liver failure cerebral blood flow is reduced, even in normocapnia, and the cerebral blood flow–Pco₂ response lines are depressed in slope.

Effect of CO₂ inhalation on the cerebral circulation (Fig. 4). Like ventilation, cerebral blood flow rose in an approximately linear relationship with increasing arterial Pco₂. After the onset of liver failure the slopes of the cerebral blood flow–Pco₂ response lines were depressed, so that given increments in arterial Pco₂ resulted in smaller increases of cerebral blood flow. The cerebral blood flow–Pco₂ plots also demonstrated that the reduction in cerebral blood flow associated with liver failure during air breathing was not due to hypocapnia alone, since the flow was still less than control values even when the Pco₂ was raised to normocapnic levels. The regression of cerebral blood flow on Pco₂ (Fig. 4) showed that liver failure was associated with a 75% reduction in the cerebral blood flow–Pco₂ slope, from the average control value of 21.07 (SEM 3.82) to 5.17 (SEM 1.13) ml min⁻¹100 g⁻¹.
Ventilation and cerebral circulation

FIG. 5. Cerebral metabolic rate for oxygen (CMRO₂) measured at different arterial PCO₂ in four goats. Duplicate experiments during a control period (●) and after (○) liver failure. CMRO₂ is not altered by hypercapnia during control observations. During liver failure, CMRO₂ is reduced and declines further when the PCO₂ is increased.

kPa⁻¹. The maximum rise in mean arterial blood pressure during CO₂ inhalation did not exceed 10% and thus the increases in cerebral blood flow during hypercapnia were largely due to reciprocal changes in cerebral vascular resistance.

Cerebral blood flow was also measured during progressive hypercapnia produced by rebreathing in six goats, including the four used in the steady-state studies. There was a linear relationship between cerebral blood flow and alveolar PCO₂, but after the onset of liver failure the slope of the cerebral blood flow–PCO₂ response lines declined from an average value of 22.20 (SEM 1.80) to 6.45 (SEM 1.35) ml min⁻¹100 g⁻¹ kPa⁻¹. The changes were observed in each animal, including the two without sagittal sinus catheters, suggesting that trauma or thrombosis associated with the preparation for cerebral venous sampling could not have been responsible for the decline in the CO₂ responsiveness of the cerebral circulation.

Effect of CO₂ inhalation on cerebral metabolism. This was assessed in four goats in conjunction with the steady-state studies of the CO₂ responsiveness of ventilation and the cerebral circulation (Fig. 5). The cerebral metabolic rate for O₂ was virtually unchanged by CO₂ breathing during the control period; the mean value was 3.46 ml min⁻¹100 g⁻¹ during air breathing and 3.44 ml min⁻¹100 g⁻¹ when CO₂ inhalation raised the mean arterial PCO₂ from 5.3 to 7.6 kPa. However, increasing the PCO₂ during liver failure from 4.0 to 7.6 kPa caused a 20% reduction in the metabolic rate from 2.69 to 2.16 ml min⁻¹100 g⁻¹. This fall occurred in seven out of eight observations and was significant (P < 0.01). Thus the reduction in cerebral metabolism produced by liver failure was accentuated when the animals were made hypercapnic.

Discussion

Acid–base measurements

Although a mixed acid–base disturbance is frequently present in liver disease (Mulhausen et al., 1967), a respiratory alkalosis due to hyperventilation is the predominant abnormality. Hypocapnia was never accompanied by a reduction in pH in either arterial blood or cerebrospinal fluid in the present group of patients. Therefore the hyperventilation could not be explained by an increased hydrogen ion stimulus in the blood or brain extracellular fluid. Cerebral hypoperfusion was not associated with an
increased \( P_{CO_2} \) difference between the brain extracellular fluid and arterial blood, since diminished cerebral blood flow was largely matched by a fall in cerebral metabolic rate. The alkaline cerebrospinal fluid confirms previous observations by Schwab & Dammaschke (1962). However, unlike this earlier study, the increase in \( pH \) of cerebrospinal fluid was much less than in arterial \( pH \), as observed in respiratory alkalosis due to pregnancy or residence at high altitude (Mitchell, Carman, Severinghaus, Richardson, Singer & Schneider, 1965), and is a further demonstration of the more efficient regulation of \( pH \) in cerebrospinal fluid than in the blood.

**Cause of hyperventilation**

Arterial hypoxaemia is a common complication in hepatic cirrhosis (Georg, Mellemgaard, Tygstrup & Winkler, 1960), but the arterial \( P_{O_2} \) usually exceeds 60 mmHg, above which the hypoxic ventilatory drive is weak (Schmidt & Comroe, 1940). It has been suggested that the ventilatory stimulation might be caused by increased circulating concentrations of ammonia (Vanamee et al., 1956), progesterone (Schwab & Dammaschke, 1962) or metabolites released from the gut (Heinemann, Emirgil & Mijnssen, 1960) which have escaped the usual detoxication processes due to liver failure or portal-systemic venous shunting. However, ammonia does not stimulate ventilation at blood concentrations far higher than those present in liver failure (Renzetti, Harris & Bowen, 1961), and the blood progesterone concentration is normal even in patients with hypocapnia (Whitmore & Chiodi, 1972). Said & Mutt (1970) have extracted a vasoactive polypeptide which stimulates the peripheral chemoreceptors. This polypeptide may have systemic effects only during hepatic failure since it is rapidly inactivated in the liver. Alternatively an intracellular acidosis occurring in liver failure (Bittar, Watts, Pateras & Parrish, 1962) could increase ventilation if it affects the respiratory chemoreceptors. Finally interstitial pulmonary oedema in liver cirrhosis (Ruff, Hughes, Stanley, McCarthy, Greene, Aronoff, Clayton & Milic-Emili, 1971) could stimulate a neural drive from the pulmonary \( J \) receptors (Paintal, 1969).

**Ventilatory response to \( CO_2 \)**

Respiratory alkalosis indicates a net stimulation of ventilation in liver failure. However, the ventilatory response to \( CO_2 \) showed that the disorder in respiratory regulation is complex, with both stimulant and depressant factors playing a role. The decrease in \( B_{CO_2} \) indicates a re-setting of the respiratory chemoreceptors, so that they are active at lower \( P_{CO_2} \) values, but the reduction in \( S_{CO_2} \) suggests that they are less sensitive to increases in \( P_{CO_2} \). Owing to the loss of \( CO_2 \) responsiveness in liver failure, net ventilatory stimulation in normocapnia was replaced by net ventilatory depression in hypocapnia.

Some reduction of \( B_{CO_2} \) may be expected in a chronic respiratory alkalosis owing to compensatory lowering of bicarbonate concentration, since a metabolic acidosis shifts the ventilation–\( P_{CO_2} \) response line to the left (Cunningham, Shaw, Lahiri & Lloyd, 1961). Nonetheless, decreased blood bicarbonate concentrations cannot explain the reduction in \( BH \) shown in Fig. 3. Fencl, Vale & Broch (1969) suggested that cerebrospinal fluid bicarbonate concentration determines \( B_{CO_2} \) in chronic metabolic acid–base disorders, but there was no significant correlation between these measurements in our patients.

The reduced \( S_{CO_2} \) in liver failure is perplexing and contrasts with an increased \( S_{CO_2} \) in respiratory alkalosis due to pregnancy (Doring & Loeschke, 1947) or residence at high altitude (Forster, Dempsey, Birnbaum, Reddan, Grover & Rankin, 1971). This depressant effect probably arises from the medullary rather than the peripheral chemoreceptors, as the latter have little influence on \( CO_2 \) responsiveness in normal oxygen concentrations (Mitchell, 1965; Wade, Larson, Hickey, Ehrenfeld & Severinghaus, 1970) and no effect in hyperoxia (Lambertsen, Hall, Wollman & Goodman, 1963; Cunningham, Patrick & Lloyd, 1964). An increase in the brain intracellular buffering capacity on hypocapnia (Kjahlquist, Nardini & Siesjo, 1969) might possibly reduce ventilatory \( CO_2 \) responsiveness at \( P_{CO_2} \) values below 40 mmHg, but \( S_{CO_2} \) was still reduced when the \( P_{CO_2} \) was increased into the hypocapnic range. In the goats depression of \( S_{CO_2} \) was always accompanied by a reduction in cerebral metabolic rate, and was found only in patients with encephalopathy, when the fall in cerebral metabolic rate is usually most profound (Posner & Plum, 1960).

Although dependence of medullary chemosensitivity on cerebral metabolism is not an established physiological principle, the association of depressed \( S_{CO_2} \) and cerebral metabolic rate for \( O_2 \) also occurs in myxoedema (Wilson & Bedell, 1960; Scheinberg,

A preliminary report by Robin, Whaley, Crump & Travis (1957) also suggested that hepatic coma is associated with a reduced $\text{ScO}_2$. The absence of severe liver failure explains why this was not a consistent finding in another study (Karetsky & I 1967).

Cerebral circulation and metabolism

In control conditions the cerebral blood flow was on average 11% higher than that observed with the inert-gas technique in the normocapnic goat (Alexander & Smith, 1969); the use of anaesthesia may account for the slightly lower values in the earlier study. Hypocapnia was only a minor cause of the reduction in cerebral blood flow during liver failure and its role was diminished by the loss of $\text{CO}_2$ responsiveness in the cerebral circulation. However, cerebral perfusion is partly regulated in relationship to the cerebral metabolic demands (Schmidt et al., 1945) and the decrease in cerebral blood flow was nearly matched by the fall in cerebral metabolic rate for $\text{O}_2$. Most of the reduction in blood flow may thus arise from the depression of cerebral metabolism, presumably due to an accumulation of toxic metabolites in hepatic failure. The animal experiments also helped to clarify another uncertainty about the behaviour of the cerebral circulation in human liver disease. Posner & Plum (1960) observed that the inhalation of 5% $\text{CO}_2$ in air evoked an increase of only 46% in cerebral blood flow of patients with hepatic cirrhosis, whereas an increase of 59% has been reported in healthy young subjects (Kety & Schmidt, 1948). The significance of this finding was then unclear, since the age of the patients suggested that arteriosclerosis might have limited the rise in cerebral blood flow. It now seems reasonable to explain this abnormality on the basis of liver failure itself rather than coexisting vascular disease. Some reduction in the response of cerebral blood flow to $\text{CO}_2$ might be expected since this tends to fall when there is a decrease in both the resting flow (Ackerman, Zilkha, Bull, DuBoulay, Marshall, Ross Russell & Symon, 1973) and cerebral metabolic rate for $\text{O}_2$ (Fujishama, Scheinberg, Busto & Reinmuth, 1971). However, the decline in the slope of the response of cerebral blood flow to $\text{CO}_2$ was proportionally far greater than the fall in the resting flow and metabolic rate, even taking into account the further reduction of metabolic rate in hypercapnia. The results therefore indicate a more fundamental cause for the depression in the cerebral circulatory $\text{CO}_2$ responsiveness. Possibly a loss of the reaction of the cerebrovascular smooth muscle to $\text{CO}_2$ (Cow, 1911; Severinghaus, 1968) or of the autonomic control mechanisms (James, Millar & Purves, 1969) may be implicated. Alternatively the findings may reflect a regional variation in the severity of the cerebral disorder with the greatest metabolic depression occurring in the brain stem; lesions at this site may depress the $\text{CO}_2$ responsiveness of cerebral blood flow proportionally much more than the change in its resting value (Shalit, Reinmuth, Shimojyo & Scheinberg, 1967). No direct information concerning this hypothesis can be provided by the present technique, which measures flow and arteriovenous $\text{O}_2$ difference across the hemispheres rather than the brain stem. However, several of the clinical (Posner & Plum, 1960) and electroencephalographic aspects of hepatencephalopathy (Parsons-Smith, Summerskill, Dawson & Sherlock, 1957) could arise from the midline structures, and a disturbance of brain-stem function could provide a common basis for the decrease in both $\text{CO}_2$ responsiveness of cerebral blood flow and of the ventilatory response to $\text{CO}_2$.

Clinical implications

The normal increase in cerebral blood flow during hypercapnia damps the effects of increased arterial $\text{PCO}_2$ on brain tissues $\text{Paco}_2$ (Lassen, 1959). However, in liver failure this homeostatic mechanism is blunted, thereby enhancing the effects of cerebral hypercapnia arising from the depression in respiratory chemosensitivity. The dangers of hypercapnia in hepatic cirrhosis were described by Posner & Plum (1960) and were confirmed in the present study by the fall in cerebral metabolic rate for $\text{O}_2$ induced by $\text{CO}_2$ breathing in the goats with liver failure. The possible clinical relevance of this adverse response to exogenous $\text{CO}_2$ is that cerebral function may be similarly impaired when a patient with liver failure is exposed to respiratory depressants, such as narcotic drugs (Loeschke, Sweel, Kough & Lambertsen, 1953), tranquillizers (Renzetti & Padget, 1957), certain diuretics (Goldring, Cannon, Heinemann & Fishman, 1968) and anaesthetic agents (Dripps & Severinghaus, 1955). These observations on the deleterious
effects of increased cerebral \( P_{CO_2} \) cast doubt on earlier suggestions that correction of alkalosis might be useful in treating liver disease (Roberts, Thompson, Poppell & Vanamee, 1956; Warren, 1958). On the contrary, the demonstration that artificially increasing the arterial pH in hepatic coma may be accompanied by clinical improvement as well as increases in cerebral blood flow and metabolic rate (James et al., 1969) indicates that the extracellular alkalosis is probably beneficial.

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