

Cerebral blood flow and oxygen uptake, and cerebrospinal fluid biochemistry in severe coma¹

POUL BRODERSEN² AND ERIK O. JØRGENSEN

From the Departments of Neurology, Clinical Physiology, Anaesthesiology, and Psychiatry, Bispebjerg Hospital, and Medical Department B, Rigshospitalet, Copenhagen, Denmark

SYNOPSIS Thirty-eight patients in coma due to head trauma, cerebrovascular accidents, hypoxia, hypoglycaemia, or barbiturate intoxication, and 15 cases of brain death were studied. Cerebral metabolic rate of oxygen (CMRO₂) was obtained from the arteriovenous oxygen difference and cerebral blood flow (CBF) measured by intra-arterial ¹³³Xenon method. If hypothermia and CNS depressants were excluded, CMRO₂ below one-third of normal was incompatible with regaining of consciousness, but this was seen in only three comatose patients. Irrespective of the clinical outcome (death, vegetative survival, or recovery), CMRO₂ values of one-third to two-thirds of normal were seen in the majority of coma patients. CMRO₂ measurements were of no practical value to predict the prognosis in coma, even when the effect of temperature and sedatives were considered. In brain death the CBF studies gave indirect evidence of cerebral circulatory arrest. The cerebrospinal fluid (CSF) was obtained for analysis of lactate, pyruvate, and bicarbonate in 29 cases. Increased CSF lactate levels were found in all groups except barbiturate intoxication. The finding of a negative correlation between CSF bicarbonate and log CBF suggests that the CSFpH determines the wide range of CBF in coma.

Kety (1949) noticed that in all conditions of semicoma or coma of whatever cause, the reduction of the level of consciousness correlated with the decrease of cerebral oxygen uptake. In coma the cerebral oxygen uptake was reduced to below 2.0 ml./100 g/min, while the normal value for awake man is about 3.3 ml./100 g/min (Kety, 1949; Lassen, 1959). Shalit *et al.* (1970) and Shalit *et al.* (1972) studied cerebral blood flow (CBF) and arteriovenous oxygen difference, (a-v) O₂ for obtaining the cerebral metabolic rate of oxygen (CMRO₂ = (a-v) O₂ × CBF × 1/100) in comatose neurosurgical patients. They found that patients who regained consciousness never had CMRO₂ values below 1.4 ml./100 g/min. When the CMRO₂ was below 1.0 ml./100 g/min, a rapid decompensation of vital brain mechanisms such as spontaneous respiration and

blood pressure regulation occurred, followed by death within a few days. Similar findings in head injury have recently been reported by Tabbador *et al.* (1972).

The existence of critical levels of CMRO₂ might be important for assessing the prognosis in comatose patients. It has been the purpose of the present study to extend the observations of Shalit *et al.* (1970). In addition to CBF, (a-v) O₂, and CMRO₂, we studied acid-base parameters in the cerebrospinal fluid (CSF). This part of the study offered the opportunity of correlating CSF acid-base parameters to CBF in a variety of comatose states.

METHODS

Sixty-seven studies were performed in 53 patients. Thirty-five were in coma defined as 'unrousable unresponsiveness' (Plum and Posner, 1972) at the time of the first study. Three patients did not fit the term coma, although they were included in the Tables and Figures as comatose. One of these was stuporous

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² Address for correspondence: Dr. Brodersen, Department of Neurology, Bispebjerg Hospital, DK-2400 Copenhagen NV, Denmark.

due to a severe migraine attack. Another was in a state of wakeful unresponsiveness during recovery after cardiac arrest. The third was a cardiac arrest patient, with electroencephalogram (EEG), clinical and necropsy findings corresponding to the description of the apallic syndrome given by Ingvar and Brun (1972). Fifteen cases had brain death when initially studied, and two more patients were studied both in a state of coma and later after brain death.

The first study was usually performed within one to three days of the lesion, but in a few was delayed between four and 14 days. Six patients had two studies, and four patients had three subsequent studies. The respiration was either spontaneous, assisted, or artificial.

The general diagnosis and the outcome are given in Table 1. None of the head trauma patients had an unoperated mass lesion at the time of the study. The

cerebrovascular group comprised five patients with subarachnoid haemorrhage due to ruptured aneurysms, two cases of intracerebral haemorrhage, and one severe migraine attack. The hypoxia group comprised three patients with a brain lesion (infarct of encephalitis) combined with respiratory insufficiency, four patients with carbon monoxide intoxication, and 10 patients resuscitated for cardiac arrest; five patients in the hypoxia group had cardiac arrest complicating a barbiturate intoxication. Eight patients were in deep coma due to severe barbiturate overdose.

The following criteria were fulfilled for a diagnosis of brain death: deep coma with no spontaneous movements or reaction to painful stimuli except spinal reflexes (Jørgensen and Brodersen, 1971); irreversible loss of spontaneous respiration and cranial nerve reflexes; a flat EEG recorded for 30 minutes. If intoxication with central nervous system (CNS) depressants were suspected or if body temperature were 32° C or below, carotid or aorto-cervical angiography was carried out before the diagnosis of brain death was accepted.

Cerebral blood flow was measured using the internal carotid ¹³³Xenon injection method (Høedt-Rasmussen *et al.*, 1966; Paulson *et al.*, 1969; Olesen *et al.*, 1971). Either a single 5 cm diameter detector or multiple detector equipments with 16 or 35 small detectors were used. The bulb of the internal jugular vein was punctured and simultaneous samples obtained for determination of the (a-v) O₂ and the venoarterial lactate difference, (v-a) lactate. After the flow study a lumbar puncture was performed if the clinical state did not contraindicate this procedure. The CSF pressure was measured and 5 ml. CSF was withdrawn for lactate, pyruvate, and bicarbonate analysis.

Lactate and pyruvate were determined in blood

TABLE 1

GENERAL DIAGNOSIS AND OUTCOME
OF 53 COMATOSE PATIENTS

| | Regained conscious- ness | Remained in coma | Brain death | Total |
|---|--------------------------------|------------------------|----------------|-------|
| Head trauma | 2 | 4 | 4 | 10 |
| Cerebrovascular lesions | 2 | 2 | 4 | 8 |
| Prolonged hypoglycaemia | — | 3 | — | 3 |
| Hypoxia | 2 | 13 | 7 | 22 |
| Barbiturate intoxication | 8 | — | — | 8 |
| Others (brain abscess, brain tumour) | — | — | 2 | 2 |
| Total | 14 | 22 | 17 | 53 |

Out of 14 patients, who regained consciousness, only the eight with barbiturate intoxication recovered completely, whereas the other six patients showed signs of intellectual reduction and/or focal neurological deficit.

TABLE 2

CEREBRAL BLOOD FLOW AND RELATED PARAMETERS IN COMA: MEDIAN AND RANGE OF MAJOR GROUPS

| | Patients (no.) | Studies (no.) | Age (yr) | Body tempera- ture (° C) | MABP (mmHg) | CSF pressure (mmHg) | PaCO ₂ (mmHg) | CBF (ml./100 g/ min) | (a-v) O ₂ (vol. %) | CMRO ₂ (ml./100 g/ min) |
|--|-------------------|------------------|-------------|--------------------------------|----------------|---------------------------|-----------------------------|----------------------------|----------------------------------|--|
| Head trauma | 7 | 9 | 26 19-62 | 37.0 33.7-39.2 | 96 50-143 | — | 35 18-57 | 26 6-48 | 5.7 3.7-8.1 | 1.8 0.3-2.4 |
| Cerebrovascular lesions | 4 | 6 | 54 23-58 | 37.0 33.0-37.1 | 99 83-180 | 15 12-18 | 32 12-39 | 29 8-61 | 7.5 4.1-8.6 | 1.6 0.6-2.1 |
| Posthypoglycaemic coma | 3 | 3 | 47 38-52 | 37.4 37.2-38.9 | 100 100-110 | 11 7-12 | 29 27-30 | 36 27-55 | 4.3 3.9-5.3 | 1.4 1.4-2.4 |
| Cardiac arrest | 9 | 13 | 60 38-77 | 37.5 37.1-39.5 | 83 67-110 | 14 4-34 | 33 22-43 | 24 11-85 | 5.3 1.3-8.2 | 1.4 0.4-2.1 |
| Cardiac arrest and barbiturate intoxication | 5 | 7 | 56 36-59 | 37.1 29.0-37.7 | 80 63-117 | 17 6-24 | 32 14-44 | 29 8-71 | 3.9 2.7-9.1 | 0.8 0.6-2.1 |
| Barbiturate intoxication | 8 | 8 | 56 32-81 | 33.7 31.5-34.9 | 89 73-107 | 11 7-13 | 27 17-39 | 16 10-21 | 6.0 3.2-8.3 | 0.85 0.6-1.1 |

and CSF using enzymatic spectrophotometric analysis (Bergmeyer, 1963). CSF bicarbonate was determined by the Conway technique (Conway, 1950). Calculation of (a-v) O₂ was made after determination of oxygen saturation percentage using saponin haemolysis and spectrophotometric analysis (Holmgren and Pernow, 1959). No correction for physically dissolved oxygen was performed. The arterial PCO₂ (PaCO₂) was determined using a Severinghaus PCO₂ electrode. PaCO₂ was measured at 38° C and corrected to body temperature using the Blood Gas Calculator (Severinghaus, 1966).

In cases of suspected brain death the EEG was recorded as previously described (Jørgensen and Brodersen, 1971).

From the first 10 minutes of the linearly recorded ¹³³Xenon clearance curve, CBF₁₀ was calculated using the height over area method (Høedt-Rasmussen *et al.*, 1966). When using the multi-detector instrument, a mean of all channels was used for CMRO₂ calculation.

Studies in hypothermic man and animals have shown that CMRO₂ decreases about 15% per degree centigrade and that there is a linear correlation between body temperature and log CMRO₂ (Bering, 1961; Olesen, in press). CMRO₂ values obtained during hypothermia were therefore corrected to 37° C using the equation (Olesen, in press): CMRO₂(1) = CMRO₂(2) × 10^{(t₁-t₂) × 0.067}. Values of CMRO₂ in febrile patients were not corrected, as no clear

correction factor for hyperthermia was available in the literature.

RESULTS

PATIENTS IN COMA CBF—CMRO₂ Table 2 gives the median and ranges of CBF, CMRO₂, and related parameters in 38 patients, grouped according to the general diagnosis. Generally CBF was reduced but a wide range of CBF levels was observed. Barbiturate intoxications all had reduced CBF and lowered body temperatures as well. CBF values far above normal were seen in two patients with cardiac arrest. The PaCO₂ levels were generally moderately hypocapnic.

Subnormal (a-v) O₂ values were observed in all groups, whereas (a-v) O₂ levels above normal were rarely met, and then only in combination with very low flows of the order of 10–20 ml./100 g/min. CMRO₂ was reduced in all patients in coma to levels below 2.5 ml./100 g/min with most of the observations in the range 1.0–2.0 ml./100 g/min. Patients with uncomplicated barbiturate intoxication usually had CMRO₂ levels below 1.0 ml./100 g/min, compatible with complete recovery.

The lumbar CSF pressures were within normal

TABLE 3
CSF ACID-BASE VARIABLES IN COMA AND BRAIN DEATH: MEDIAN AND RANGE

| | Patients (no.) | Samples (no.) | CSF | | | | Blood | | |
|--|-------------------|------------------|----------------------|-----------------------|---------------------|--|----------------------------------|---|--|
| | | | Lactate (mmol/l.) | Pyruvate (mmol/l.) | Lactate pyruvate | HCO ₃ ⁻ (mmol/l.) | Arterial lactate (mmol/l.) | Int. jug. ven. lactate (mmol/l.) | Average v-a lac- tate diff. (mmol/l.) |
| Posthypoglycaemic coma | 3 | 3 | 4.05 2.86–4.30 | 0.360 0.274–0.425 | 12.0 6.7–14.8 | 16.1 15.3–20.0 | 1.24 1.10–2.04 | 1.16 1.12–2.33 | 0.08 SD 0.11 NS |
| Cardiac arrest | 8 | 12 | 4.05 2.26–8.71 | 0.240 0.150–0.465 | 16.5 11.6–22.1 | 22.3 17.9–27.6 | 1.41 0.71–3.08 | 1.42 0.81–3.35 | 0.17 SD 0.04 P < 0.01 |
| Cardiac arrest and barbiturate intoxication | 5 | 5 | 3.83 1.98–7.29 | 0.275 0.144–0.418 | 17.4 13.8–23.6 | 21.6 12.6–23.2 | 1.93 0.54–4.99 | — | — |
| Barbiturate intoxication | 5 | 5 | 1.76 1.22–2.54 | 0.111 0.101–0.131 | 15.6 11.1–22.4 | 24.1 18.5–27.3 | 1.54 0.98–2.51 | 1.75 1.01–2.34 | 0.06 SD 0.14 NS |
| Brain death | 8 | 8 | 7.44 2.82–10.99 | 0.256 0.093–0.420 | 32.4 17.5–49.8 | 17.0 10.3–31.8 | 1.73 0.74–3.25 | 2.52 0.95–2.94 | 0.32 SD 0.43 NS |
| Normal values | | | | | | | | | |
| Mean | 13 | 13 | 1.54 | 0.124 | 12.3 | 23.6 | 0.70 | — | — |
| SD | | | 0.31 | 0.010 | 1.9 | 0.9 | 0.35 | | |

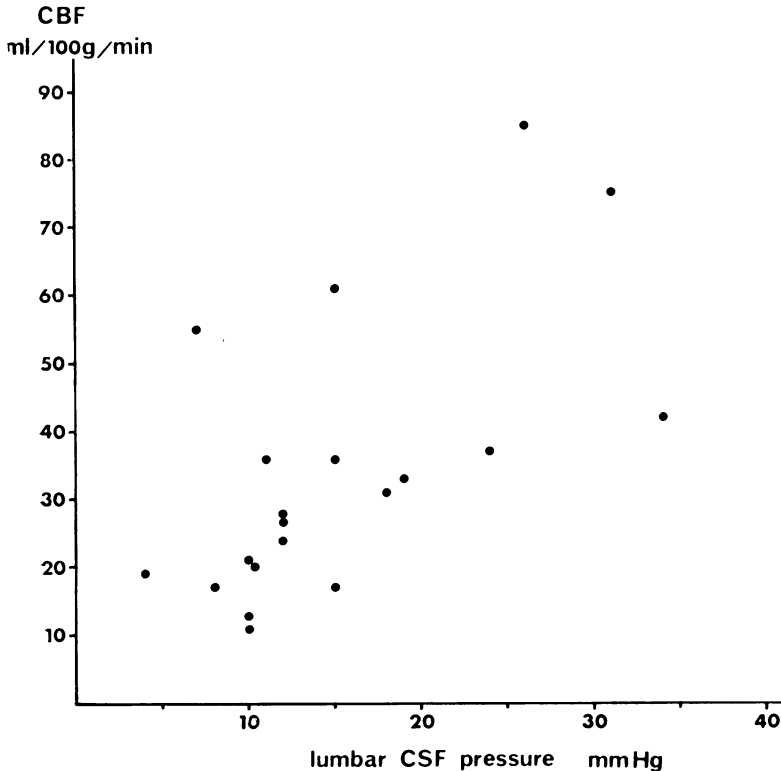


FIG. 1. The relationship between the lumbar CSF pressure and CBF in coma. The line of regression with a coefficient of correlation, $r=0.62$ was not shown because of uneven distribution of the observations.

limits except in four studies where moderately elevated pressures (about 30 mmHg) were observed. None of the head trauma patients had a lumbar puncture.

In every case of head trauma, cardiac arrest, or posthypoglycaemic coma where the multi-detector instrument was applied, a strikingly uneven distribution of flow was noticed.

Cerebrospinal fluid The CSF data and blood lactate levels are given in Table 3. Patients with uncomplicated barbiturate intoxication had CSF lactate, pyruvate, lactate/pyruvate (L/P) ratios, and bicarbonate levels that did not deviate significantly from normal. The combination of hypocapnia and normal CSF bicarbonate levels in this group of patients suggests a CSF pH above normal.

The other groups studied all showed evidence of a CSF lactacidosis. Patients in posthypoglycaemic coma probably had increased CSF lactate levels because of respiratory insufficiency

after correction of the hypoglycaemia. In cardiac arrest patients the CSF changes seemed to be independent of additional barbiturate overdose. The combination of increased CSF lactate and L/P ratio in these patients pointed to the recent hypoxic-ischaemic episode. Wide ranges of lactate levels were observed, probably reflecting differences in the duration of the cardiac arrest and different time intervals from resuscitation to CSF sampling. An elevated arterial lactate concentration was noted in all the groups. Despite a large concentration gradient between CSF and arterial blood, only small v-a lactate differences were found. This observation is in agreement with a rather low blood-brain barrier permeability for lactate (Oldendorf, 1972).

Correlations The wide CBF ranges could not be explained by differences in PaCO_2 , because there was no correlation between PaCO_2 and CBF.

Figure 1 shows the lumbar CSF pressures and CBF. It appears that the CSF pressure was not a

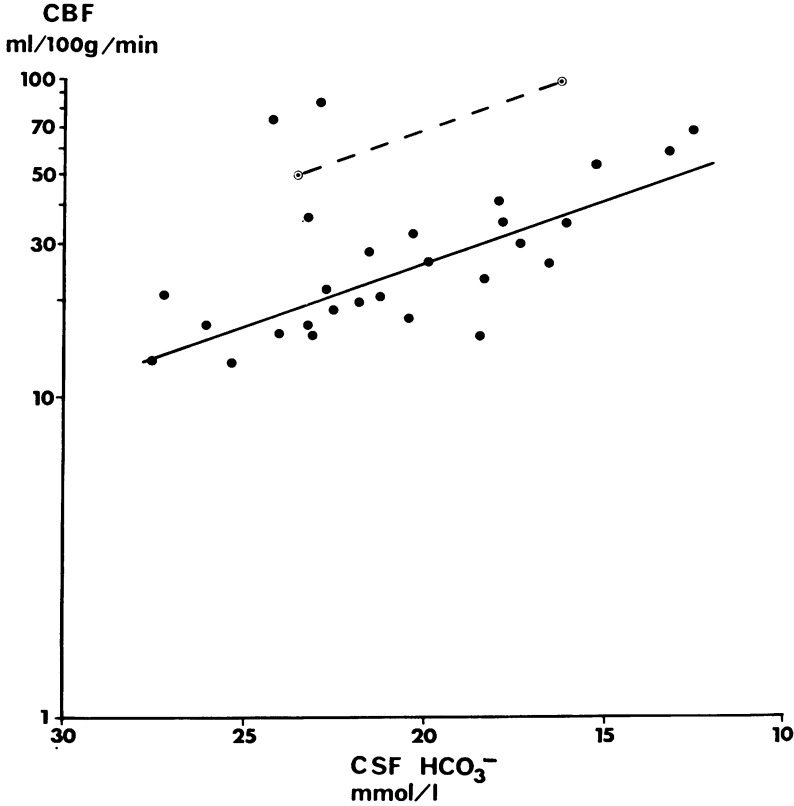


FIG. 2. The relationship between CSF bicarbonate and log CBF in coma. The line of regression: $y = \bar{y} 0.04x + 2.23$, $r = 0.8$, $P < 0.001$. The broken line indicates an expected correlation for normal man. Assuming a doubling of flow at PaCO_2 60 mmHg, a CSF pH of 7.20 was calculated. Then a CSF bicarbonate of 16.3 mmol/l. was calculated assuming a PaCO_2 of 40 mmHg and a CSF pH of 7.20.

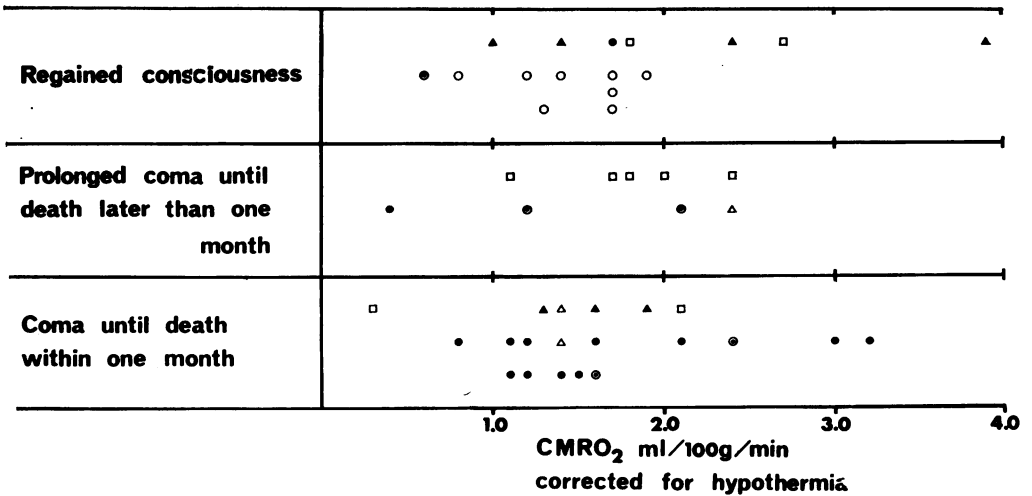


FIG. 3. Temperature corrected CMRO_2 values in coma correlated with the outcome. \square head trauma, \blacktriangle cerebrovascular lesions, \triangle hypoglycaemia, \bullet hypoxia, \circ barbiturate intoxication, \odot barbiturate intoxication + cardiac arrest.

limiting factor inducing low flow. On the contrary, the CSF pressure may be considered a function of CBF in this group of patients.

Figure 2 gives the relationship between the CSF bicarbonate and log CBF. Patients with PaCO₂ levels in the range 18–44 mmHg were included. All observations in Fig. 2 seemed to fit a linear correlation, except two studies in one patient. The linear CSF bicarbonate–log CBF correlation may be considered evidence of a CSFpH–log CBF correlation with some reservations (see Discussion).

No absolute correlation between CBF and prognosis was observed. Generally CBF below half of normal or considerably above normal was a bad prognostic sign, if barbiturate overdose or hypothermia were excluded.

Looking for a possible correlation between CMRO₂ and the outcome, CMRO₂ values were corrected for hypothermia (Fig. 3). There was a marked overlapping of the CMRO₂ ranges in the three groups with a different outcome. When patients with barbiturate overdose were excluded, only CMRO₂ levels below 1.0 ml./100 g/min seemed to predict a poor outcome. This was, however, observed in only three cases, two of which died within 24 hours whereas the third remained in an apallic state until death after seven months. The data shown in Fig. 3 indicate that CMRO₂ measurements were of no practical value in predicting the prognosis in coma, not even when the effects of sedatives and body temperature were considered.

BRAIN DEATH Eighteen studies were performed in 17 cases of brain death. The CBF study in every case showed severely abnormal ¹³³Xe washout curves. The configuration of these curves indicated that the isotope did not reach the brain, and this was considered indirect evidence of cerebral circulatory arrest. The (a-v) O₂ was reduced to a range of 0–5.5 vol% with a median of 1.3 vol%.

A marked increase of the CSF lactate concentration was observed in brain death (Table 3), but there was some overlapping with the CSF lactate ranges seen in comatose patients after cardiac arrest. A striking increase of the CSF L/P ratio was noticed only in brain death.

DISCUSSION

Our CBF, (a-v) O₂, and CMRO₂ results in acute head trauma, post-hypoglycaemic coma, and cardiac arrest corresponded with previous studies (Fazekas *et al.*, 1951; Lindgren *et al.*, 1968; Shalit *et al.*, 1970, 1972; Bruce *et al.*, 1972; Fieschi *et al.*, 1972). The lowest CBF and CMRO₂ levels in barbiturate intoxication were only about half of those previously reported (Malmlund, 1968; Bès *et al.*, 1971). This may be explained by selection of patients. Our patients were considered the severest type of overdose. They all needed artificial ventilation, and their serum barbiturate concentrations ranged from 8 to 50 mg/100 ml. (read as aprobarbital or barbital). Their EEGs showed 'burst-suppression' with flat periods of 3 to 100 seconds.

We found no report in the literature on CSF data in patients after cardiac arrest, prolonged hypoglycaemia, or during barbiturate overdose. In animal experiments transient elevations of CSF lactate, pyruvate, and L/P ratio have been demonstrated after either asphyxia or hypotension (Kaasik *et al.*, 1970a, b). Such experimental conditions differ markedly from resuscitation of a patient suffering from cardiac arrest. The CSF changes of our cardiac arrest patients lasted several days, whereas similar CSF changes in the animal experiments lasted only minutes to hours.

It may be questioned whether the lumbar CSF pressures given in Fig. 1 really corresponded to the intraventricular fluid pressure. As most of the pressures were within normal limits, no major discrepancies would be expected. Fieschi *et al.* (1972) in head trauma patients with rather low intraventricular pressures found a correlation between the intraventricular fluid pressure and CBF similar to our Fig. 1. In patients with mass lesions and high intraventricular fluid pressure levels, the relationship between intraventricular fluid pressure and CBF may be more complex (Bruce *et al.*, 1972).

We did not find a correlation between CBF and PaCO₂, not even when the CBF values were corrected to a normal CMRO₂ by multiplying by 3.3/CMRO₂. Since our patients had relatively stable PaCO₂ levels for several hours, their CSF pH might be considered 'adapted' to the PaCO₂ level. PaCO₂ changes influence CBF by

changes in the extracellular fluid pH around the brain arterioles (Skinhøj, 1966; Lassen, 1968). The CSF pH, which at a steady state is assumed to equal the pH of the brain extracellular fluid, is mainly determined by the ratio between bicarbonate and CO_2 . The latter rapidly crosses the blood brain barrier, whereas the bicarbonate ion is impeded. After a reduction of the PaCO_2 , the CSF PCO_2 decreases and CSF pH increases. During some hours the CSF bicarbonate is gradually reduced and CSF pH approaches normal. This sequence is usually named CSF pH adaptation.

As our patients were considered adapted to their PaCO_2 level, a lack of correlation between PaCO_2 and CBF was to be expected. In these circumstances, the finding of a close correlation between CSF bicarbonate and log CBF speaks in favour of the CSFpH determining CBF, even in coma with the wide range of flows observed.

Based on [the Henderson-Hasselbach equation, pK values, and solubility coefficients for CO_2 (Mitchell *et al.*, 1965), CSF bicarbonate, and estimates of CSF PCO_2 , we calculated the CSF pH. We estimated the CSF PCO_2 as PaCO_2 plus 8 mmHg, which is the normal difference between CSF PCO_2 and PaCO_2 . There was also a linear correlation between calculated CSF pH and log CBF. It should be admitted, however, that the estimation of CSF PCO_2 involves considerable uncertainty in patients with a brain lesion (Gordon and Rossanda, 1968). For this reason we preferred to show only data that were measured—that is, CSF bicarbonate and CBF.

The line of regression in Fig. 2 was situated below and parallel to a line of regression assumed to be valid for awake normal man. This means that changes of the CSF pH cannot account for a reduction of CBF, when wakefulness changes to coma. Variations of CBF in comatose states seem, however, to depend upon the CSF pH.

It might be expected that in case of severe brain oedema, low CBF might occur in the presence of CSF and brain tissue acidosis (Frei *et al.*, 1971). Such coma patients were not exposed to lumbar puncture in the present study because of the risk of herniation.

Two observations in one patient on the first and second day after cardiac arrest were situated far above all other observations in Fig. 2. It is tempting to suggest that the luxury perfusion

(Lassen, 1966) in this patient might have been caused by some other agent than the hydrogen ion. Potassium which has been shown to cause cerebral vasodilatation (Kuschinsky *et al.*, 1972) might be suspected, but no analysis for CSF potassium concentration was performed in this patient.

A main purpose of this study was to analyse the relationship between CMRO_2 and the prognosis in coma. Generally, our findings were in agreement with those of Shalit *et al.* (1970, 1972), Tabbador *et al.* (1972), and the study of Gordon and Bergval (1972). We also found that recovery was seen after CMRO_2 depression to values below half of normal. Our study especially showed that CMRO_2 levels below about one-third of normal were only followed by recovery if either hypothermia and/or sedatives were present. These factors significantly influence both CBF- CMRO_2 and the clinical examination. Body temperature and sedatives should therefore always be taken into account when evaluating comatose patients.

Our data in Fig. 3 led us to conclude that CBF- CMRO_2 measurements were of no help in predicting the outcome in comatose patients. We therefore find it without clinical implications to look further for critical CMRO_2 levels.

BRAIN DEATH Although characteristic abnormalities were identified in every ^{133}Xe washout curve in brain death, we would not recommend this method for the diagnosis of brain death. The washout curve abnormalities were interpreted as indirect evidence of no CBF, but the curve analysis might be inconclusive unless several precautions with regard to position of catheter and isotope injection were taken. Similar experience was published by Hadjidimos *et al.* (1969). Furthermore, the intra-arterial ^{133}Xe method measures CBF only supratentorially, which is not quite sufficient for a diagnosis of brain death.

The (a-v) O_2 was of no value for the diagnosis of brain death, as suggested by Bès *et al.* (1969). Although usually reduced to below 3 vol% in brain death, similar levels were seen in patients with luxury perfusion.

CSF lactate levels seemed to be of no help either because of overlap with the range in cardiac arrest patients. Thus we were unable to

confirm the suggestion by Paulson *et al.* (1972).

It is the experience of several authors as well as ourselves that a four vessel angiography is the method of choice for cases where a prompt diagnosis of brain death is required irrespective of distracting lesions, sedation, or hypothermia (Jørgensen and Brodersen, 1971).

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