ACID-BASE AND GAS TENSION MEASUREMENTS IN CEREBROSPINAL FLUID

M. ROSSANDA AND E. P. SGANZERLA

The acid-base balance of cerebrospinal fluid (c.s.f.) has been studied extensively during the last 25 years, especially in connection with the respiratory physiology and the central regulation of ventilation. Great attention has also been paid to the significance of hydrogen ion homeostasis in c.s.f., and to the mechanisms involved in the maintenance of a constant c.s.f. pH in various conditions associated with acid-base derangements in blood. These topics have been reviewed previously (Cameron, 1969; Leusen, 1972; Siesjo, 1972; Plum and Siesjo, 1975). In the last decade, interest in c.s.f. acid-base balance and gas tension has increased further in the neurological sciences, following the realization that c.s.f. acidosis can reflect an impaired cerebral redox state. In the same period, it has been demonstrated that c.s.f. pH plays a central role in the regulation of cerebral blood flow (Lassen, 1968). The measurement of c.s.f. pH, bicarbonate and gas tensions has also been identified as a possible clinical approach to the study of cerebral blood flow and metabolism in conditions associated with brain hypoxia. However, the clinical application of c.s.f. tests in neuroanaesthesia and neurosurgical intensive care has been limited by both theoretical and practical considerations.

C.S.F. ACID-BASE PARAMETERS IN MAN

The normal c.s.f. acid-base parameters shown in table I were found by Van Heijst, Maas and Visser (1966) in the most accurate study available in normal men under steady-state respiratory conditions with simultaneous sampling from an artery, the lumbar space and the cisternae. Normal controls from Plum and Price (1973) are also shown. Several other studies on humans in near-normal conditions, reported in detail by Siesjö (1972) and Plum and Siesjö (1975), confirm that c.s.f. pH is less than arterial plasma pH by 0.06–0.10 units, and that this difference is caused by greater PCO₂ in c.s.f., with the bicarbonate concentration being substantially the same in c.s.f. and plasma. In lumbar cerebrospinal fluid, the pH is less by 0.02 units and the PCO₂ greater by 3 mm Hg than in cisternal fluid.

In patients with metabolic acid-base disturbances the same relations were found between lumbar and cisternal fluid (Plum and Price, 1973). These authors observed that this relationship can be lost in critically ill patients; therefore, lumbar c.s.f. should not be used as a reliable index of the cerebral acid-base state, especially in patients with acute circulatory imbalance (Rossanda, 1969; Kalin et al., 1975).

In cerebral diseases not associated with severe systemic changes (table I) the difference between lumbar and intracranial fluids is not so important as completely to invalidate measurements on lumbar samples.

FACTORS INFLUENCING C.S.F. ACID-BASE COMPOSITION

In c.s.f., pH depends only on the carbon dioxide tension and the bicarbonate concentration; no other buffer anions are normally present in significant amounts. The acid–base composition of c.s.f. will therefore be influenced by the following factors: (i) the diffusion equilibria of carbon dioxide between blood and c.s.f. in the different compartments of the cerebrospinal cavity, (ii) the distribution of hydrogen and bicarbonate ions across the blood–brain and the blood–c.s.f. barriers and (iii) the rate of release, from the brain cells, of acid metabolites which titrate bicarbonate.

Carbon dioxide diffusion. Carbon dioxide diffuses rapidly across the blood–brain and the blood–c.s.f. barriers. A change of PaCO₂ is therefore reflected within a few minutes in the intracranial fluid and...
<table>
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<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>Arterial blood</th>
<th>Intra-cranial fluid</th>
<th>Lumbar fluid</th>
<th>Arterial blood</th>
<th>Intra-cranial fluid</th>
<th>Lumbar fluid</th>
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<td>—</td>
<td>43.5</td>
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<td>—</td>
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<td>—</td>
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<td>40.5</td>
<td>43.2</td>
<td>20.6</td>
<td>20.8</td>
</tr>
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</table>

* Van Heijst, Maas and Visser (1966); † Plum and Price (1973); ‡ Gordon and Rossanda (1970); § Christensen and colleagues (1973); || Kalin and colleagues (1975); (* † § ||: cisternal samples; ‡ ventricular samples).
somewhat later in the lumbar fluid (Fisher and Christianson, 1963). Full equilibrium may require a longer time, up to 30 min (Bradley, Semple and Spencer, 1965). During a steady state of respiration c.s.f. $P_{CO_2}$ is about 1 mm Hg greater than the arithmetic mean of arterial and venous $P_{CO_2}$ (Pontén and Siesjö, 1966; Plum and Price, 1973). This corresponds to the reported c.s.f.–arterial $P_{CO_2}$ difference of 6 mm Hg for cisternal fluid. The c.s.f.–arterial $P_{CO_2}$ difference is much greater in experimental conditions of reduced cerebral blood flow, such as severe hypotension (Siesjö and Zwetnow, 1970) and brain oedema (Siesjö et al., 1967).

Ion distribution across the blood–brain and the blood–c.s.f. barriers. These are influenced by concentration gradients, electrochemical gradients and possibly active transport processes taking place within the barriers themselves. Active transport of hydrogen ion has been assumed by Severinghaus and colleagues (1963), and questioned by Siesjö and Kjällquist (1969). Maren (1972) suggested that bicarbonate ions are secreted by the choroid plexus during the process of c.s.f. production. Whatever the mechanism involved, it is well established that a difference in hydrogen ion concentration prevails between arterial plasma and c.s.f. in normal conditions, and that this difference can be greatly increased and maintained for long periods in subjects with non-respiratory acid–base derangements (Posner, Swanson and Plum, 1965).

The rate of release of acid metabolites from the brain cells. The extracellular fluid (e.c.f.) of the brain and the intracranial c.s.f. are not separated by any anatomical barrier, and are actively mixing and exchanging during the slow c.s.f. circulation. They can be considered identical in their ionic composition therefore, at least in conditions which are not associated with massive obstacles either to c.s.f. circulation or to brain pulsation and movement.

The end-product of glycolysis, lactic acid, is normally released into c.s.f. by non-ionic diffusion and reacts stoichiometrically with c.s.f. bicarbonate as a result of the absence of other buffer anions. When the rate of glycolysis increases, larger amounts of lactate enter the c.s.f., causing a corresponding decrease of bicarbonate; this occurs in two different situations, both of interest to neuroanaesthetists: respiratory alkalosis and cerebral hypoxia.

C.S.F. ACID–BASE CHANGES IN RESPIRATORY ALKALOSIS

Considerable experimental and clinical evidence, recently reviewed by Siesjö and colleagues (1974) and Plum and Siesjö (1975), leads to the following conclusions.

(1) In respiratory alkalosis, glycolysis increases because of activation of phosphofructokinase, but there is no evidence of tissue hypoxia; in particular, the lactate/pyruvate (L/P) ratio is not increased, showing the absence of changes in the equilibrium of the redox system:

$$\frac{NADH}{NAD^+} = \frac{\text{lactate}}{\text{pyruvate}} \cdot K$$

Only in cases of extreme hypocarbia, when $P_{CO_2}$ is decreased to less than 15 mm Hg, is there some evidence of tissue hypoxia. This can be attributed, perhaps, to the summation of a severely reduced cerebral blood flow and the Bohr effect leading to increased oxygen affinity of haemoglobin.

(2) In hyperventilation resulting from altitude there is a progressive reduction in the bicarbonate concentration and a correction of c.s.f. pH from the original alkalotic value towards normal.

(3) A full correction of the c.s.f. alkalosis produced by hypocarbia is never seen in experiments with passive non-hypoxic hyperventilation. This follows from the data reported by Paddle and Semple (1969), Hunter (1970) and Campkin and colleagues (1974) who measured bicarbonate, lactate and pyruvate ion concentrations during anaesthesia with hyperventilation for neuroradiological or neurosurgical procedures.

It can be concluded that anaesthesia with hyperventilation, as usually practised in neurosurgery, is not accompanied in man by any evidence of cerebral hypoxia or activation of glycolysis that may reduce e.c.f. pH to normal, at least in a few hours. The lack of rapid compensation in man is at variance with the experimental evidence mentioned above. This is also relevant to anaesthetic management because, if a rapid correction took place during hypocarbic anaesthesia, an undesirable hyperaemia caused by rebound e.c.f. acidosis could be expected when hyperventilation was stopped.

C.S.F. ACID–BASE CHANGES IN CEREBRAL HYPOXIA AND ISCHAEMIA

The c.s.f. lactate concentration increases abruptly in animals subjected to hypoxic hypoxia (Cotev, Cullen and Severinghaus, 1968), to asphyxia or stagnant
hypoxia (Kaasik, Nilsson, and Siesjö, 1968) and to cerebrovascular ischaemia resulting from an acute deliberate increase of intracranial pressure (Zwetnow, 1968). The c.s.f. changes are usually delayed in comparison with the corresponding tissue changes; also, during recovery from the hypoxic insult, the disappearance of c.s.f. lactate may be slowed. The lactic acidosis is also accompanied by an increase in the L/P ratio. It is then possible to distinguish between the increase in lactate caused by hypoxaemia and that caused by cerebral hypoxia, because the former is accompanied by an actual alkalosis of c.s.f. and no change in L/P ratio, the latter by a low c.s.f. pH and an increased L/P ratio.

Unfortunately, the time relation between the hypoxic changes in brain tissue and c.s.f. in human subjects has not been clarified and the quantitative relation between brain tissue and c.s.f. changes is difficult to define. Clinical conditions associated with cerebral ischaemia do not involve the brain diffusely and homogeneously (Nilsson, Norberg and Siesjö, 1975). The e.c.f. composition will therefore vary between different regions of the brain and c.s.f. samples will hardly be representative of an “average” brain e.c.f. Moreover, the methods of assessment of cerebral hypoxia are still debated even in animal experiments, and there is simply no method of quantitative evaluation of cerebral hypoxia which can be applied to patients for clinical studies. However, even if one cannot expect a quantitative correlation, there is good clinical evidence that a non-respiratory acidosis of c.s.f. is indicative of cerebral hypoxia.

In a study of neurosurgical patients, Pontén and colleagues (1968) demonstrated that c.s.f. lactate was increased above 2 mmol/litre in most of the cases examined, with a fairly good correlation between increase of lactate and decrease of bicarbonate concentrations. In the same study most cases with increased lactate also showed an increased L/P ratio which confirmed the hypoxic nature of the lactic acidosis.

In comatose patients with brain lesions, Gordon and Rossanda (1968, 1970) found that c.s.f. pH was significantly decreased in comparison with non-comatose subjects, both in lumbar and ventricular samples. In these studies, the c.s.f. acidosis was not only of non-respiratory origin, as demonstrated by the decreased c.s.f. bicarbonate concentration, but also the result of a relatively great c.s.f. Pco₂. The c.s.f.–arterial Pco₂ difference was significantly increased, a finding indicative of poor tissue perfusion. Non-respiratory c.s.f. acidosis, sometimes associated with relatively great c.s.f. Pco₂, has also been described by Katsurada, Sugimoto and Onji (1969).

In patients with severe brain injury a non-respiratory c.s.f. acidosis was reported by Vapalahi (1970), by Zupping (1970), and by Metzel and Zimmermann (1971), who also demonstrated a marked increase in lactate in the most severe cases. Overgaard and Tweed (1974) found a lactic acidosis in the c.s.f. of patients with brain trauma during the first week after the injury.

According to Crockard and Taylor (1972) and Puig and Roda (1976), there is usually a correlation between the evolution of the c.s.f. lactic acidosis and the final outcome of the patient. However, in individual patients a bad prognosis may be associated with a low c.s.f. lactate concentration. A discrepancy between c.s.f. data and prognosis is not surprising. A marked cerebral ischaemia causing acute tissue hypoxia is typical of the severe brain injury (Pontén, Jagodziński, and Nilsson, 1973); in the subsequent course which is accompanied by serious circulatory derangements, the severity of tissue hypoxia can be influenced by several factors, such as hypoxaemia, high intracranial pressure and oedema. When patients are given treatment intended to minimize secondary brain hypoxia, such as fluid restriction, dexamethasone and hyperventilation, c.s.f. lactate may be found to be low even in cases of severe brain involvement (Fieschi et al., 1974). During hyperventilation, c.s.f. lactate was found to decrease in patients with brain injuries (Crockard, Coppel and Morrow, 1973), and an initial low c.s.f. bicarbonate increased towards the normal value during prolonged hypocarbia (Gordon and Rossanda, 1968).

At variance with these observations, Christensen and colleagues (1973) reported a study on patients following a stroke, who were hyperventilated for 3 days and showed a decrease of bicarbonate and increase of lactate in c.s.f. This was interpreted as a sign of adaptation to prolonged hypocarbia. C.s.f. pH was not measured directly but was calculated from the bicarbonate concentration and an assumed c.s.f.–arterial Pco₂ difference. This discrepancy may be caused by a different technique of ventilation, which involved prolonged anaesthesia and curarization without hyperoxia, accompanied by arterial hypotension; otherwise it is possible that elderly patients with focal lesions behave differently from patients with diffuse injury.

The occurrence of c.s.f. lactic acidosis has been described also in other acute cerebral diseases; in meningitis and encephalitis (Posner, Swanson, and
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Plum, 1965; Le Clainche, 1967; Riegel and Harms, 1967; Lyders-Hansen et al., 1974), in infantile hydrocephalus (Granholm and Siesjö, 1970), in asphyxiated neonates (Svenningsen and Siesjö, 1972), in some cases of Alzheimer's disease (Gottfries et al., 1974), and in coma following cardiac arrest (Brodersen, 1974; Kalin et al., 1975).

In a group of patients in coma after head injury and apoplexy, Zattoni and colleagues (1971) found a direct correlation between the degree of c.s.f. lactic acidosis and the severity of unconsciousness and of e.g. changes.

Subarachnoid haemorrhage (SAH) is often accompanied by a low c.s.f. pH, a low bicarbonate concentration (Froman and Crampton-Smith, 1966, 1967; Plum and Price, 1973) and a high lactate concentration with increased L/P ratio (Kagstrom, 1971). However, the significance of c.s.f. acidosis in SAH has been questioned because the blood shed in c.s.f. could be directly responsible for lactate production. This objection can be applied also to meningitis in cases of severe pleocytosis. However, Granholm (1968) argued that the changes found in SAH must be the result, at least in part, of actual cerebral hypoxia because there is a simultaneous increase in the L/P ratio, which cannot be explained by simple blood admixture; but the presence of blood and a high white cell count should be considered as a possible source of error in the evaluation of c.s.f. acidosis.

In an unpublished series of head injuries, Pontén (personal communication) noticed, in comatose patients, that high c.s.f. lactate and low bicarbonate were often associated with low arterial Po2. On the other hand, these patients were also the most severely injured, and the relationship was far from being constant. An attempt to correlate, in individual cases, the c.s.f. acid-base status, the clinical condition and outcome gave inconsistent results.

In conclusion, there is evidence that c.s.f. lactic acidosis can be interpreted as indicative of cerebral hypoxia in severe brain lesions, but the values recorded in single patients should be used with some caution as a diagnostic and still more as a prognostic tool.

C.S.F. OXYGEN TENSION

The oxygen tension in cerebrospinal fluid of man has been the subject of a number of studies (Bloor et al., 1961; Mollaret et al., 1964; Dunkin and Bondurant, 1966) but has found a much more limited place in clinical research than has c.s.f. acid-base balance. The study by Kazemi and colleagues (1968) concerning the dynamics of oxygen transfer in c.s.f. of dogs has cast some doubt on the validity of c.s.f. Po2 as representative of a mean cerebral e.c.f. Po2. The Po2 gradients between the different c.s.f. compartments are greater than for Pco2: the values are higher in the cisterna magna and lower in the lumbar space (47 and 31 mm Hg according to Ganshirt, 1968). During oxygen breathing a greater transfer is likely to take place from the vascular network of the choroid plexus to c.s.f. than across the blood–brain barrier. Evidence of direct oxygen transfer from the arteriolar blood to c.s.f. can be found during hyperbaric oxygen therapy (Hollin et al., 1968).

All these considerations, together with the technical difficulties of accurate measurement which will be discussed in the next section, may have discouraged further attempts to use c.s.f. Po2 in clinical research. However, if one looks at the reports in man mentioned above, the variability of c.s.f. Po2 under normal conditions is not so much greater than for other measurements widely accepted in clinical chemistry. In diseases associated with reduced cerebral blood flow and other signs of brain hypoxia, decreased values have been consistently reported (Jarnum, Lorenzen and Skinhoj, 1964; Heyne, 1968; Katsurada, Sugimoto and Onji, 1969; Rossanda and Gordon, 1970; Metzel and Zimmermann, 1971) although there is a rather large individual variability in some studies.

In the same kind of patients, cerebral venous Po2 is usually greater than normal: this has been interpreted as a sign of maldistribution of cerebral blood flow in conditions associated with brain ischaemia (Rossanda and Gordon, 1970). Although this interpretation could be debated from theoretical considerations of the significance of Po2 measurements both in c.s.f. and in jugular venous blood, subsequent experimental studies (Eklof, MacMillan and Siesjö, 1972) have demonstrated that in cerebral ischaemia, tissue hypoxia frequently coexists with high oxyhaemoglobin saturation in the venous blood draining the ischaemic areas. On the other hand, the very assumption of inhomogeneity of blood flow in cerebral ischaemia makes it more difficult to identify a "critical" c.s.f. Po2 to be of possible use in clinical practice.

The information which might be obtained from c.s.f. Po2 on the actual redox state of the brain is of more limited value than the information given by the determination of c.s.f. lactate and L/P ratio. However, it could still be worth while investigating the
behaviour of c.s.f. $P_O_2$ in clinical situations associated with rapid changes of cerebral perfusion, for example during hypotensive anaesthesia.

PROBLEMS OF SAMPLING AND MEASUREMENT

The common methods used for blood-gas tension and pH measurement cannot be applied to c.s.f. Special care should be taken to avoid even the small carbon dioxide losses and oxygen gains resulting from the presence of air bubbles or from the use of plastic syringes. The presence of air bubbles in a small sample can occur when syringes are not air-tight or when their deadspace is filled with air or any fluid equilibrated with air. When a syringe is used, the safest procedure is to draw some c.s.f. into the syringe and quickly discard it leaving the deadspace filled with the fluid; then the sample can be collected. This obviously entails the use of a large amount of c.s.f. Very small samples require special fitting capillary tubes, or syringes without deadspace.

The use of plastic syringes or tubing allows gas exchange to occur through the plastic in a very short time. They should not be used if the measuring apparatus is not immediately available as it is in an experimental laboratory. The reason why a small carbon dioxide loss gives rise to a greater error in c.s.f. than in blood is to be found in the absence of buffer anions such as proteins and haemoglobin. The gas loss induces a remarkable decrease of $P_CO_2$ and increase of pH with the bicarbonate concentration remaining unchanged. A loss of carbon dioxide can take place also in the measurement chambers of both pH and $P_CO_2$ electrodes, especially if the chambers have been filled previously with fluid of very different pH and $P_CO_2$, and insufficiently flushed with the same c.s.f. before the readings.

If two different chambers are used for pH and $P_CO_2$, the error arising from gas loss also causes an error in the calculation of bicarbonate. Perhaps the best way would be to use a titration method for bicarbonate, the most stable parameter, and an air-tight $P_CO_2$ electrode and then to calculate pH from the above-mentioned values. This can be the safest way with very small samples when the apparatus does not have a single micro-chamber for both pH and $P_CO_2$ or when it is not suitable for anaerobic filling and rinsing.

The same consideration can be applied to $P_O_2$ measurement. In c.s.f. there is no haemoglobin for binding oxygen in equilibrium with $P_O_2$. Therefore the entrance of small amounts of air causes an uncompensated increase of $P_O_2$. Here again, the error can be made during sampling, or carrying the sample in unsuitable containers, and during the measurement if the $P_O_2$ electrode is filled with an oxygen-rich mixture which is insufficiently rinsed out before reading.

The permeability of plastic material to gases raises a further complication. If the patient has an indwelling ventricular catheter for monitoring of intracranial pressure, this could be a very suitable source of c.s.f., but the fluid should be sampled close to the entrance of the catheter into the skull. Otherwise c.s.f. should be first discarded from the whole length of the plastic catheter in order to obtain an anaerobic sample. This entails a waste of c.s.f. and sometimes makes sampling impossible if the ventricles are very small as in brain oedema. On the other hand, patients with brain oedema are most interesting to study, and in those patients obviously there may be a strong objection against sampling from the spinal space.

There may be a serious objection even to sampling from the catheter, as it has been observed that the risk of infection introduced via the catheter is greatly increased by frequent opening of the connection between catheter and transducer.

REFERENCES


