Intracranial pressure changes following aneurysm rupture

Part 2: Associated cerebrospinal fluid lactacidosis

Bo Voldby, M.D., and Erna M. Enevoldsen, M.D.

University Department of Neurosurgery, Aarhus Kommunehospital, Aarhus, Denmark

Lactate concentrations and pH were measured serially in the cerebrospinal fluid (CSF) of 52 patients with ruptured intracranial aneurysms. Measurements were made during continuous monitoring of the intraventricular pressure (IVP) in the first 12 days after the initial subarachnoid hemorrhage. A total of 226 samples of CSF were analyzed. The clinical condition of the patients was graded according to the Hunt and Hess system. The degree of cerebral arterial spasm was measured on angiograms taken on admission and again approximately 7 days later. Results showed that the lactate concentrations in hemorrhagic and xanthochromic CSF were significantly higher than in clear CSF, indicating lactate production from shed blood cells. However, regardless of the degree of blood admixture to CSF, lactate increased with deteriorating clinical condition. Patients with a moderately increased IVP (20 to 40 mm Hg) had lactate levels of about 3 mmol/liter. A rising IVP or the development of severe spasm was accompanied by a persistent elevation or an increase in lactate. These results suggest that increased CSF concentrations of lactate reflected an increased production of lactate by partially ischemic cerebral tissue. A CSF lactate value above 3.5 mmol/liter was associated with a poor prognosis.

KEY WORDS • subarachnoid hemorrhage • cerebral aneurysm • intracranial pressure • vasospasm • cerebrospinal fluid • lactacidosis

Inadequate perfusion of brain tissue caused by increased intracranial pressure or arterial hypotension leads within a short time to anaerobic production of lactic acid. This metabolic tissue lactacidosis is, with some lag in time, reflected in the cerebrospinal fluid (CSF), which constitutes part of the extracellular fluid of the brain. Experimental work in animals has shown that the concentration of CSF lactate increases following the induction of subarachnoid hemorrhage (SAH), as an expression of cerebral hypoxia.

Clinically, determination of CSF lactate concentrations has been used in various neurological conditions to estimate the degree of brain damage and the prognosis in these patients. Studies concerning patients with SAH have primarily focused on the role of blood in CSF and on respiration as important factors contributing to the lactacidosis, while ischemic factors have received relatively little attention.

In the first part of this study on pathophysiological consequences of rupture of an intracranial saccular aneurysm, we found that changes in intraventricular pressure (IVP) correlated with changes in the clinical condition of the patients. Furthermore, severe vasospasm was associated with raised or increasing IVP. In this second part of the study, we have repeatedly measured the lactate concentration and pH of ventricular fluid in the early period following aneurysm rupture. The main purpose was to study the relationship between changes in CSF lactate and IVP as well as changes in lactate in relation to the development of cerebral vasospasm. We also studied the relationship between lactate and the clinical condition, the operative findings, and the outcome of the patients.

Clinical Material and Methods

Summary of Cases

A detailed description of clinical material and methodology of this study has been presented in the
The series studied included 52 patients (35 females and 17 males) with rupture of an intracranial saccular aneurysm within 1 week before admission. The mean age of the patients was 46 years (range 16 to 68 years). The diagnosis was confirmed by angiography. Patients with intracranial hematomas were excluded. Based on daily clinical assessment, the patients were divided into three groups according to the grading system of Hunt and Hess: 12 patients were Grade I-II, 19 were Grade II-III, and 20 were Grade III-V. Surgical repair of the ruptured aneurysm was done in 34 patients (65%). At operation, the cortex of the brain was inspected before dissection of the aneurysm, and the presence of discoloration and edema was observed.

Cerebral angiography was performed in all 52 patients on admission and was repeated approximately 7 days later in 34 patients. The degree of vasospasm was measured on angiograms and defined as follows: when the reduction in arterial diameter was 50% or more, the spasm was considered severe; when the reduction was 25% to 50%, the spasm was considered slight; and when the reduction was less than 25%, no spasm was considered to have occurred. Severe spasm was found in 19 (37%) of our patients, slight spasm in 17 (32%), and no spasm in 16 (31%).

The IVP was measured continuously in all patients by Lundberg's method for an average period of 8 days (2 to 16 days). Mean IVP (diastolic pressure + one-third of the pulse pressure) was measured hourly and used for calculations of the mean IVP for each day and for the entire period of monitoring in each patient. When IVP exceeded 25 mm Hg for more than 30 minutes, ventricular drainage of CSF was instituted.

Follow-up examination was performed in all surviving patients 1 to 2 years after the initial SAH. Seventeen patients recovered and 12 patients became disabled. Twenty-three patients died, and neuropathological examination of the brain was carried out in all but three of them.

**Measurement of CSF Lactate and pH**

During the period of study, samples of CSF were withdrawn from the ventricular catheter close to the patient's head daily or every second day. On the average, four samples (two to nine) were collected per patient, and a total of 226 samples was analyzed. For the measurement of lactate, 2 ml of CSF was mixed

---

**FIG. 2.** The correlation between mean cerebrospinal fluid lactate concentrations and mean intraventricular pressure (IVP) in 52 patients with ruptured intracranial aneurysm. Regression line is shown (y = 8.17x - 2.16).
ICP changes after aneurysm rupture: Part 2

immediately with metaphosphoric acid and later analyzed by an enzymatic method. For the concurrent measurement of pH, 1 ml of CSF was withdrawn anaerobically.

The degree of blood admixture to CSF was estimated macroscopically and divided into three categories. Samples with heavy blood content were discarded. Forty percent of the samples were clear, 25% xanthochromic, and 35% hemorrhagic. Blood disappeared rapidly from the ventricular fluid, as judged by the color of the CSF: hemorrhage was evident in 77% of samples obtained between Days 1 and 3, 33% between Days 4 and 7, and only 7% after Day 7.

**Results**

**CSF-Blood Mixture and Lactate**

For the entire series, the mean CSF lactate concentration increased concomitantly with the degree of blood admixture. The lactate concentration of clear CSF was 2.32 ± 0.08 mmol/liter (mean ± SEM), which was significantly lower than that of xanthochromic CSF (2.66 ± 0.14, p < 0.05). On the other hand, the lactate concentration of hemorrhagic CSF (2.77 ± 0.11) was not significantly raised compared to that of xanthochromic CSF. In Fig. 1, the mean lactate concentrations of different CSF colors are shown in relation to the clinical grades. Generally, patients in bad clinical condition had higher CSF lactate levels than patients in good clinical condition, irrespective of the degree of blood admixture to CSF.

**Intraventricular Pressure and CSF Lactate**

We found a positive correlation between IVP and CSF lactate (Fig. 2). Lactate concentrations in relation to different levels of IVP are shown in Table 1. Lactate measured at moderately and severely increased IVP was significantly higher than at normal or slightly increased IVP (p < 0.001). By following dynamic changes in lactate concentrations in relation to IVP in individual patients, some general tendencies could be identified. In the 34 patients who had a stable or decreasing IVP, a gradual fall in lactate was observed. However, if IVP stabilized at a high level, as seen in eight of these patients, lactate remained elevated. In the remaining 18 patients in the total series, IVP increased during the period of monitoring, and in most of them lactate levels increased to 3 to 4 mmol/liter. In Fig. 3, characteristic pressure tracings and associated CSF lactate values are shown.

Ventricular drainage was performed in 30 patients. Usually, the amount of CSF drained per day decreased gradually from an initial 100 to 200 ml. Simultaneously, lactate and IVP decreased. However, in 11 patients with increasing IVP, lactate increased during drainage.

**Cerebral Vasospasm and CSF Lactate**

As seen in Table 2, both CSF lactate and IVP correlated well with the degree of vasospasm. Patients with no or slight spasm had significantly lower mean lactate values than patients with severe spasm.

Changes in mean CSF lactate concentrations in relation to degree of spasm during the first 12 days after the initial SAH are shown in Fig. 4. Lactate decreased slowly in patients with no or slight spasm. The pronounced fall on Day 6 for slight spasm was perhaps caused by the ventricular drainage that was instituted in two-thirds of the patients at about that time. Patients who later developed severe spasm had lactate concentrations of about 3 mmol/liter already from Day 2. For these patients, the lactate remained significantly elevated after Day 5 compared to patients with no or slight spasm. Infarctions were found in 15 out of 17 patients (88%) with severe spasm either at autopsy or on follow-up CT scanning. A gross evaluation of the size of the infarcted brain area did not disclose any certain relationship to the increased lactate concentrations found in connection with spasm.

**Clinical Findings and CSF Lactate/pH**

Corresponding values of CSF lactate and pH in relation to clinical grade are shown in Fig. 5. The pH in CSF ranged between 7.20 and 7.61, the majority of pH values being within the normal range (7.30 to 7.36). No significant correlations between pH and lactate concentrations, clinical grade, or CSF color were disclosed. Patients in Grade I–II had normal or slightly increased lactate concentrations (normal range 0.8 to 2.2 mmol/liter), whereas patients in Grades II–III and III–V had significantly higher lactate values (p < 0.05).

Hyperventilation which lowers PaCO₂ to about 30 mm Hg or less may increase the concentration of CSF lactate. However, artificial respiration at moderate hypocapnia (PaCO₂ 30 to 40 mm Hg) did not seem to influence CSF lactate concentrations in 15 poor-risk patients. In seven of these, the lactate level decreased, in five it remained unchanged, and in three it increased during ventilation.

At operation, the cortex was red and swollen in 16 patients. The mean lactate value for this group was clearly elevated (2.71 ± 0.14 mmol/liter). In 17 other patients whose cortex appeared normal, the mean

*All values are mean ± standard error of the mean. IVP = intraventricular pressure; CSF = cerebrospinal fluid.

† p < 0.05 for slight vasospasm compared to none and severe.

‡ p < 0.02 for severe vasospasm compared to slight.
Fig. 3. Typical examples of cerebrospinal fluid (CSF) pressure recordings and associated lactate values in three patients of different clinical grades. **Upper:** Grade II patient (Case 16). The intraventricular pressure (IVP) increased slightly with B-waves on Day 4; the lactate level was normal. On Day 7, both parameters were within normal range; the CSF was clear throughout. **Center:** Grade III patient (Case 46). The IVP and lactate level were moderately increased on Day 5; the CSF was hemorrhagic. Angiography on Day 7 showed severe focal spasm. On Day 11, after ventricular drainage for 6 days, the IVP and lactate level had decreased; the CSF was xanthochromic. **Lower:** Grade IV patient (Case 21). Controlled ventilation and ventricular drainage was performed during the whole course of study. Angiography revealed severe diffuse spasm on Day 8. The patient deteriorated to Grade V on Day 9, with severe increase in both IVP and lactate level, although the CSF was clear. Lactate values are given in mmol/liter.

The relationship between outcome and the maximal lactate concentrations measured in each patient is shown in Fig. 6. Patients who recovered had significantly lower lactate values than patients who became disabled or died (p < 0.001). A maximal lactate value above 3.5 mmol/liter was associated with a poor prognosis.
ICP changes after aneurysm rupture: Part 2

![Graph](image)

**Fig. 4.** Changes in lactate levels in the cerebrospinal fluid after aneurysm rupture, in relation to the degree of vasospasm. Each point represents mean lactate values of four to 10 patients.

**Discussion**

Previous studies have shown that the CSF lactate level is increased following SAH. Apart from a single study on CSF obtained by the suboccipital route, most investigators have used lumbar CSF. The lactate concentration of lumbar CSF is higher than that of cisternal and ventricular CSF, and it has been stated that in nonsteady-state situations, as in acutely ill patients, analyses of lumbar CSF may give unreliable information as to the acid-base status of cerebral extracellular fluids. In patients with impaired CSF flow and absorption following SAH, samples of ventricular CSF probably comprise a mixture of both cisternal and ventricular fluid due to ventricular reflux.

Froman and Smith found a fall in CSF pH and bicarbonate associated with a rise in lactate in 19 patients with SAH, and termed this CSF acid-base disturbance "primary metabolic acidosis." They considered the lactate to be derived primarily from glycolysis in shed blood cells in the subarachnoid space, a view which has been supported by both experimental and clinical work. This lactate production may invalidate the use of CSF lactate as an indicator of cerebral tissue hypoxia. The lactate/pyruvate ratio, which is assumed to reflect the redox state of cerebral tissue, has been proposed as an index of cerebral hypoxia in the presence of hemorrhagic CSF, since the production of lactate and pyruvate from blood cells will not change this ratio significantly. However, several studies have shown that a rise in the lactate/pyruvate ratio is paralleled by an increase in lactate in bloody CSF, indicating cerebral hypoxia. The fact that the lactate concentrations increased concomitantly with clinical deterioration, irrespective of the degree of blood admixture, indicates that factors other than glycolysis in shed blood cells contributed to the lactate production, especially in the period following the first 4 to 6 days after SAH when blood disappeared from the CSF.

Zwetnow and co-workers have demonstrated experimentally that an increase in CSF pressure with

![Graph](image)

**Fig. 5.** Corresponding values of lactate and pH of ventricular cerebrospinal fluid in relation to clinical grade in 52 patients (184 samples). *Horizontal lines* indicate normal range (n.r.).

*J. Neurosurg. / Volume 56 / February, 1982*
reduction of the cerebral perfusion pressure below 40 mm Hg gives rise to a pronounced and long-lasting increase in CSF lactate, indicating an impaired oxidative metabolism of the brain tissue which may even continue after the return of CSF pressure to normal levels. They also showed that moderate pressure elevations, with perfusion pressure still within the autoregulatory range, cause an increase in CSF lactate. Furthermore, studies involving the induction of SAH have shown a more rapid and sustained elevation of CSF lactate/pyruvate ratio after hyperbaric than after isobaric SAH. In the present study, an IVP below 20 mm Hg was usually associated with normal lactate concentrations. At higher pressures, concomitant lactate rises were measured. The majority of patients had a slightly or moderately increased IVP insufficient to reduce the perfusion pressure beyond the critical limit of 40 mm Hg. Thus, our findings suggest that even moderate elevations of IVP contributed to a slight shift toward anaerobic glycolysis in the brain tissue. Very high lactate concentrations were found only in poor-risk patients with severely elevated IVP. This finding is in accordance with the results of other authors, who also found that lactate levels in the range of 5 to 8 mmol/liter were associated with stupor or coma.

In patients with no or slight spasm, CSF lactate decreased during the period of monitoring, whereas severe spasm was associated with a constantly elevated or increasing lactate level. This difference was especially pronounced from about the 6th day when delayed spasm occurred. Measurements of cerebral blood flow and oxygen consumption in aneurysm patients have shown that severe vasospasm profoundly reduces both parameters. Granholm, et al., measured the lactate/pyruvate ratio in the lumbar CSF of 34 patients with SAH, and demonstrated a significant increase in seven patients with clinical signs of vasospasm. Our results support the view that arterial vasoconstriction of 50% or more significantly diminishes cerebral perfusion and consequently oxygen supply. This is further supported by the fact that cerebral infarction almost invariably developed in patients with severe spasm. Studies concerning patients with ischemic stroke have also shown elevated CSF lactate with cerebral infarction.

The mechanism of clearance of lactate from CSF is not completely understood. Probably lactate is removed slowly by bulk flow and diffusion. Impairment of CSF absorption due to SAH may thus contribute to an accumulation of lactate in the CSF. During drainage of CSF, lactate decreased unless severe spasm occurred or IVP increased, indicating lactate production from ischemic brain tissue. An accumulation of lactate in brain tissue is likely to impede the washout of lactate by rapidly saturating the carrier-mediated transport mechanism across the blood-brain barrier.

The association between elevated lactate levels and a red and swollen cortex may represent edema or hyperemia, or both, due to cerebral tissue lactacidosis. Lactacidosis may aggravate cerebral edema and initiate vasomotor paralysis leading to loss of autoregulation and luxury perfusion. In aneurysm patients with an initial ischemic edema caused by the aneurysm rupture, a secondary reduction of cerebral perfusion due to intracranial hypertension or vasospasm may aggravate, globally or focally, tissue hypoxia. Subsequently, increased anaerobic glycolytic production of lactic acid may further impair tissue oxygenation by worsening the edema, thus starting a vicious cycle. The therapeutic implications of increased CSF lactate in a patient in poor clinical state must primarily be to combat the underlying brain-tissue lactacidosis by securing sufficient supply of oxygen and by moderate hyperventilation. Besides removing accumulated lactate from the CSF space, ventricular drainage may improve the perfusion of brain tissue by reducing a raised intracranial pressure.

Like other authors, we found that CSF lactate values correlated fairly well with prognosis (Fig. 5). Recent experimental studies have suggested that the persistence of brain lactic acidosis might impede functional recovery. The outcome of patients in the present study, who had elevated lactate concentrations despite a satisfactory clinical condition, was significantly worse than the outcome of patients with normal lactate prior to operation. The increase in lactate...
ICP changes after aneurysm rupture: Part 2

in these patients was associated with an increased IVP and edema of the cortex. It is possible that slight progressive brain edema during the period preceding operation was responsible for this increase in lactate and IVP, which consequently may be considered as a warning of an "angry" and vulnerable brain, requiring postponement of surgical intervention. If so, determination of CSF lactate and measurement of IVP may be useful parameters in monitoring patients with ruptured aneurysm and may result in better timing of operation.

Acknowledgments

The authors wish to thank Ms. Lone Bruus for her technical assistance and Ms. Norma Nissen for preparation of the manuscript.

References


J. Neurosurg. / Volume 56 / February, 1982


Manuscript received May 18, 1981.
Accepted in final form October 21, 1981.

Address reprint requests to: Bo Voldby, M.D., Department of Neurosurgery, Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark.