Cerebrospinal Fluid and Arterial Lactate, Pyruvate and Acid-Base Balance in Patients With Intracranial Hemorrhages

BY MASATOSHI FUJISHIMA, M.D., TOMEI SUGI, M.D., JUNICHIRO CHOKI, M.D., TAKENORI YAMAGUCHI, M.D., AND TERUO OMAE, M.D.

Abstract: Lactate and pyruvate concentrations and acid-base balance in cerebrospinal fluid (CSF) and arterial blood were determined in patients with intracranial hemorrhages (28 subarachnoid hemorrhages and 15 intracerebral hemorrhages).

A greater increase in CSF lactate and lactate-pyruvate ratio (L/P ratio) was observed in patients with impairment of consciousness, focal neurological deficits, poor prognosis, or CSF pressures higher than 300 mm H2O. A combination of CSF lactate greater than 2.5 mM per liter, L/P ratio above 20, bicarbonate less than 20.4 mEq per liter, pH below 7.276, or arterial PCO2 below 31.5 mm Hg seems to indicate a poor prognosis from intracranial hemorrhage.

The mechanism of hyperventilation in acute cerebrovascular diseases and of CSF pH regulation in acid-base disturbances was also discussed.

Additional Key Words

- subarachnoid hemorrhage
- hyperventilation
- CSF pressure
- prognostic indicator

Introduction

Extensive studies have been made on acid-base and metabolic changes in cerebrospinal fluid (CSF) in patients with acute cerebrovascular diseases. Zuppinger et al. have described a significant increase in CSF lactate and pyruvate with a concomitant decrease in CSF bicarbonate (HCO3) in acute ischemic strokes. Schnaberth and Summer have reported that the derangement of CSF acid-base balance and an increase in CSF lactate developed frequently in acute cerebrovascular diseases, and these were associated with severity of clinical symptoms.

In hemorrhagic cerebrovascular diseases, however, metabolic changes in CSF are not always identical to those in ischemic strokes, since in the former there is the possible effect on CSF biochemistry of the presence of shed blood per se in the subarachnoid space in addition to a disturbance of normal metabolism by injured brain tissue. Therefore, measurements were made of lactate, pyruvate and acid-base parameters of bloody or xanthochromic CSF in patients with subarachnoid hemorrhage or cerebral hemorrhage in order to find any correlation with other laboratory findings and the clinical status of these patients.

Methods

For this study, we selected 28 patients with subarachnoid hemorrhage (SAH) and 15 patients with intracerebral hemorrhage (ICH). There were 26 men and 17 women between the ages of 22 and 74. The diagnosis was made on the basis of a carefully taken history, physical examination and CSF findings.

Lumbar CSF (2 ml) was obtained anaerobically for acid-base and metabolic determinations. Under a steady state following lumbar puncture, 5 ml of arterial blood were withdrawn for determinations of the same parameters as CSF. Immediately after sampling, 1.5 ml of CSF and 4 ml of arterial blood were separately added to the same amount of 10% perchloric acid, stored in ice and, after removal of protein and neutralization with potassium hydroxide, were analyzed by standard enzymatic methods for lactate and pyruvate.

The partial pressure of carbon dioxide (PCO2), oxygen (PO2), and the pH in CSF and arterial blood were measured with the IL-Meter Model 113. HCO3 was calculated by using the Henderson-Hasselbalch nomogram and Mitchell's correction for CO2 solubility and pK' for CSF. Beside the acid-base parameters, lactate and pyruvate concentrations, protein and glucose levels in CSF were determined as a routine laboratory test.

The time intervals from the onset to sampling CSF were varied as shown in table 1. Six determinations were made within 24 hours, 18 between one and five days, and 31 samples were obtained six days or more after the onset.

In 15 patients with ICH the level of consciousness at the time of onset was as follows: coma in seven, semicoma in one, somnolence or confusion in six, and normal in one. The level of consciousness at the time of onset in the 28 SAH patients was: coma in five, semicoma in four, stupor in three, somnolence or confusion in ten, and alert in six. Eight patients with ICH had a complete or incomplete hemiplegia on the right, and five had it on the left; the remaining two had quadriplegia. Of the 28 patients with SAH, there were seven cases with hemiplegia or hemiparesis on the right.
eight on the left, one with paraplegia, one with quadriplegia, and ten with no apparent neurological deficits. The motor or sensory impairment developed at the time of onset in all cases with neurological deficits but one, in which left hemiparesis occurred on the eighth day after the onset of SAH.

With ICH, seven died between two and 36 days, an average of 10.7 days after the onset. On the other hand, with SAH, six died within 24 hours to 18 days, an average of 4.3 days. Two patients died from recurrent SAH on the sixth and eighteenth days. According to the neurological state one month after the onset, the severity of clinical status was divided into four grades: death as Grade 4, worsened or unchanged as Grade 3, slightly improved as Grade 2, and cured as Grade 1. There were six patients with ICH and six with SAH with Grade 4, three and five with Grade 3, six and ten with Grade 2, and none and seven, respectively, with Grade 1.

The intravenous or parenteral administration of corticosteroid hormone was given in eight cases with ICH and 13 with SAH to reduce increased intracranial pressure. Cerebral metabolic stimulating agents were administered in seven and 11 cases of ICH and SAH, respectively, and no drug was given in one ICH patient and five SAH patients during observation. Surgery was performed in six SAH patients; three of these had clipping or wrapping of an aneurysm, one had clipping of the feeding arteries to an arteriovenous malformation, and one had a shunting operation.

Results
Table 2 shows CSF and arterial lactate, pyruvate and acid-base values in patients with ICH or SAH within five days from onset.

One case with ICH was excluded from the statistical analysis because of a high Paco₂ of 136 mm Hg due to concomitant respiratory failure. An average value for CSF lactate of 3.58 ± 0.42 mM per liter (mean ± SEM) in ICH was not significantly different from the 4.24 ± 0.51 mM per liter in SAH. CSF lactate/pyruvate ratio (L/P ratio) was 21.1 ± 1.4 in ICH, and 19.3 ± 0.8 in SAH, respectively. There was no difference in mean values for CSF pH, Pco₂, HCO₃⁻ or arterial parameters between ICH and SAH. Compared with values for each parameter of 13 control subjects, CSF lactate, pyruvate and L/P ratio increased, and CSF Pco₂ and HCO₃⁻ were decreased in patients with ICH, whereas arterial lactate, pyruvate, L/P ratio and HCO₃⁻ showed no difference between control and ICH or SAH. However, arterial Pco₂ was lower with inversely higher pH in ICH or SAH than in control, indicating that acute ICH might cause
hyperventilation resulting in arterial pH becoming alkalotic.

Figure 1 shows CSF lactate values at various intervals from the onset.

Within a few days after onset, CSF lactate increased to the maximum level, and thereafter it tended to decrease and return to control levels during the first two weeks. In one case, CSF lactate remained high at 3.15 mM per liter, even 15 days after the onset.

CSF LACTATE AND L/P RATIO AND THEIR RELATIONSHIPS TO CLINICAL FINDINGS WITHIN 15 DAYS OF ICH OR SAH

Level of Consciousness (Fig. 2)
CSF lactate and L/P ratio were 3.88 ± 0.41 mM per liter in 19 determinations and 20.0 ± 1.1 in 18, respectively, of 17 patients having severely impaired consciousness such as coma or semicoma at the time of onset, while 2.91 ± 0.41 mM per liter and 19.8 ± 1.2, respectively, were found in ten patients with a mild disturbance of consciousness. In eight conscious patients, CSF lactate was 2.48 ± 0.36 mM per liter and CSF L/P ratio was 16.9 ± 1.0. These findings indicate that an increase in both CSF lactate and L/P ratio is well correlated with the level of consciousness at onset.

Neurological Deficits (Fig. 3)
Of 37 patients with ICH or SAH, there were 28 with hemiparesis or hemiplegia; the remaining nine patients with SAH had no apparent neurological deficit. Average values for CSF lactate and L/P ratio in the former were 3.42 ± 0.32 mM per liter and 19.8 ± 0.9, respectively, and in the latter 2.98 ± 0.47 mM per liter and 17.8 ± 0.7, respectively.

Prognosis (Fig. 4)
An average CSF lactate level was 4.63 ± 0.49 mM per liter in 13 cases with ICH or SAH of Grade 4 neurological severity, which was significantly higher than the 3.19 ± 0.40 mM per liter in 11 cases of Grade 3. Patients who had a good prognosis (Grade 2 or 1)
had CSF lactate of 2.25 ± 0.16 mM per liter. Similarly, CSF L/P ratio was the highest at 21.5 ± 1.3 in Grade 4 patients, 19.8 ± 1.1 in Grade 3, and 17.4 ± 0.9 in Grade 2 or 1.

CSF LACTATE AND L/P RATIO AND THEIR RELATIONSHIPS TO COLOR OR PRESSURE OF CSF

Color of CSF (Fig. 3)
The CSF was studied and divided by color into three groups: bloody (B), bloody-xanthochromic (B-X), and xanthochromic (X). The mean value for CSF lactate was 4.47 ± 0.46 mM per liter in (B), 3.16 ± 0.33 mM per liter in (B-X), and 2.09 ± 0.12 mM per liter in (X). Mean CSF L/P ratio was 20.7 ± 1.1 in (B), 19.5 ± 1.9 in (B-X), and 17.5 ± 0.8 in (X).

Initial Pressure of CSF (Fig. 6)
There was a tendency for a greater increase in CSF lactate and L/P ratio in patients having higher CSF pressure greater than 300 mm H2O. In one case with an extremely high CSF pressure, however, CSF lactate or L/P ratio did not increase markedly.

CSF LACTATE AND L/P RATIO AND THEIR RELATIONSHIPS TO ARTERIAL AND CSF ACID-BASE BALANCE

CSF pH (Fig. 7)
In more than half of the cases, CSF pH was maintained within the normal range. In seven of 16 cases having CSF lactate greater than 2.5 mM per liter, however, CSF pH was shifted to acidotic range below 7.276 and CSF PCO2 was lowered in all of these cases except one, who had severe hypercapnia due to respiratory failure. A correlation between CSF lactate and pH was of statistical significance (r = 0.508, P < 0.01).

CSF Bicarbonate (Fig. 8)
There was an inverse relation between CSF HCO3 and CSF lactate (r = -0.548, P < 0.001). When CSF lac-
Relation of CSF lactate to CSF pH. There is an inverse correlation between these two parameters \( r = -0.508, P < 0.01 \), although one case with a pronounced CSF acidosis is excluded from a statistical analysis because he had a concomitant respiratory failure resulting in a marked increase in \( P_{\text{aCO2}} \) more than 100 mm Hg.

Arterial \( P_{\text{aCO2}} \) (Fig. 9)

There was a significant correlation between CSF lactate and \( P_{\text{aCO2}} \) \( r = -0.0412, P < 0.05 \). In five of six patients with increased CSF lactate greater than 5 mM per liter, \( P_{\text{aCO2}} \) decreased below the normal range. On the other hand, there was no relation between CSF pH and \( P_{\text{aCO2}} \) \( r = 0.124, P > 0.4 \).
Discussion
The present study revealed that CSF lactate increased with a concomitant rise in L/P ratio in patients with ICH or SAH shortly after the onset, followed by a gradual fall to a normal level within two weeks. A greater increase in CSF lactate and L/P ratio was observed in patients who had impaired consciousness at the time of onset, focal neurological deficits, a poor prognosis or increased intracranial pressure.

CSF lactate increases not only in hemorrhagic cerebrovascular diseases, but also in various diseases such as ischemic stroke,9 head injury,20 hypoxemia,10 and meningitis,11 or in conditions interfering with blood or oxygen delivery to the brain.12 13 Our previous study,5 as well as others,24 have shown that a lowering of the cerebral perfusion pressure is accompanied by an increased CSF L/P ratio.

CSF lactate increases not only in hemorrhagic cerebrovascular diseases, but also in various diseases such as ischemic stroke,9 head injury,20 hypoxemia,10 and meningitis,11 or in conditions interfering with blood or oxygen delivery to the brain.12 13 Our previous study,5 as well as others,24 have shown that a lowering of the cerebral perfusion pressure is accompanied by an increased CSF L/P ratio. In these rats, however, tissue lactate of the brain tissue might be diffused into the CSF space, in addition to CSF lactate from shed blood cells. As frequently seen in patients with SAH17 cerebral vasospasm due to extravascular blood cells seemed to develop in the in vivo study, causing cerebral ischemia and excess lactate production in tissue.

L/P ratio of CSF as well as of brain tissue reflects the redox state of the cytoplasmatic NADH/NAD+ system.18 This implies that measurement of L/P ratio of the extracellular fluid in diffusion equilibrium with tissue may give valuable information on the presence of tissue hypoxia. Siesjo and Zwetnow19 have shown that a lowering of the cerebral perfusion pressure is accompanied by an increased CSF L/P ratio. During passive hyperventilation reducing Paco2 below 20 to 25 mm Hg, CSF L/P ratio rises possibly due to cerebral vasospasm resulting in decreased cerebral blood flow.20 Although in the present study there was no obvious difference in Paco2 or arterial lactate concentrations between ICH and SAH, CSF L/P ratio was higher in ICH than in SAH, indicating that the brain tissue might be more hypoxic in ICH than in SAH. Moreover, an increase in CSF L/P ratio was greater in patients with neurological deficits or in those having a poor prognosis. These results suggest that CSF L/P ratio reflects changes in the brain tissue metabolism of glucose and is a useful indicator of ischemia or hypoxia in the brain tissue following ICH or SAH.

In an in vivo study, Shannon et al.15 demonstrated that a progressive increase in lactate with a concomitant decrease in HCO3 and pH with time developed in CSF following the intracisternal injection of red blood cells in dogs. Granholm14 reported the similar results revealing a greater increase in in vivo production of lactate than in in vitro, but the L/P ratio was unchanged for the three-hour study. From our experience, however, CSF lactate increased progressively with time following the intracisternal injection of blood in dogs, but also CSF L/P ratio started to increase at three hours after injection. Granholm14 described no significant changes in lactate or pyruvate of the feline brain tissue for three hours after the intracisternal injection of blood cells. Our previous study revealing a late increase in CSF L/P ratio in in vivo canine experiments18 suggests that lactate produced in the brain tissue might be diffused into the CSF space, in addition to CSF lactate from shed blood cells per se. As frequently seen in patients with SAH,17 cerebral vasospasm due to extravascular blood cells seemed to develop in the in vivo study, causing cerebral ischemia and excess lactate production in tissue.

No obvious changes in L/P ratio occurred. In an in vivo study, Shannon et al.15 demonstrated that a progressive increase in lactate with a concomitant decrease in HCO3 and pH with time developed in CSF following the intracisternal injection of red blood cells in dogs. Granholm14 reported the similar results revealing a greater increase in in vivo production of lactate than in in vitro, but the L/P ratio was unchanged for the three-hour study. From our experience, however, CSF lactate increased progressively with time following the intracisternal injection of blood in dogs, but also CSF L/P ratio started to increase at three hours after injection. Granholm14 described no significant changes in lactate or pyruvate of the feline brain tissue for three hours after the intracisternal injection of blood cells. Our previous study revealing a late increase in CSF L/P ratio in in vivo canine experiments18 suggests that lactate produced in the brain tissue might be diffused into the CSF space, in addition to CSF lactate from shed blood cells per se. As frequently seen in patients with SAH,17 cerebral vasospasm due to extravascular blood cells seemed to develop in the in vivo study, causing cerebral ischemia and excess lactate production in tissue.

L/P ratio of CSF as well as of brain tissue reflects the redox state of the cytoplasmatic NADH/NAD+ system.18 This implies that measurement of L/P ratio of the extracellular fluid in diffusion equilibrium with tissue may give valuable information on the presence of tissue hypoxia. Siesjo and Zwetnow19 have shown that a lowering of the cerebral perfusion pressure is accompanied by an increased CSF L/P ratio. During passive hyperventilation reducing Paco2 below 20 to 25 mm Hg, CSF L/P ratio rises possibly due to cerebral vasospasm resulting in decreased cerebral blood flow.20 Although in the present study there was no obvious difference in Paco2, PO2 or arterial lactate concentrations between ICH and SAH, CSF L/P ratio was higher in ICH than in SAH, indicating that the brain tissue might be more hypoxic in ICH than in SAH. Moreover, an increase in CSF L/P ratio was greater in patients with neurological deficits or in those having a poor prognosis. These results suggest that CSF L/P ratio reflects changes in the brain tissue metabolism of glucose and is a useful indicator of ischemia or hypoxia in the brain tissue following ICH or SAH.

Eklöf and Siesjo21 22 found that when cerebral blood flow was reduced to 50%, 44% and 42% of the resting value in rats with bilateral carotid ligation plus a concomitant lowering of systemic blood pressure, CSF lactate increased by 49%, 97% and 168%, respectively, calculated by the authors from their data. CSF L/P ratio also rose by 15%, 44% and 112%, respectively. In these rats, however, tissue lactate of the
supratentorial part increased by 88%, 1,120% and 1,533%, respectively, and tissue L/P ratio rose by 23%, 875% and 3,580%, respectively. Although an increase in lactate and L/P ratio in CSF following the lowered perfusion was much less than that in brain tissue, changes in CSF lactate and L/P ratio were qualitatively similar to brain tissue. In hypocapnia or hyperventilation, despite a quantitative difference of lactate or L/P ratio between CSF and brain tissue, they also change in a very similar manner. From these studies, even a small increase in CSF lactate, with a concomitant rise in CSF L/P ratio, indicates that severe hypoxia or hypoperfusion of brain tissue might exist.

Sambrook et al.,17 similar to our previous study,5 demonstrated that a decrease in Paco2 was associated with an increase in CSF lactate in all patients but to a much greater extent following SAH than after non-hemorrhagic strokes. Similar clinical observations have been made by Zupping et al.,1 Schnabberth and Summer,2 and Lane et al.4 In our experimental study,24 we found that there was an inverse relationship between brain tissue lactate and Paco2 in rats, in which cerebral ischemia was induced by ligating the bilateral carotid arteriolar supply. Similarly, hyperventilation with a consequent decrease in Paco2 has been observed frequently after acute cerebrovascular disease.1, 2, 4, 6, 16, 20, 26, 28 serious head injuries,29 and a variety of brain lesions in patients.27 These three possible mechanisms of hyperventilation in acute cerebrovascular diseases have been considered. They include hypoxic drive, extracellular fluid acidosis, and central neurogenic drive.

In the present study, Paco2 in patients with ICH or SAH was not different from that in control subjects, suggesting that hypoxia seemed unlikely to be an important cause of hyperventilation. Hypoxia as a cause of hyperventilation is also excluded by Froman and Smith,28 who had one case with ICH in which hyperventilation might be explained by hypoxia, but restoration of a normal Paco2 by increasing oxygen content in the inspired air did not influence his ventilatory volume. They concluded that hyperventilation was not caused by hypoxia, but rather by a low CSF pH, due to probable metabolic breakdown of blood cells in the CSF.

However, there was no obvious correlation between CSF pH and Paco2 in this study as well as other observations.4, 22 Particularly, Lane et al.4 demonstrated that some patients with SAH had CSF pH more acidic than normal, whereas others with an increased CSF lactate had normal CSF pH. Therefore, they, like Posner et al.,28 concluded that CSF acidosis is not responsible for hyperventilation.

Although there was no significant relationship between CSF pH and Paco2, in other words, more acidic CSF pH did not cause lower Paco2, the possibility of CSF pH controlling respiration could not be excluded in acute cerebrovascular diseases. It has been shown that there is constancy of CSF pH in non-respiratory and, to some extent, in respiratory acid-base disturbances.24 The regulatory mechanisms for CSF constancy are the compensatory mechanisms of pulmonary ventilation and the renal re-absorption of HCO3 which regulate Pco2 and HCO3 concentrations. In addition to those compensatory adjustments, there are two specific mechanisms regulating CSF pH: (1) changes in cerebral blood flow, and (2) changes in HCO3 ratio between CSF and plasma. Siesjö20 stated that although changes in cerebral blood flow induce regulatory variations in CSF Pco2 during acute respiratory acid-base imbalance, the mechanism is of little importance in most chronic disorders.

Leusen31 observed that pulmonary ventilation was increased when cerebral ventricles were perfused with solutions high in Pco2 or low in Hco3. Similar observations have been made by Mitchell et al.,32 who concluded that there are superficial chemoreceptor structures on the ventrolateral surface of the medulla which respond to changes in extracellular fluid pH. Pappenheimer et al.34 found in conscious goats that ventilation increased from 5 to 45 liters per minute for a pH change of 0.15 unit. Fencil and his coworkers34 showed in human volunteers a greater sensitivity of CSF pH changes to ventilatory increase from 3 to 30 liters per minute with changes in extracellular fluid pH of 0.05 unit. These results suggest very likely that CSF pH serves as an important regulator of pulmonary ventilation.

In the present study, Pco2 differences between CSF and plasma were 8.7 mm Hg in ICH and 10.8 mm Hg in SAH, which are lower than the 11.4 mm Hg in normal subjects. Although cerebral blood flow in general reduces in patients with ICH or SAH, a narrowing of Pco2 difference between CSF and plasma indicates that respiratory compensation might be the reason the CSF acidosis disappeared. Beside the Pco2 difference, HCO3 concentration difference between CSF and blood could become wider in primary metabolic acidosis of CSF, resulting in a greater concentration gradient of HCO3 between two components. Therefore, HCO3 tended to move passively from plasma to CSF, while there is a slight difference in HCO3 even at the normal steady state.30

The severity of the clinical symptoms runs parallel to changes in acid-base balance. Schnabberth and Summer1 found that CSF HCO3 of less than 18 mEq per liter is associated with a poor prognosis. Sambrook et al.17 reported that CSF HCO3 of less than 20 mEq per liter or CSF lactate greater than 5 mM per liter during the first two days following the onset of hemorrhage was associated with an adverse prognosis. In addition, if the CSF pH decreases below 7.300 at any period following attacks, it indicates a poor prognosis. Abnormal respiration in cerebrovascular diseases have been long recognized, particularly the poor prognosis with hyperventilation, Cheyne-Stokes breathing and irregular respirations. Based on these results, the authors selected some CSF
and arterial parameters as prognostic indicators. These include CSF lactate, CSF L/P ratio, CSF HCO₃⁻, CSF pH and arterial Pco₂. It is concluded that a combination of parameters such as CSF lactate greater than 2.5 mM per liter, CSF L/P ratio greater than 20, CSF HCO₃⁻ less than 20.4 mEq per liter, CSF pH below 7.276, and Paco₂ less than 31.5 mm Hg indicate a poor prognosis for patients with ICH.

Acknowledgments
The authors wish to thank Drs. Iino and Kusunoki of Kyushu Central Hospital, Dr. Inazuka of Yamashita Hospital, and Dr. Ohya of Ohya Hospital for allowing us to study patients under their care, and also Miss Y. Sonoda and Miss K. Shirozu for their skilled assistance.

References
Cerebrospinal Fluid and Arterial Lactate, Pyruvate and Acid-Base Balance in Patients With Intracranial Hemorrhages

MASATOSHI FUJISHIMA, TOMEI SUGI, JUNICHIRO CHOKI, TAKEORI YAMAGUCHI and TERUO OMAE

*Stroke*. 1975;6:707-714
doi: 10.1161/01.STR.6.6.707

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1975 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/6/6/707

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/