

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

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

■ 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 H<sub>2</sub>O. 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 Pco<sub>2</sub> 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**  
neurological deficits

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.<sup>1-6</sup> Zupping et al.<sup>1</sup> have described a significant increase in CSF lactate and pyruvate with a concomitant decrease in CSF bicarbonate (HCO<sub>3</sub><sup>-</sup>) in acute ischemic strokes. Schnaberth and Summer<sup>2</sup> 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.<sup>2-6</sup> 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 (Pco<sub>2</sub>), oxygen (Po<sub>2</sub>), and the pH in CSF and arterial blood were measured with the IL-Meter Model 113. HCO<sub>3</sub><sup>-</sup> was calculated by using the Henderson-Hasselbalch nomogram and Mitchell's correction for CO<sub>2</sub> solubility and pK' for CSF.<sup>7</sup> 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,

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**TABLE 1**  
Numbers of CSF Determinations at Various Time Intervals From Onset in 15 Cases With ICH and 28 Cases With SAH

	Days after onset						Total
	<1	1-5	6-10	11-15	16-30	>30	
ICH	2	8	3	1	1	2	17
SAH	4	10	4	5	6	9	38

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  $P_{aCO_2}$  of 136 mm Hg due to concomitant respiratory failure. An average value for CSF lactate of  $3.58 \pm 0.42$  mM per liter (mean  $\pm$  SEM) in ICH was not significantly different from the  $4.24 \pm 0.51$  mM per liter in SAH. CSF lactate/pyruvate ratio (L/P ratio) was  $21.1 \pm 1.4$  in ICH, and  $19.3 \pm 0.8$  in SAH, respectively. There was no difference in mean values for CSF pH,  $P_{aCO_2}$ ,  $HCO_3^-$  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  $P_{aCO_2}$  and  $HCO_3^-$  were decreased in patients with ICH, whereas arterial lactate, pyruvate, L/P ratio and  $HCO_3^-$  showed no difference between control and ICH or SAH. However, arterial  $P_{aCO_2}$  was lower with inversely higher pH in ICH or SAH than in control, indicating that acute ICH might cause

**TABLE 2**  
Average Values for CSF and Arterial Parameters in ICH and SAH Within Five Days From Onset, and in Control Subjects

	Lactate (mM/L)	Pyruvate (mM/L)	L/P ratio	pH	$P_{aCO_2}$ (mm Hg)	$HCO_3^-$ (mEq/L)	$P_{aO_2}$ (mm Hg)
CSF							
ICH	$3.58 \pm 0.42(9)^*$	$0.170 \pm 0.018(8)$	$21.1 \pm 1.4(8)$	$7.317 \pm 0.020(8)$	$39.8 \pm 1.5(8)$	$19.4 \pm 1.1(8)$	
SAH	$4.24 \pm 0.51(14)$	$0.213 \pm 0.023(13)$	$19.3 \pm 0.8(13)$	$7.315 \pm 0.017(14)$	$41.7 \pm 0.9(14)$	$20.4 \pm 1.0(14)$	
Control	$1.50 \pm 0.05(13)$	$0.098 \pm 0.004(13)$	$15.5 \pm 0.6(13)$	$7.336 \pm 0.009(13)$	$47.0 \pm 0.9(13)$	$23.8 \pm 0.5(13)$	
Arterial							
ICH	$1.60 \pm 0.29(9)$	$0.094 \pm 0.022(9)$	$21.2 \pm 3.7(9)$	$7.471 \pm 0.020(9)$	$31.1 \pm 1.6(9)$	$22.2 \pm 1.3(9)$	$78.2 \pm 11.2(9)$
SAH	$1.62 \pm 0.30(13)$	$0.094 \pm 0.024(11)$	$23.2 \pm 5.3(11)$	$7.485 \pm 0.008(14)$	$30.9 \pm 1.0(14)$	$23.3 \pm 1.0(14)$	$77.9 \pm 4.9(14)$
Control	$0.92 \pm 0.05(13)$	$0.059 \pm 0.005(13)$	$16.8 \pm 1.4(13)$	$7.432 \pm 0.004(13)$	$35.6 \pm 0.6(13)$	$23.4 \pm 0.4(13)$	$82.6 \pm 2.3(13)$

Values are mean  $\pm$  SEM.

\*Numbers in parentheses designate the number of determinations.

## CSF AND ARTERIAL LACTATE, PYRUVATE AND ACID-BASE BALANCE

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  $3.88 \pm 0.41$  mM per liter in 19 determinations and  $20.0 \pm 1.1$  in 18, respectively, of 17 patients having severely impaired consciousness such as coma or semicoma at the time of onset, while  $2.91 \pm 0.41$  mM per liter and  $19.8 \pm 1.2$ , respectively, were found in ten patients with a mild disturbance of consciousness. In eight conscious patients, CSF lactate was  $2.48 \pm 0.36$  mM per liter and CSF L/P ratio was  $16.9 \pm 1.0$ . 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  $3.42 \pm 0.32$  mM per liter and  $19.8 \pm 0.9$ , respectively, and in the latter  $2.98 \pm 0.47$  mM per liter and  $17.8 \pm 0.7$ , respectively.

#### Prognosis (Fig. 4)

An average CSF lactate level was  $4.63 \pm 0.49$  mM per liter in 13 cases with ICH or SAH of Grade 4 neurological severity, which was significantly higher than the  $3.19 \pm 0.40$  mM per liter in 11 cases of Grade 3. Patients who had a good prognosis (Grade 2 or 1)

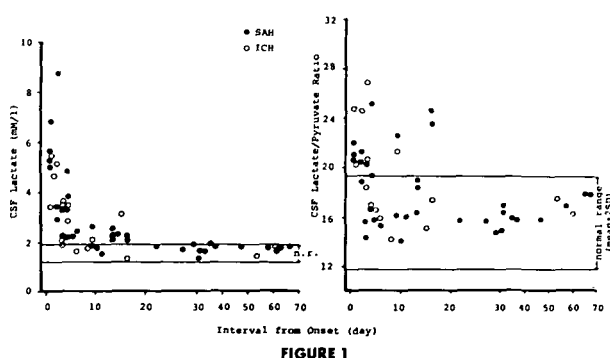


FIGURE 1

CSF lactate and L/P ratio at the various time intervals from the onset of SAH or ICH. An increase in CSF lactate or L/P ratio shortly after the onset is followed by a gradual fall to the control level two weeks later.

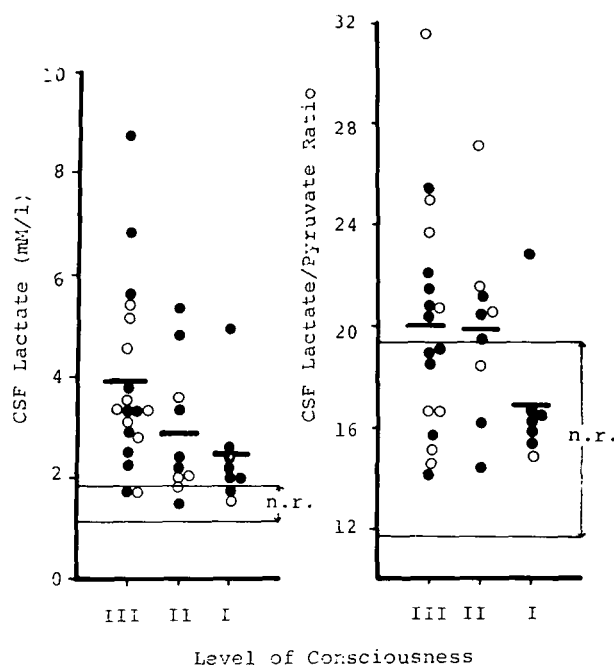


FIGURE 2

CSF lactate and L/P ratio relating to the level of consciousness at the time of onset. An increase in CSF lactate or L/P ratio is greater in patients having the impairment of consciousness such as coma or semicoma (Grade 3), or stupor or somnolence (Grade 2) than in those who were alert (Grade 1).

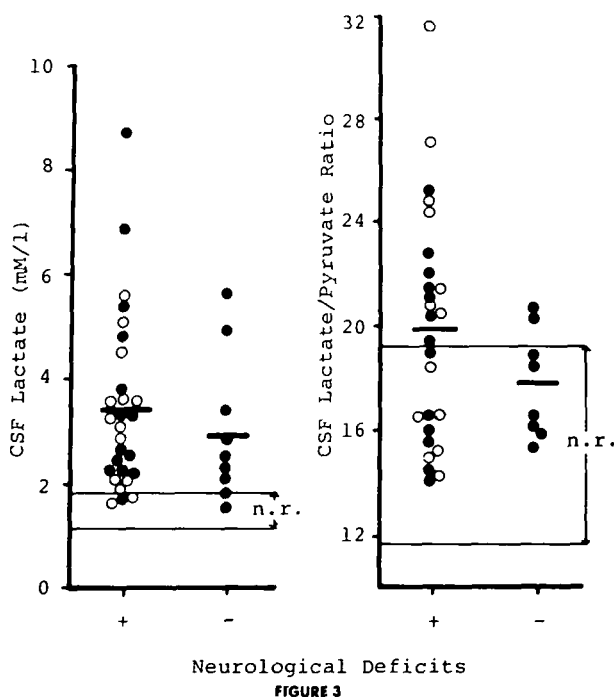
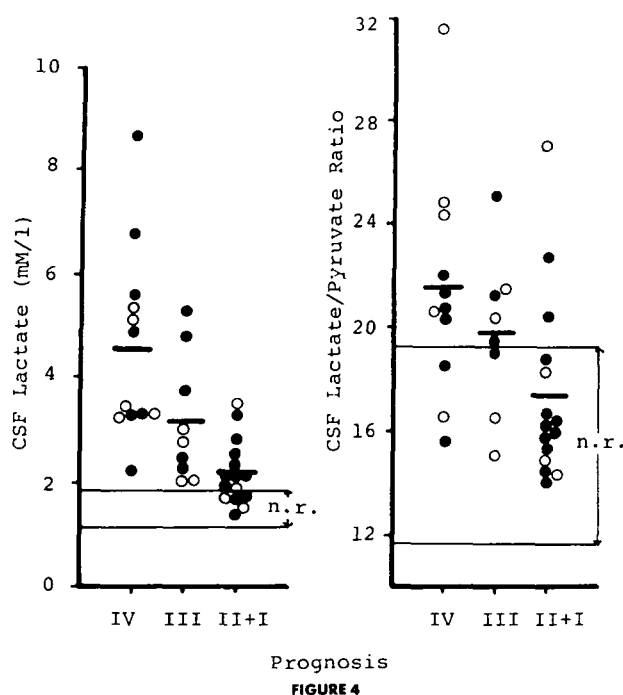
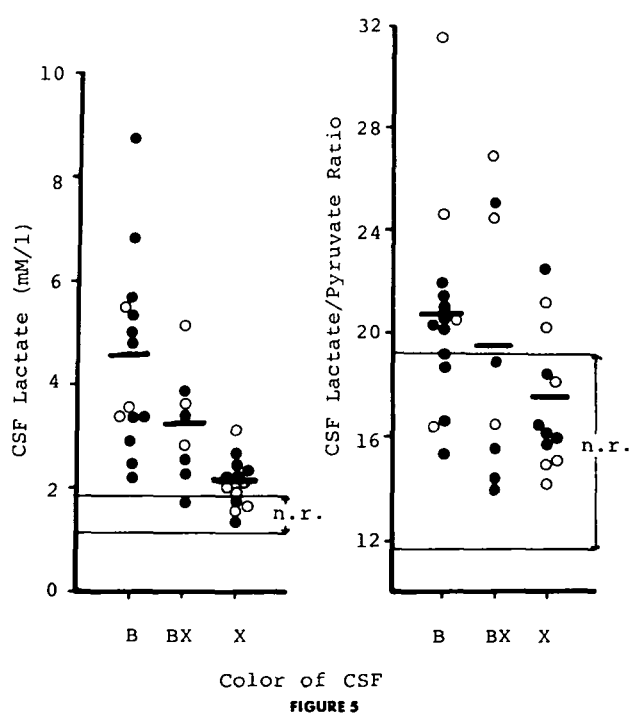


FIGURE 3

CSF lactate and L/P ratio in patients with or without neurological deficits.



**FIGURE 4**  
Relation of CSF lactate or L/P ratio to prognosis. Increases in CSF lactate and L/P ratio are greater in patients with a poor prognosis such as Grade 4 (dead) and Grade 3 (worsened) than in those with a good prognosis as Grade 2 (improved) or Grade 1 (cured).



**FIGURE 5**  
Relation of CSF lactate or L/P ratio to color of CSF. They increase to the greater extent in bloody CSF (B) than in xanthochromic CSF (X).

had CSF lactate of  $2.25 \pm 0.16$  mM per liter. Similarly, CSF L/P ratio was the highest at  $21.5 \pm 1.3$  in Grade 4 patients,  $19.8 \pm 1.1$  in Grade 3, and  $17.4 \pm 0.9$  in Grade 2 or 1.

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

##### Color of CSF (Fig. 5)

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  $4.47 \pm 0.46$  mM per liter in (B),  $3.16 \pm 0.33$  mM per liter in (B-X), and  $2.09 \pm 0.12$  mM per liter in (X). Mean CSF L/P ratio was  $20.7 \pm 1.1$  in (B),  $19.5 \pm 1.9$  in (B-X), and  $17.5 \pm 0.8$  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 H<sub>2</sub>O. In one case with an extremely high CSF pressure, however, CSF lactate or L/P ratio did not increase markedly.

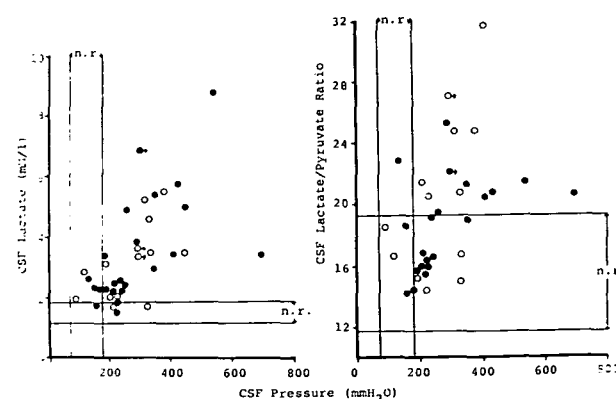
#### CSF LACTATE AND L/P RATIO AND THEIR RELATIONSHIPS TO ARTERIAL AND CSF ACID-BASE BALANCE

##### 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 Pco<sub>2</sub> 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 HCO<sub>3</sub><sup>-</sup> and CSF lactate ( $r = -0.548$ ,  $P < 0.001$ ). When CSF lac-



**FIGURE 6**  
Relation of CSF lactate or L/P ratio to the opening pressure of CSF. There is a positive correlation between CSF lactate and CSF pressure ( $r = 0.581$ ,  $P < 0.001$ ) as well as between CSF L/P ratio and CSF pressure ( $r = 0.452$ ,  $P < 0.01$ ).

# CSF AND ARTERIAL LACTATE, PYRUVATE AND ACID-BASE BALANCE

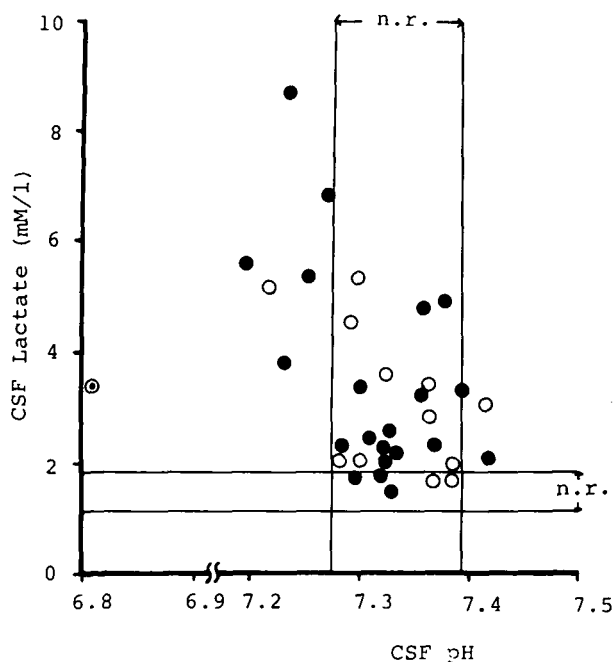


FIGURE 7

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  $Paco_2$  more than 100 mm Hg.

tate increased by 1 mM per liter, CSF  $HCO_3^-$  decreased by approximately 3 mEq per liter.

## Arterial $Pco_2$ (Fig. 9)

There was a significant correlation between CSF lactate and  $Paco_2$  ( $r = -0.0412$ ,  $P < 0.05$ ). In five of six patients with increased CSF lactate greater than 5 mM per liter,  $Paco_2$  decreased below the normal range. On the other hand, there was no relation between CSF pH and  $Paco_2$  ( $r = 0.124$ ,  $P > 0.4$ ).

## CSF AND ARTERIAL PARAMETERS AS PROGNOSTIC INDICATORS

CSF lactate, L/P ratio,  $HCO_3^-$ , pH and arterial  $Pco_2$  were selected as possible neurological prognostic indicators in patients studied within five days after onset in nine ICH and 13 SAH patients. As depicted in table 3, CSF lactate greater than 2.5 mM per liter was observed in five of seven cases, or 72%, with Grade 1 or 2 neurological severity (improved), and in all of those, or 100%, with Grade 3 or 4 (unimproved). CSF L/P ratio more than 20, with concomitant increase in CSF lactate, was seen in 29% of the former group and 73% of the latter. In addition to high CSF lactate and L/P ratio, a low  $Paco_2$  below 31.5 mm Hg was observed in 14% of the improved cases and in 40% of the unimproved cases. Instead of  $Paco_2$ , CSF pH or CSF  $HCO_3^-$  seemed more useful as prognostic indicators. CSF  $HCO_3^-$  below 20.4 mEq per liter plus high CSF lactate and L/P ratio were obtained in nine

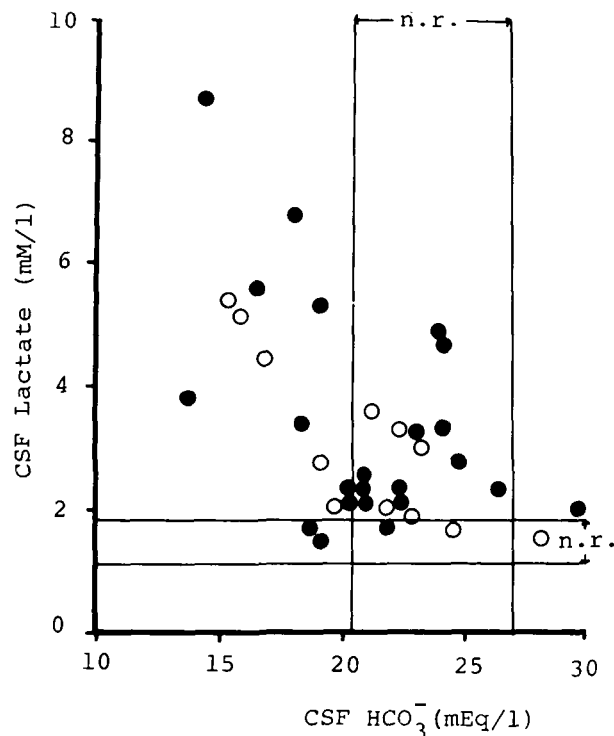


FIGURE 8

Relation of CSF lactate to CSF  $HCO_3^-$ . A correlation between two parameters is of statistical significance ( $r = -0.548$ ,  $P < 0.001$ ).

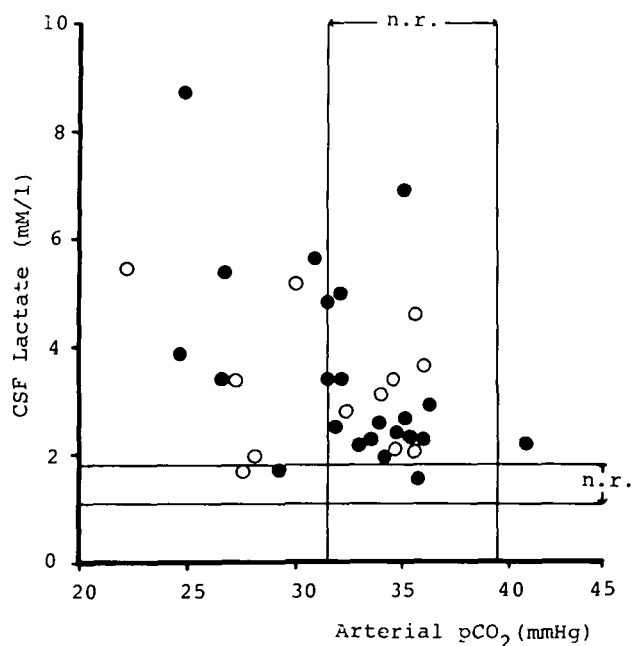


FIGURE 9

Relation of CSF lactate to arterial  $Pco_2$ . An inverse correlation between two parameters ( $r = -0.412$ ,  $P < 0.05$ ) indicates that patients with the higher value for CSF lactate might hyperventilate, resulting in lowered  $Paco_2$ .



TABLE 3

CSF and Arterial Parameters Determined Within Five Days After Onset as Prognostic Indicators

	ICH		SAH		Total	
	3 & 4* (7)†	1 & 2 (2)	3 & 4 (8)	1 & 2 (5)	3 & 4 (15)	1 & 2 (7)
CSF lactate (> 2.5 mM/L)	7	0	8	5	15(100%)	5(72%)
CSF lactate + CSF L/P ratio (> 20)	5	1	6	1	11(73%)	2(29%)
CSF lactate + CSF L/P ratio + PaCO <sub>2</sub> (< 31.5 mm Hg)	2	0	4	1	6(40%)	1(14%)
CSF lactate + L/P ratio + CSF pH (< 7.276)	2	0	5	0	7(47%)	0(0%)
CSF lactate + CSF L/P ratio + CSF HCO <sub>3</sub> <sup>-</sup> (< 20.4 mEq/L)	4	0	5	1	9(60%)	1(14%)

\*Severity scale. See text for explanation.

†Number in parentheses indicates the number of cases.

of 15 cases, or 60%, with Grade 3 or 4, whereas it was seen in only one of seven cases, or 14%, with Grade 2 or 1. On the other hand, none of the cases in the improved group had a lowered CSF pH below a normal range, whereas almost one-half of those with a poor prognosis had an acidotic CSF below 7.276.

## 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 obtained 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,<sup>1-5</sup> head injury,<sup>8,9</sup> hypoxemia,<sup>10</sup> and meningitis,<sup>11</sup> or in conditions interfering with blood or oxygen delivery to the brain.<sup>12,13</sup> Our previous study,<sup>5</sup> as well as others,<sup>2-4</sup> have shown that an increase in CSF lactate was more pronounced in hemorrhagic cerebrovascular diseases than in ischemic strokes. It is probable that shed blood cells' metabolism per se in CSF produced lactate. This was confirmed by Froman and Smith,<sup>6</sup> who demonstrated in an in vitro study that the mean rate of lactate production was 7.4  $\mu$ mol per gram per hemoglobin per hour in a mock CSF with blood admixture. Furthermore, Granholm<sup>14</sup> found a linear relationship of the production of both lactate and pyruvate with time in feline CSF samples tonometered for one to three hours with blood. No obvious changes in L/P ratio occurred.

In an in vivo study, Shannon et al.<sup>15</sup> demonstrated that a progressive increase in lactate with a concomitant decrease in HCO<sub>3</sub><sup>-</sup> and pH with time developed in CSF following the intracisternal injection of red blood cells in dogs. Granholm<sup>14</sup> 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,<sup>16</sup> however, CSF lactate increased progressively with time following the intracisternal in-

jection of blood in dogs, but also CSF L/P ratio started to increase at three hours after injection. Granholm<sup>14</sup> 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 experiments<sup>16</sup> 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,<sup>17</sup> 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 cytoplasmic NADH/NAD<sup>+</sup> system.<sup>18</sup> 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. Siesjö and Zwetnow<sup>19</sup> have shown that a lowering of the cerebral perfusion pressure is accompanied by an increased CSF L/P ratio. During passive hyperventilation reducing PaCO<sub>2</sub> below 20 to 25 mm Hg, CSF L/P ratio rises possibly due to cerebral vasoconstriction resulting in decreased cerebral blood flow.<sup>20</sup> Although in the present study there was no obvious difference in PaCO<sub>2</sub>, PO<sub>2</sub> 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 Siesjö<sup>21,22</sup> 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 hypercapnia,<sup>23</sup> 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,<sup>21-23</sup> 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.,<sup>3</sup> similar to our previous study,<sup>5</sup> demonstrated that a decrease in  $P_{aCO_2}$  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.,<sup>1</sup> Schnaberth and Summer,<sup>2</sup> and Lane et al.<sup>4</sup> In our experimental study,<sup>24</sup> we found that there was an inverse relationship between brain tissue lactate and  $P_{aCO_2}$  in rats, in which cerebral ischemia was induced by ligating the bilateral carotid arteries. Similarly, hyperventilation with a consequent decrease in  $P_{aCO_2}$  has been observed frequently after acute cerebrovascular disease,<sup>1, 2, 4, 6, 25</sup> serious head injuries,<sup>26</sup> and a variety of brain lesions in patients.<sup>27</sup> 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,  $P_{aO_2}$  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,<sup>28</sup> who had one case with ICH in which hyperventilation might be explained by hypoxia, but restoration of a normal  $P_{aO_2}$  by increasing oxygen content in the inspired air did not influence his ventilation 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  $P_{aCO_2}$  in this study as well as other observations.<sup>4, 29</sup> Particularly, Lane et al.<sup>4</sup> 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.,<sup>29</sup> concluded that CSF acidosis is not responsible for hyperventilation.

Although there was no significant relationship between CSF pH and  $P_{aCO_2}$ , in other words, more acidotic CSF pH did not cause lower  $P_{aCO_2}$ , 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.<sup>30</sup> The regulatory mechanisms for CSF constancy are the compensatory mechanisms of pulmonary ventilation and the renal re-absorption of  $HCO_3^-$  which regulate  $P_{CO_2}$  and  $HCO_3^-$  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  $HCO_3^-$  ratio between CSF and plasma. Siesjö<sup>30</sup> stated that although changes in cerebral blood flow induce regulatory variations in CSF  $P_{CO_2}$  during acute respiratory acid-base imbalance, the mechanism is of little importance in most chronic disorders.

Leusen<sup>31</sup> observed that pulmonary ventilation was increased when cerebral ventricles were perfused with solutions high in  $P_{CO_2}$  or low in  $HCO_3^-$ . Similar observations have been made by Mitchell et al.,<sup>32</sup> 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.<sup>33</sup> found in conscious goats that ventilation increased from 5 to 45 liters per minute for a pH change of 0.15 unit. Fencel and his coworkers<sup>34</sup> 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,  $P_{CO_2}$  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  $P_{CO_2}$  difference between CSF and plasma indicates that respiratory compensation might be the reason the CSF acidosis disappeared. Beside the  $P_{CO_2}$  difference,  $HCO_3^-$  concentration difference between CSF and blood could become wider in primary metabolic acidosis of CSF, resulting in a greater concentration gradient of  $HCO_3^-$  between two components. Therefore,  $HCO_3^-$  tended to move passively from plasma to CSF, while there is a slight difference in  $HCO_3^-$  even at the normal steady state.<sup>30</sup>

The severity of the clinical symptoms runs parallel to changes in acid-base balance. Schnaberth and Summer<sup>2</sup> found that CSF  $HCO_3^-$  of less than 18 mEq per liter is associated with a poor prognosis. Sambrook et al.<sup>3</sup> reported that CSF  $HCO_3^-$  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 respirations 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  $\text{HCO}_3^-$ , CSF pH and arterial  $\text{Pco}_2$ . 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  $\text{HCO}_3^-$  less than 20.4 mEq per liter, CSF pH below 7.276, and  $\text{Paco}_2$  less than 31.5 mm Hg indicate a poor prognosis for patients with ICH.

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