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Time Course of CSF Lactate Level in Subarachnoid Haemorrhage

Correlation with Clinical Grading and Prognosis

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Summary

Cisternal and/or ventricular cerebrospinal fluid (CSF) and arterial blood lactate and acid-base balance were measured serially in 38 patients with aneurysmal subarachnoid haemorrhage (SAH). Based on daily clinical assessment, the patients and accordingly the samples were divided into two groups according to the grading of the World Federation of Neurosurgical Societies (W.F.N.S.). In cisternal CSF, samples of Grade III-V showed significantly higher lactic acidosis than those of Grade I-II. The time course of lactate and pH in poor prognosis groups had a significant tendency of lactic acidosis, especially on the 5th, 6th, 7th day after SAH. Ventricular CSF lactate increased even without CSF acidosis in Groups III-V. Measurement of CSF lactate, especially from the cisterna magna is useful as an indicator of prognosis and changes of intracranial environment following SAH.

Keywords: Intracranial aneurysm; subarachnoid haemorrhage; cerebrospinal fluid; lactic acidosis; cisternal drainage.

Introduction

Increased anaerobic metabolism in brain tissue leads to cerebrospinal fluid (CSF) lactic acidosis, and arterial blood respiratory alkalosis results from the activation of the brain stem respiratory centre[9, 10, 16]. Many investigators reported that the rise in CSF lactate concentration resulted from brain tissue hypoxia, such as oligaemic shock[6], circulatory arrest[28], hypoxaemia[17], hyperventilation[19], head injury[5, 15], bacterial meningitis[3, 4] and brain infarction[9, 10]. Measurement of CSF acid-base balance and lactate concentration has been well known as a significant clinical indicator of prognosis and intracranial circumstances, especially in cases with head injury[5, 15] and brain infarction[11, 29].

It is also well known that admixture of blood to CSF gives rise to a progressive increase in the CSF lactate concentration produced by anaerobic glycolysis in shed blood cells[13, 24]. Increased CSF lactate concentration following subarachnoid haemorrhage (SAH) has also been explained in this way[8]. However, recent studies reported that the increase of CSF lactate concentration reflected not only glycolysis of shed blood cells but also brain tissue hypoxia caused by primary SAH.

In this study, we measured daily cisternal and/or ventricular CSF lactate concentrations, acid-base balance and electrolytes following SAH, and investigated the correlation between these parameters and prognosis.

Clinical Material and Methods

Summary of Cases

The series consists of 38 patients (21 males and 17 females) with SAH due to ruptured aneurysms within 48 hours prior to admission. The diagnosis was confirmed by computed tomography and cerebral angiography. The mean age of the patients was 53 years (ranging from 34 to 73 years). The outcome of the patients was divided into two groups according to the Glasgow Outcome Scale, that is, good recovery and moderate disability were defined as Group 1, and severe disability, vegetative state and dead as Group 2. The clinical grade of the patients according to the grading of the World Federation of

Table 1. *Clinical Grading of Cases After SAH of World Federation of Neurosurgical Societies.* GCS: Glasgow coma scale

Grade	GCS	Neurological Deficit (Paralysis and/or aphasia)
I	15	−
II	13−14	−
III	13−14	+
IV	7−12	+ or −
V	3− 6	+ or −

Table 2. *Relationship Between Clinical Grade on Admission and Outcome.* Parenthesis is the number of case with cisternal drainage, double parenthesis is that with ventricular drainage. Grading according to W.F.N.S.

Grade \ Outcome	Group 1	Group 2
Gr. I – II	22 (22) ((4))	9 (6) ((7))
Gr. III – V	1 (0) ((1))	6 (0) ((6))

Neurosurgical Societies (W.F.N.S.) on admission is shown in Table 1 and its outcome in Table 2. Fifty-one percent (23/38) of the patients were among the Group 1.

The ruptured aneurysms were located at the anterior cerebral artery complex in 18 individuals, the internal carotid artery complex in 8, middle cerebral artery in 15, basilar artery in 1. Six of these patients had multiple aneurysms. In 82% of the patients (31/38), surgical obliteration for ruptured aneurysm was performed within 82 hours after SAH. Cisternal and/or ventricular drainage was placed in all patients: cisternal in 28 cases, ventricular in 18 cases and both in 7 cases (Table 2).

Analysis of CSF

Samples of arterial blood and CSF were periodically analyzed for the partial pressure of carbon dioxide (pCO_2), bicarbonate (HCO_3^-) and pH using IL-1303 Gas Analyzer with attention given to prevent exposure to room air. Lactate concentration was measured in arterial blood and CSF by using Lactate Analyzer HER 100 (OMRON Tateishi Electronics) after samples were withdrawn into chilled syringes with sodium fluoride. Arterial blood and CSF electrolytes (Na, K and Cl) and CSF cell counts, protein and glucose were also measured simultaneously.

Results

Based on daily clinical assessment, the samples obtained from the cisterna or ventricle were divided into two groups according to the grading of the W.F.N.S.: in cisternal CSF, 125 samples were from Grade I–II, 44 samples were from Grade III–V, while in ventricular CSF, 42 samples were from Grade I–II, 72 samples were from Grade III–V. Values of CSF and arterial blood parameters in relation to daily clinical grade are shown in Tables 3 and 4. In cisternal CSF, samples in Grade III–V had statistically significantly higher lactate values ($p < 0.01$) and lower pH values ($p < 0.01$) than those in Grade I–II. On the other hand, in ventricular CSF, samples in Grade III–V had definitely higher lactate values ($p < 0.01$) than those in Grade I–II, but pH values showed no significant difference between Grade I–II and III–V (Figs. 1 and 2). In both cisternal and ventricular drainage groups, samples in Grade III–V had significantly higher arterial blood lactate, CSF and arterial blood Na and Cl than those in

Table 3. *Values of CSF Parameters in Relation to Daily Clinical Grade.* Values are means ± standard deviations. Significance: ** = $p < 0.01$, * = p 0.05 by non-paired T-test compared with values of Grade I–II to Grade III–V

	Cisternal CSF		Ventricular CSF	
Grade	I – II	III – V	I – II	III – V
pH	7.424±0.047	7.399±0.054**	7.404±0.045	7.393±0.058
pCO_2 (mmHg)	33.8±5.0	34.9±3.9*	34.8±3.8	35.3±6.5
HCO_3^- (mmol/l)	22.2±2.3	21.8±2.3	21.9±1.9	21.5±2.4
lactate (mg/dl)	25.1±5.5	32.6±7.4**	21.8±7.0	35.8±18.8**
cell count	445±1138	419±901	182±240	254±454
protein (mg/dl)	71.5±49.3	124.2±125.2**	45.1±55.3	80.5±180.7
glucose (mg/dl)	84.7±25.8	93.9±39.9	87.2±29.7	103.4±33.3*
Na (mEq/l)	145.6±4.5	150.6±8.3**	145.4±5.4	148.9±8.0*
K (mEq/l)	2.6±0.3	2.7±0.4	2.3±0.2	2.6±1.3**
Cl (mEq/l)	123.5±5.2	129.4±8.8**	123.7±6.1	126.5±9.1*

Table 4. *Values of Arterial Blood Parameters in Relation to Daily Clinical Grade.* Values are means ± standard deviations. Significance: ** = $p < 0.01$, * = $p < 0.05$ by non-paired T-test compared with values of Grade I–II

	Cisternal CSF		Ventricular CSF	
Grade	I – II	III – V	I – II	III – V
pH	7.465±0.025	7.469±0.029	7.462±0.032	7.460±0.041
pCO_2 (mmHg)	34.0±3.7	33.2±4.0	33.2±4.4	33.4±4.8
HCO_3^- (mmol/l)	24.7±2.5	24.3±2.6	23.8±2.1	24.0±3.5
lactate (mg/dl)	14.4±16.4	14.4±4.8*	13.0±5.9	20.4±13.9**
Na (mEq/l)	139.2±4.2	143.0±5.9**	137.2±5.4	142.8± 6.3**
K (mEq/l)	4.0±0.5	3.9±0.5	3.9±0.6	3.8± 0.5
Cl (mEq/l)	103.0±6.3	108.4±4.8**	102.7±6.0	106.1± 6.8**

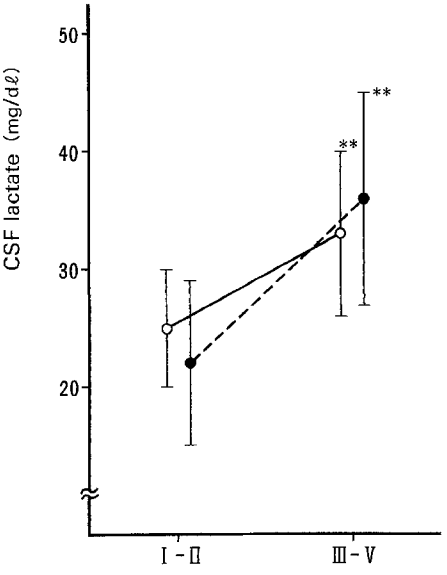

Fig. 1. Correlation between CSF lactate concentration and daily clinical grade. Open circles are values from cisternal CSF, and solid circles are values from ventricle. Values are means ± standard deviations. Significance: ** = $p < 0.01$ by non-paired T-test compared with Grade I–II to Grade III–V

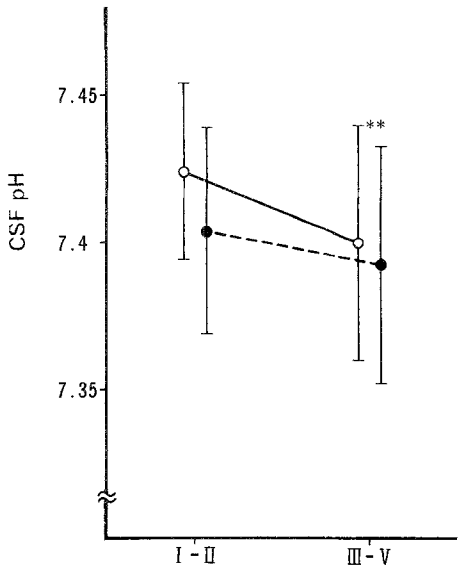

Fig. 2. Correlation between CSF pH and daily clinical grade. Open circle are values from cistern, and solid circles are values from ventricle. Values are means ± standard deviations. Significance: ** = $p < 0.01$ by non-paired T-test compared with Grade I–II to Grade III–V

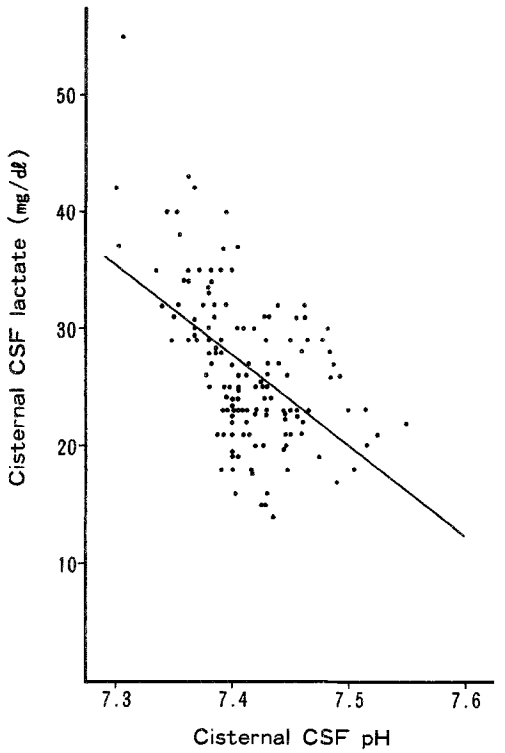

Fig. 3. Correlation between CSF lactate concentration and pH from cisternal drainage ($n = 141$, $r = -0.529$, $p < 0.01$, CSF lactate = 600.8 — 77.5 CSF pH)

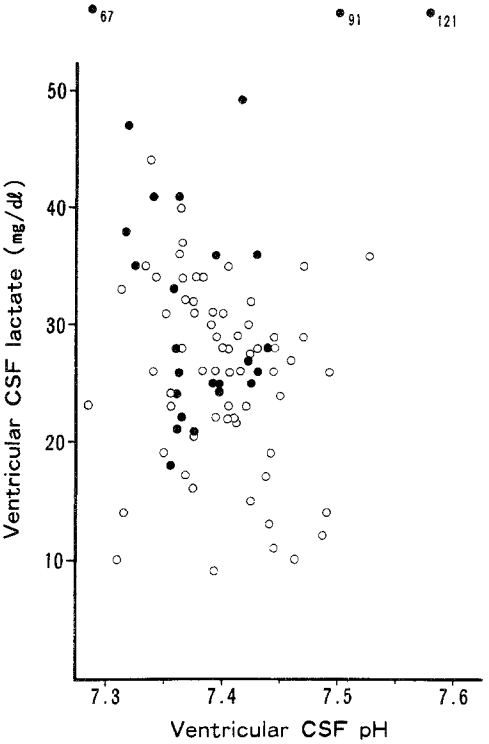

Fig. 4. Correlation between ventricular CSF lactate concentration and pH. Open circles are values of cases without ventricular haemorrhage, and solid circles are values with ventricular drainage

Group I–II. By multivariate statistical analysis, one parameter which demonstrated the highest correlation coefficient with cisternal CSF lactate concentration, was the CSF pH not having regard to the presence of intraventricular haemorrhage (Fig. 4). There was no significant relationship between electrolytes, lactate and acid-base balance in either CSF or arterial blood, but a high correlation coefficient with CSF protein concentration ($p < 0.01$) (Fig. 5).

The correlation between prognosis and the time course of lactate concentrations and pH in both cisternal and ventricular CSF during the first 10–16 days after SAH are shown in Figs. 6, 7, 8, 9. In cisternal CSF, each daily lactate value in Group 2 was significantly higher than those in Group 1, especially on the 5th, 6th, 7th day. Daily cisternal CSF pH values in Group 2 were lower than those in Group 1, especially on the 7th day following SAH ($p < 0.05$). In ventricular CSF, lactate values in Group 2 were also higher than those in Group 1 on the 4th, 5th, 6th day from the onset ($p < 0.05$). Ventricular CSF pH values were lower in Group 2 than in Group 1 between the 3rd and 5th days, however, this was not statistically significant. Six patients deteriorated with the appearance of focal

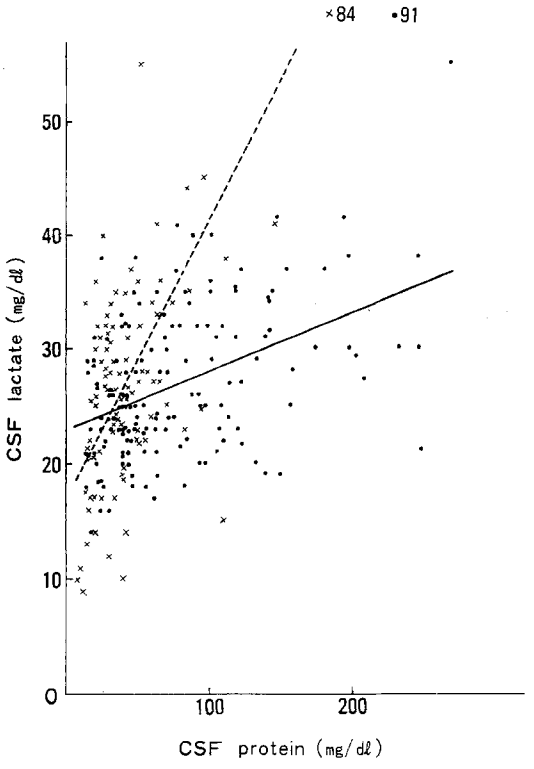

Fig. 5. Correlation between CSF lactate concentrations and CSF protein. Dots are values from cistern, and crosses are values from ventricle (values from cistern: n = 149, r = 0.441, $p < 0.01$, CSF lactate = 22.9 + 0.05 CSF protein, values from ventricle: n = 97, r = 0.708, $p < 0.01$, CSF lactate = 17.1 + 0.25 CSF protein)

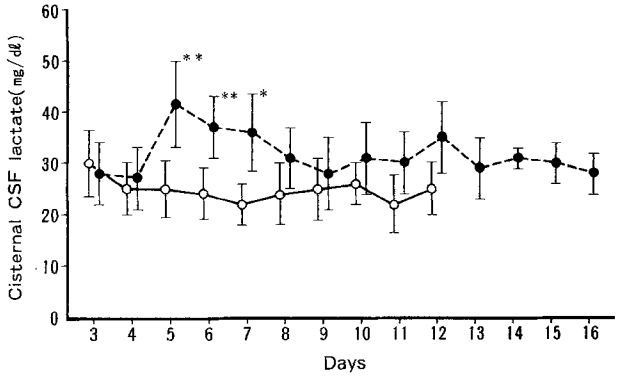

Fig. 6. Correlation between prognosis and the time course of cisternal CSF lactate concentrations. Open circles are values of Group 1, and solid circles are values of Group 2. Values are means ± standard deviations. Significance: ** – $p < 0.01$, * = $p < 0.05$ by non-paired T-test compared with Group 1 and 2

neurological signs due to cerebral vasospasm, which was verified by cerebral angiography. Cisternal CSF lactate value usually increased for the last 1 or 2 days before the day of deterioration (Fig. 10). But, cisternal CSF pH values were increased in 2 of 3 cases (Fig. 11).

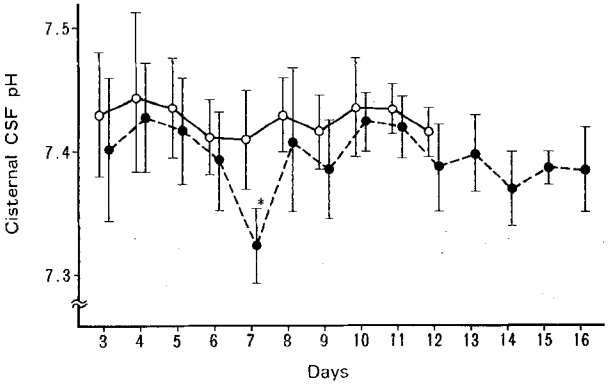

Fig. 7. Correlation between prognosis and the time course of cisternal CSF pH. Open circles are values of Group 1, solid circles are values of Group 2. Values are means ± standard deviations. Significance: * = $p < 0.05$ by non-paired T-test compared with Group 1 and 2

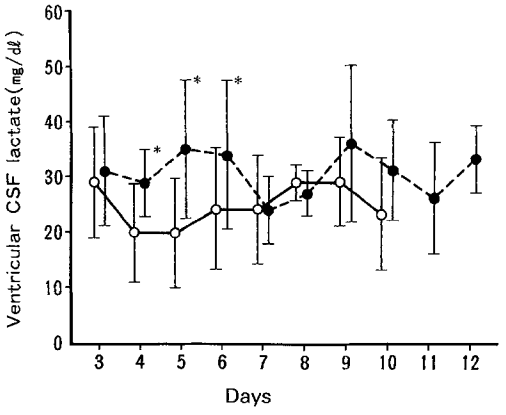

Fig. 8. Correlation between prognosis and the time course of ventricular CSF lactate. Open circles are values of Group 1, and solid circles are values of Group 2. Values are means ± standard deviations. Significance: * = $p < 0.05$ by non-paired T-test compared Group 1 and 2

In ventricular CSF, changes of lactate and pH values after deterioration were variable (Figs. 10 and 11). In one case deterioration was due to aneurysmal rupture, ventricular CSF lactate concentration increased remarkably after rerupture (Fig. 10).

Seven patients developed meningitis. The diagnosis was confirmed by renewed elevation of CSF cell counts over 1000/3/mm while they had been declining to the normal range after the acute phase of SAH. Neutrophil leucocytosis, decrease of CSF glucose, increase of CSF protein and clinical signs of meningitis such as fever and neck stiffness were recorded. The causative organism was found in only one of the 7 cases. CSF lactate concentrations increased remarkably after the onset of meningitis (Fig. 12).

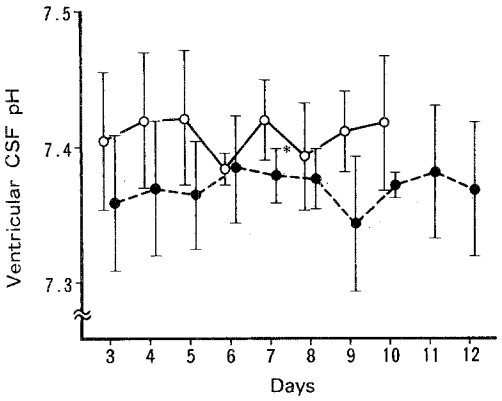

Fig. 9. Correlation between prognosis and the time course of ventricular CSF pH. Open circles are values of Group 1, and solid circles are values of Group 2. Values are means ± standard deviations. Significance: * = $p < 0.05$ by non-paired T-test compared Group 1 and 2

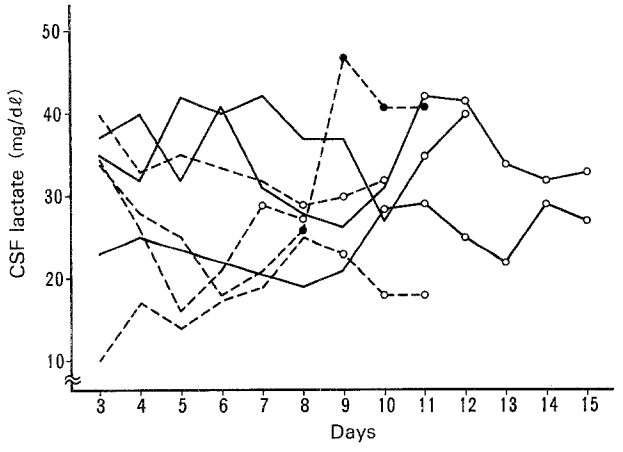

Fig. 10. The time course of CSF lactate concentrations in cases with deterioration due to cerebral vasospasm. Open circles are appearance of typical focal sign, solid circles are case with rerupture. Solid lines are values from cistern, and dotted lines are from ventricle

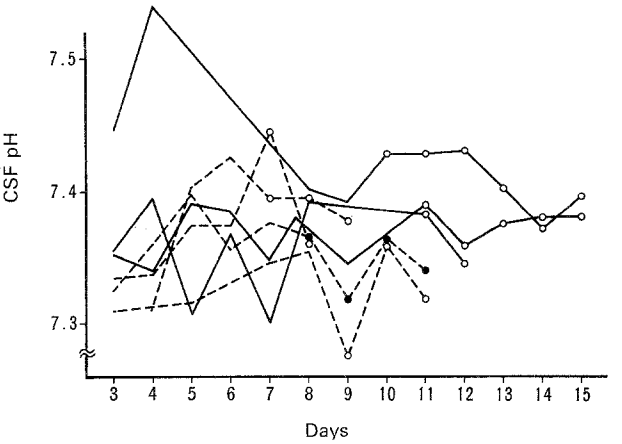

Fig. 11. The time course of CSF pH in cases with deterioration due to cerebral vasospasm. Open circles are appearance of typical focal sign, solid circles are case with rerupture. Solid lines are values from cistern, dotted lines are from ventricle

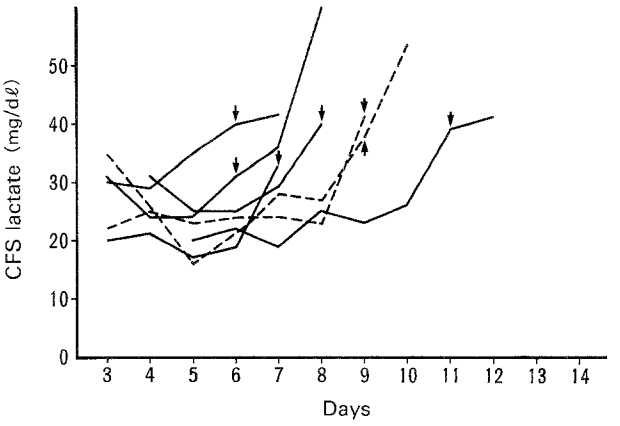

Fig. 12. The time course of CSF lactate concentration in cases with meningitis. Arrows are appearance of signs of meningitis

In 7 cases, both cisternal and ventricular drainage was instituted and 27 CSF samples were obtained from these sites. By Wilcoxon's two paired test, lactate concentrations, cell counts and protein in cisternal CSF were significantly higher than those in ventricular CSF. By contrast, CSF HCO_3^-, and glucose were significantly lower from the cisterna than from the ventricle (Table 5). But no difference in pH and pCO_2 values could be found between the two groups.

Arterial blood Na and Cl were significantly correlated with those of CSF, that is the coefficient correlation ratio was Na:0.805, Cl:0.772 in cisternal CSF ($p < 0.01$), Na:0.857, Cl:0.728 in ventriclar CSF ($p < 0.01$). However, there was no statistically significant correlation between arterial blood and CSF K.

Table 5. *Correlation Between Cisternal and Ventricular CSF in Paired Samples.* Values are means ± standard deviations. Significance: ** = $p < 0.01$, * = < 0.05 by Wilcoxon's two paired test

		cistern	ventricle
pH		7.418 ± 0.085	7.409 ± 0.038
pCO_2	(mmHg)	32.9 ± 5.6	34.7 ± 4.0
HCO_3^-	(mmol/ℓ)	21.2 ± 2.1	22.1 ± 2.2*
lactate	(mg/dℓ)	31.9 ± 9.0	23.0 ± 9.5**
cell count	(/3/mm)	1288 ± 2772	217 ± 307**
protein	(mg/dℓ)	180 ± 184	66 ± 80**
glucose	(mg/dℓ)	82 ± 37	101 ± 44**
Na	(mEq/ℓ)	147 ± 8	148 ± 7
K	(mEq/ℓ)	2.7 ± 0.6	2.8 ± 1.9
Cl	(mEq/ℓ)	125.7 ± 8.9	127.3 ± 8.1

By multivariate statistical analysis, the highest coefficient correlation ratio documented with CSF K was cisternal HCO_3 and ventricular CSF protein in these parameters.

Discussion

Froman and Smith[8] found a fall in CSF pH and bicarbonate associated with a rise in lumbar CSF lactate concentration following SAH, and it was concluded that this increase of lactate was due to the glucose metabolism of shed blood cells. Similar observations showing a rise of lactate in haemorrhagic CSF have also been reported[13, 24]. Sugi *et al.*[25] reported that an increase in CSF lactate and lactate/pyruvate ratio in experimentally induced SAH in dogs seemed to be caused by two different factors; the lactate producing glycolytic process in the shed blood cells and blood in the subarachnoid space causing secondary changes in brain tissue metabolism due to a probable reduction of cerebral blood flow. Accordingly, CSF lactate concentration may be invalid as an indicator of cerebral hypoxia, but CSF lactate/pyruvate ratio is assumed to reflect the redox state of cerebral hypoxia in the presence of haemorrhagic CSF[14], since the production of lactate and pyruvate from blood cells will not change this ratio significantly[13]. In our study excluding the cases with rerupture, cisternal CSF lactate concentration in Group 2 increased remarkably with a fall in CSF pH in the period following the first 5 to 7 days after SAH during which blood disappeared from the CSF. The changes in CSF lactate concentration from the cisterna magna ran parallel with the clinical signs particularly in patients who deteriorated due to cerebral vasospasm. Although bloody CSF lactate concentrations in such circumstance as reruptured aneurysm increased, lactate clearance from CSF is a relatively slow process[21, 26], with the bulk accounted for by diffusion into the brain tissue. However, CSF lactate concentration indicates cerebral hypoxia when blood disappeared from the CSF.

Another factor reported by Sambrook *et al.*[22] contributing to the increased CSF lactate production after SAH was hyperventilation. In our study, CSF lactate concentration had no significant correlation with arterial blood acid-base balance. This seems to be the effect of other CSF lactate increasing factors and general complications such as pneumonitis and cardiac failure etc. that affect arterial blood acid-base balance.

Most investigators have used lumbar CSF for studies of CSF lactate concentrations following SAH, but the lactate values of lumbar CSF are higher than that of cisternal and ventricular CSF due to stagnation of blood in the lumbar sac[20]. Voldby *et al.*[27] reported that ventricular lactate concentrations following SAH correlated fairly well with clinical grading; with intraventricular pressure and prognosis, however, no significant correlations with CSF pH, lactate concentrations and clinical grading were noted. They also described that samples of ventricular CSF probably comprise a mixture of both cisternal and ventricular CSF due to ventricular CSF reflux in patients with impaired CSF flow and absorption following SAH. Our results were in accordance with cisternal CSF lactate concentrations; pCO_2 and pH were well correlated with clinical grading, but ventricular CSF parameters excluding lactate were not. The time course of changes in ventricular CSF lactate concentrations and pH after deterioration due to cerebral vasospasm were variable. On the other hand, changes in cisternal CSF lactate concentrations increased with a concurrent clinical deterioration. Acid-base balance in CSF obtained simultaneously from cistern and ventricle were not much different in either CSF from the cisterna or ventricle excluding HCO_3^- values, but CSF lactate concentrations from the cisterna were significantly higher than that from the ventricle. These results suggest that cisternal CSF lactate concentrations are more sensitive than ventricular ones in patients with clinical signs of vasospasm.

It is thought that cerebral tissue acidosis resulted from supernumerary production of lactate due to accumulation of the anaerobic metabolites following cerebral tissue hypoxia[18]. This increasing intra-tissue lactate (and pyruvate) dilutes to CSF and H^+ is neutralized by HCO_3^-. Therefore, CSF lactate is inversely proportional to CSF HCO_3^-. Furthermore, cerebral hypoperfusion may contribute to impede the intra-tissue CO_2 excretion and this intra-tissue CO_2 accumulation subsequently increased CSF pCO_2. Consequently, cerebral tissue hypoxia leads to CSF respiratory acidosis in addition to CSF metabolic acidosis[11]. In our study, no significant correlation between CSF lactate concentrations and CSF HCO_3^- were noted, but the factor with a high correlation coefficient with CSF lactate concentrations from both the cisterna and ventricle was the CSF protein concentration. Our results and the fact that the amount of red blood cells in the CSF parallels the CSF protein concentration[2] suggest that a glycolytic process in the shed blood cells attenuate correlation between lactate and acid-base balance such as in non-haemorrhagic CSF. We spec-

ulate that the significant increase in cisternal CSF lactate concentration in Group 2 resulted from cerebral hypoxia due to not only brain oedema caused by SAH and/or surgical intervention but also cerebral vasospasm, because this difference was especially pronounced on the 5, 6, 7th day after SAH, when vasospasm occurred.

Sambrook *et al.*[23] reported that serial changes in CSF Na and CL occurred in association with alternation in these ions in plasma, and CSF CL tended to decrease by Donnan's effect following increase of CSF protein[7]. However, in our study, arterial blood and CSF Na and CL in Grade III–V were higher than those in Grade I–II regardless of increased CSF protein. This result might be related to osmotherapy applied for patients in a poor clinical state. The result appears to come from the fact that there is a tendency in which serious patients following SAH are being dehydrated for oedema. Alexander *et al.*[1] reported that elevations of blood dl-lactic acid concentration have been noted to have little effect on CSF lactate level. Accordingly, a significantly higher arterial blood lactate concentration in Grade III–V results from peripheral circulatory disturbance due to dehydration.

Surprisingly, changes of CSF K were not related to changes of arterial blood K. Sambrook *et al.*[23] reported that a decrease in CSF K was related to the severity of disturbances of consciousness. On the contrary, in our study K in Grade III–V from ventriclar CSF was significantly higher than that in Grade I–II and these results cannot yet be explained. Goldstein *et al.*[12] suggested that the decrease of CSF K after SAH may result from a promotion of K removal from CSF by glial cells and brain endothelial cells during the chemical meningitis following SAH. Anyway, at the present time, measurement of CSF electrolytes are of no clinical significance.

In conclusion, measurement of CSF lactate concentration, especially from the cisterna magna is useful as an indicator of prognosis and changes of intracranial circumstances such as brain oedema, hypoperfusion and meningitis following SAH. We institute cisternal drainage during acute aneurysmal surgery for the purpose of not only removing of cisternal blood but for monitoring of parameters and for serial CSF analysis to obtain valuable information about the clinical course and prognosis.

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