Lactate in the Cerebrospinal Fluid and Pressure-Flow Relationships in Canine Cerebral Circulation

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Abstract:
In 11 dogs, lactate and pH in the cerebrospinal fluid and in the arterial and the venous blood were measured during stepwise reductions of the arterial blood pressure by controlled bleeding. Increase in lactate and decrease in pH of the cerebrospinal fluid occurred with lowering of the mean arterial blood pressure even within the pressure ranges of 110 to 50 mm Hg, where autoregulation was fairly observed. Reductions of the blood pressure by 20 to 40 mm Hg led to a significant increase in lactate, and reductions by 60 mm Hg led to a significant decrease in pH of the cerebrospinal fluid.

The relation of decrease in pH and increase in lactate was linear, suggesting that lactacidosis occurred. In the arterial and the venous blood, a marked increase in lactate and decrease in pH also were observed. Lactate concentrations of the cerebral venous blood were significantly higher than those of the arterial blood until the arterial blood pressure had been reduced below 70 mm Hg. Therefore, it was suggested that increase in lactate of the cerebrospinal fluid might be attributed solely to increase in lactate of the brain tissue, so far as the blood pressure was not lowered below 70 mm Hg at least. The possibility of participation of the cerebrospinal fluid lactacidosis in autoregulation of the cerebral blood flow was discussed.

Additional Key Words: autoregulation, cerebral blood flow, lactacidosis, extracellular pH, regulation of blood flow

Methods
Eleven mongrel dogs weighing from 11 to 19 kg were anesthetized by intravenous injection of pentobarbital sodium, 25 mg/kg, and immobilized with gallamine triethiodide, 2 mg/kg initially and 1 mg/kg as required. They were ventilated through an endotracheal tube by a Harvard respirator pump, which was adjusted to keep the tracheal CO2 constant. Tracheal CO2 was monitored by an infrared gas analyzer (CG 119, Godart). Systemic arterial blood pressure was measured through a polyethylene tube connected to a pressure transducer (NP-4, Nihonkoden), which was inserted into the abdominal aorta via the femoral artery. The other femoral artery was cannulated by a polyethylene tube for removal of arterial blood samples and for withdrawing arterial blood to reduce the blood pressure. Another polyethylene tube was placed in the femoral vein for injections of gallamine triethiodide and heparin. The animals were heparinized by means of an intravenous injection of 0.5 ml/kg of a solution containing 1,000 I.U. of heparin per millilitre. The animal was in the prone position and the head was fixed in a holder. A needle was introduced percutaneously into the cisterna magna for removal of cerebrospinal fluid samples.

The cerebral blood flow was measured by cannulating the posterior third of the dorsal sagittal sinus. The cerebral venous blood from the dorsal sagittal sinus was drained to the jugular vein passing...
through a transducer probe of an electromagnetic
flowmeter (MF-12, Nihonkoden), as shown in figure 1.
The cerebral venous blood pressure was monitored
and cerebral venous blood samples were taken just
upstream to the flowmeter. The mean systemic arterial
blood pressure was reduced stepwise by 20 mm Hg and
maintained for about six minutes at each pressure by
removing or restoring the arterial blood. The cerebral
blood flow was measured at each pressure tested, and
the pressure-flow relationships were observed. The mean
arterial blood pressure was considered as the cerebral
perfusion pressures because the venous pressure
was between 2 to 7 cm H$_2$O during the experiments and the
variations of the venous pressure were so small. Arterial
and venous blood samples (4 ml) and cerebrospinal
fluid samples (0.5 ml) were taken after the mean
systemic blood pressure had been maintained at the
pressure tested for about six minutes. In arterial and
venous blood samples, $P_{O_2}$, $P_{CO_2}$, pH, oxygen saturation
and lactate concentrations were measured. Lactate and
$P_{O_2}$ were measured in cerebrospinal fluid samples. For
analyses of $P_{O_2}$, $P_{CO_2}$ and pH, a pH/gas analyzer
(Model 113-S1, Instrumentation Laboratory) was used.
The oxygen saturation was measured by a co-oximeter
(Model 182, Instrumentation Laboratory). For analysis
of lactate, samples of the cerebrospinal fluid and the
blood were immediately transferred to test tubes
containing ice-cold perchloric acid of 0.6 N. After
centrifugation and filtration, the samples were enzymat-
ically analyzed using test combination for lactate (TC-
B, No. 15972, supplied by C. F. Boehringer and Son,
Mannheim, Germany). Significant differences were
tested by Student's t test for paired data.

Results

PRESSURE-FLOW RELATIONSHIPS

The cerebral blood flow was measured during
stepwise reduction by 20 mm Hg of the mean
arterial blood pressures from 110 to 30 mm Hg. In
all of the 11 dogs the cerebral blood flow was
maintained almost constant in spite of lowering of the
arterial blood pressure between 110 and 50 mm Hg. When the mean arterial blood pressure was
reduced from 50 to 30 mm Hg, the cerebral blood
flow fell abruptly, showing loss of autoregulation.
The pressure-flow relationships are shown in figure
2. During the experiments, arterial $P_{CO_2}$ and oxygen
saturation of the animals were between 28 and 44
mm Hg, and above 90%, respectively.

LACTATE CONCENTRATION

Cerebrospinal Fluid

Increase in lactate concentration of the cerebrospinal
fluid was observed during stepwise reduction of
arterial blood pressure even within the pressure
ranges in which autoregulation was distinctly
observed. Figure 3 showed mean values of lactate
concentrations of 11 dogs at each pressure tested.
Lactate increased concomitantly with reduction of
the blood pressure. However, reduction of 20 mm
Hg in the arterial blood pressure did not induce a
statistically significant increase in lactate concentra-
tion of the cerebrospinal fluid between 110 and 50
mm Hg, except between 110 and 90 mm Hg
($P<0.02$).

When the arterial blood pressure was reduced
by 40 mm Hg, increases in lactate were statistically
significant between 110 and 50 mm Hg. The P
values at reductions of the blood pressure from 110
to 70 mm Hg and from 90 to 50 mm Hg were 0.05

![Figure 1](http://stroke.ahajournals.org/)

**FIGURE 1**

Schematic drawing of experimental design. PT = pressure
transducer. See text for explanation.

![Figure 2](http://stroke.ahajournals.org/)

**FIGURE 2**

Pressure-flow relationships of 11 dogs. The mean values
of the cerebral blood flow were plotted against the mean
arterial blood pressure. The cerebral blood flow remained
almost constant until the mean arterial blood pressure had
been reduced below 50 mm Hg.
LACTATE IN THE CEREBROSPINAL FLUID

![Graphs showing pH and lactate levels](image)

**Mean arterial blood pressure**

*Lactate and pH in the cerebrospinal fluid during stepwise reduction of the arterial blood pressure. With lowering of the blood pressure, increase in lactate concentration and decrease in pH occurred even within the pressure ranges where autoregulation was usually observed.*

and 0.01, respectively. The mean values of lactate were 13.9 mg/dl at 110 mm Hg, 14.5 mg/dl at 90 mm Hg, 14.9 mg/dl at 70 mm Hg, 16.1 mg/dl at 50 mm Hg, and 18.2 mg/dl at 30 mm Hg.

**Arterial and Cerebral Venous Blood**

Accompanying with reduction of blood pressure, lactate concentrations in both arterial and cerebral venous blood increased consistently in all of 11 dogs. The increases were larger and sharp, comparing with those in the cerebrospinal fluid (fig. 4). The mean values of lactate at 110, 90, 70, 50 and 30 mm Hg were 14.1, 17.4, 19.6, 25.4, and 39.3 mg/dl in the arterial blood, and 15.4, 18.2, 20.2, 26.1, and 40.3 mg/dl in the cerebral venous blood, respectively. The lactate concentrations were higher in the cerebral venous blood than in the arterial blood at each pressure tested (fig. 5), and the differences were statistically significant at the pressures between 110 and 70 mm Hg (P < 0.05 at 110 mm Hg, P < 0.01 at 90 mm Hg, and P < 0.001 at 70 mm Hg). There was no tendency to increase with reduction of blood pressures in the differences of lactate between the arterial and the venous blood.

**Cerebrospinal Fluid**

The mean values of pH in the cerebrospinal fluid are illustrated in figure 3. Between 110 and 70 mm Hg, pH was almost constant or slightly decreased. Below 70 mm Hg, all of the dogs showed decreases of pH with reductions of blood pressure. When the blood pressure was lowered from 110 to 50 mm Hg, the decrease of pH from 7.381 to 7.358 was statistically significant (P < 0.001). However, decreases in pH during the reduction of blood pressure from 110 to 90 or 70 mm Hg were not statistically significant. Figure 6 showed that the relation between the increase in lactate and the decrease in pH of the cerebrospinal fluid was linear, and that lactacidosis occurred.

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Arterial and Cerebral Venous Blood

The pH in arterial and cerebral venous blood was decreased with lowering of blood pressure, and paralleled inversely with the increase in lactate of the blood (fig. 4).

PrCO₂ in Arterial and Cerebral Venous Blood

During the experiments, the arterial PrCO₂ of the dogs was between 28 and 44 mm Hg. The arterial PrCO₂ of the individual animals was kept almost constant during stepwise reductions of the blood pressure from 110 to 50 mm Hg, and the mean variations of PrCO₂ were within 2 mm Hg. However, below 50 mm Hg of the blood pressure the arterial PrCO₂ decreased distinctly and the mean variations of PrCO₂ were 2 to 4 mm Hg in spite of adjustment of respirator. The differences of PrCO₂ between the arterial and the cerebral venous blood were slightly increased with reduction of the blood pressure as shown in figure 7. The increase in arteriovenous difference of PrCO₂ was 2.8 mm Hg when the blood pressure fell from 110 to 50 mm Hg. But the difference was not statistically significant. When the blood pressure was reduced from 50 to 30 mm Hg, the increase (9.8 mm Hg) was statistically significant (P < 0.001).

Discussion

Kjällquist et al. observed that reductions of the cerebral perfusion pressure by 25 to 40 mm Hg led to a significant increase in lactate of the cerebrospinal fluid, though the perfusion pressure remained above 50 mm Hg. In the present experiments, lactate concentration and pH of the cerebrospinal fluid, and of the arterial and the cerebral venous blood, were investigated during stepwise reductions of the mean arterial blood pressure by controlled bleeding. Increase in lactate and decrease in pH of the cerebrospinal fluid occurred with lowering of the mean arterial blood pressure, even within the pressure ranges of 110 to 50 mm Hg where autoregulation was fairly observed. Reductions of the blood pressure by 20 to 40 mm Hg led to a significant increase in lactate, and reductions by 60 mm Hg led to a significant decrease in pH of the cerebrospinal fluid. The decrease in pH of the cerebrospinal fluid may be the consequence of the increase in lactate, because the reduction of decrease in pH and increase in lactate was linear, and the difference of PrCO₂ between the arterial and the cerebral venous blood remained almost constant, suggesting that there was no significant change in PrCO₂ of the brain tissue until the mean arterial blood pressure had decreased below 50 mm Hg. In the arterial and the cerebral venous blood, a
LACTATE IN THE CEREBROSPINAL FLUID

Changes in $P_{CO_2}$ of the arterial ($o-o$) and the cerebral venous ($-\cdots-\cdots$) blood, and the differences in $P_{CO_2}$ ($[v-A]$) between the arterial and the cerebral venous blood. See text for explanation.

marked increase in lactate and decrease in pH also were observed. When the blood pressure was lowered from 110 to 50 mm Hg, lactate of the blood increased by about 1.8 times that of a blood pressure of 110 mm Hg, though in the cerebrospinal fluid the increase was about 1.2 times. Possibly an increase in lactate of the arterial blood might be concerned in the increase in lactate of the cerebrospinal fluid. However, lactate concentrations of the cerebral venous blood were significantly higher than those of the arterial blood until the arterial blood pressure had been reduced below 70 mm Hg. This fact suggested that lactate was removed from the brain to the cerebral venous blood. For this reason, an increase in lactate of the cerebrospinal fluid might be attributed to the increase in lactate of the brain tissue and not to that of the arterial blood, as the blood pressure was not lowered below 70 mm Hg. Klein and Olsen found that almost none of the lactate which was injected intravenously entered the brain in 40 minutes and concluded that transfer of lactate from blood to brain must be slow. A similar result was reported by Alexander et al. Prockop studied clearance of lactate in the reverse direction, from cerebrospinal fluid to blood, and observed low clearance rates of lactate. Posner and Plum also found that the lactate concentrations in the cerebrospinal fluid are largely independent of blood levels and reflect cerebral metabolism. In the present studies, there were no definite increases in the difference of lactate concentrations between the arterial and the dorsal sagittal sinus blood with reductions of the blood pressure. This might be explained by slow clearance of lactate through blood-brain barrier as mentioned above.

Siesjö and Zwetnow observed in the brain tissue of rats that reductions of the cerebral perfusion pressure by increased intracranial pressures caused small but relatively consistent increases in the lactate concentration and in the lactate/pyruvate ratio of supratentorial brain tissue and of cerebellum, although there were no changes in the tissue concentrations of phosphocreatine, ATP, ADP and AMP until the cerebral perfusion pressure had decreased below 30 mm Hg. Accordingly, increase in lactate of the cerebrospinal fluid may be accounted for by hypoxia of brain tissue (though pyruvate was not measured) associated with a transient decrease in flow when the arterial blood pressure was reduced.

There has been an opinion that extracellular pH in the brain tissue may play a leading role in controlling cerebral blood flow, though there are some arguments regarding the site of action of pH changes responsible for control of cerebrovascular resistance—extracellular or intracellular pH of the smooth muscle cells of arteriolar wall. Wahl et al. changed locally the extracellular pH in the perivascular space by means of micropuncture techniques, and demonstrated that an acidic pH dilates the arterioles under study and an alkaline pH constricts. Therefore, decrease in pH of the cerebrospinal fluid by lactacidosis during reductions of the arterial blood pressure may dilate the arterioles of the brain and act to maintain the cerebral blood flow constant. However, significant decrease in pH of the cerebrospinal fluid did not occur until the mean arterial pressure had been reduced by 60 mm Hg, and reduction of the blood pressure by 60 mm Hg caused the decrease in pH of only 0.02 unit, although cerebral blood flow can increase while cerebral cortical pH decreases by about 0.4 unit. Increase in lactate of the cerebrospinal fluid continued for more than 20 minutes after the mean arterial blood pressure had been reduced by 20 mm Hg and maintained constant, although the cerebral blood flow remained constant except for initial reduction of the cerebral blood flow which was almost restored within one minute (unpublished data).

In addition, once lactacidosis occurred in the cerebrospinal fluid, it required more than one hour.
to be corrected. For these reasons it might be improbable that lactacidosis could be a main factor responsible for cerebral autoregulation at slight to moderate reductions of the cerebral perfusion pressure.

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References
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