Experimental study on the effect of antegrade cerebral perfusion on brains with old cerebral infarction

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Objective: Patients with old cerebral infarction who undergo aortic arch operations are susceptible to postoperative neurologic dysfunction. To verify such susceptibility, we performed this experimental study.

Methods: A cerebral infarct model was created in mongrel dogs by means of injection of cylindrical silicone embolus through the internal carotid artery. The dogs that had obvious neurologic deficits 1 day later and survived for 4 weeks or more were included in the cerebral infarct model. One month after cerebral infarction was induced, deep hypothermia and selective cerebral perfusion were used in 14 mongrel dogs (infarct group, n = 7; control group, n = 7). During this procedure, serum glutamate concentration and venous-arterial lactate difference were measured. Histopathologic study of the brain was also performed.

Results: Changes in venous-arterial lactate difference in both groups were almost similar, except in the rewarming phase. At 32°C during rewarming, the venous-arterial lactate difference in the infarct group was significantly higher than that in the control group (P = .006). Although precooling concentrations of serum glutamate were similar in both groups, the values in the infarct group at the end of rewarming were significantly higher than those in the control group (P = .046). On histologic examination, the presence of old cerebral infarction with gliosis was confirmed in the infarct group, but neither new cerebral infarction nor destruction of the blood-brain barrier was found.

Conclusion: We observed an accelerated anaerobic metabolism and an increased extracellular glutamate release in the infarct group. The brain with old cerebral infarction is more susceptible to ischemia during arch operation than noninfarcted brain.

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Brain protection in patients who undergo aortic arch operations is a very important issue that influences postoperative outcome. Recently, the postoperative morbidity has decreased because of advances in surgical techniques and a better understanding of the mechanism of neurologic dysfunction.[1,2] However, in operations with cardiopulmonary bypass (CPB), there is a patient subgroup with heightened vulnerability to postoperative neurologic dysfunction. In coronary artery bypass grafting, a history of neurologic disease has been identified as an independent predictor of severe postoperative neurologic damage.[3] Similarly, history of cerebrovascular disease has

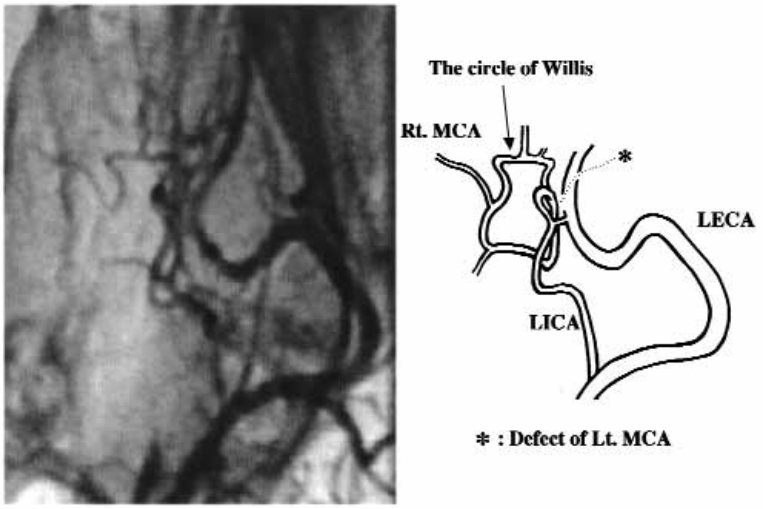

Figure 1. Angiography after injection of silicone cylinder embolus. Nonvisualization of the left MCA indicates that the cylindrical silicone embolus was in a proximal location in the left MCA. *LECA*, Left external carotid artery; *LICA*, left internal carotid artery.

been shown to be an independent predictor of postoperative stroke in aortic arch operations assisted with deep hypothermic circulatory arrest alone.[4] Although selective cerebral perfusion (SCP) has been said to be the best among the existing brain protection methods with respect to energy metabolism and time limitation,[5,6] it does not eliminate the risk of postoperative neurologic dysfunction in patients with a history of cerebrovascular disease. In one of our previous studies of 220 patients with total arch replacement assisted with SCP, old cerebral infarction was an independent predictor of postoperative neurologic dysfunction, as determined with multivariable analysis.[7] Although a history of cerebrovascular disease generally suggests that an existing pathologic cerebrovascular condition, such as impaired cerebral blood flow and autoregulation or inadequate collateral vessels, may predispose patients to stroke after cardiac and aortic operations, it is not clearly understood why these patients with prior cerebrovascular disease are more predisposed to higher postoperative neurologic dysfunction. So far as we know, no experimental studies about the influence of CPB on the brain with infarction have been published. Therefore, we sought to examine, in an animal model, the effect of aortic arch operations with SCP on brains with old cerebral infarction and to investigate why these patients are at a higher risk of postoperative neurologic dysfunction.

Materials and Methods

This study was approved by the Animal Care and Use Committee of Hamamatsu University School of Medicine. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (National Institutes of Health publication No. 85-23, revised 1985) and the "Guidelines for Animal Experimentation" formulated by Hamamatsu University School of Medicine (published 1987, revised 1991).

Infarct Model

A cerebral infarct model was created in mongrel dogs by injection of cylindrical silicone embolus through the internal carotid artery. We adopted the method of creating experimental cerebral infarction reported by Molinari,[8,9] with slight modification. After achievement of general anesthesia, the left common carotid artery (LCCA), the left external carotid artery, and the left internal carotid artery were exposed through a cervical longitudinal incision. Angiography was performed to confirm that the intended vessels were exposed.[10] Then one cylindrical silicone embolus, 1.1 mm in diameter and 15 mm in length, was injected into the left internal carotid artery through a small arteriotomy in the LCCA. Angiography was performed again, and nonvisualization of the left middle cerebral artery (MCA) suggested that the cylindrical silicone embolus was located in the proximal portion of the left MCA (Figure 1). The LCCA was then reconstructed with 6-0 monofilament running sutures. The next day, the dogs that underwent the above-mentioned procedure were evaluated with a neurologic scoring system consisting of 5 grades.[11] Neurologic scores in this system have been defined as follows: score 0, no neurologic deficit; score 1, walks with limp or circles to side of lesion; score 2, walks poorly and stands but cannot support body with left limbs held off ground; score 3, cannot stand without support; and score 4, dead. The dogs that had neurologic scores of 2 or 3 at the first postoperative day and survived for 4 weeks or more were included in the cerebral infarct model.

Animal Preparation

After subcutaneous injection of ketamine hydrochloride (15 mg/kg) and intravenous injection of pentobarbital sodium (30 mg/kg), tracheal intubation was performed, and mechanical venti-

TABLE 1. Blood gas and pressure data in both groups

	1	2	3	4	5	6	7	8
Control group								
Pao_2 (mm Hg)	423.6 ± 244.2	761.5 ± 94.3	730.4 ± 116.1	744.0 ± 137.1	556.3 ± 126.8	525.2 ± 105.7	415.5 ± 120.4	310.8 ± 151.8
$Paco_2$ (mm Hg)	27.1 ± 8.9	48.8 ± 6.9	27.6 ± 5.3	21.1 ± 4.9	39.4 ± 6.1	39.3 ± 6.4	41.2 ± 3.9	40.1 ± 6.7
Brachial artery pressure (mm Hg)	54.3 ± 7.1	54.1 ± 15.4	56.8 ± 12.7	50.8 ± 10.9	52.5 ± 7.8	49.6 ± 6.1	50.6 ± 3.9	48.4 ± 6.9
Infarct group								
Pao_2 (mm Hg)	578.0 ± 77.7	780.4 ± 51.9	789.1 ± 28.9	777.0 ± 59.0	630.8 ± 108.8	606.2 ± 53.8	584.4 ± 95.0	557.9 ± 42.0
$Paco_2$ (mm Hg)	27.8 ± 14.1	47.0 ± 23.7	29.3 ± 17.8	23.1 ± 15.2	42.4 ± 22.9	36.1 ± 20.5	34.9 ± 17.7	34.8 ± 15.4
Brachial artery pressure (mm Hg)	67.3 ± 12.7	53.6 ± 16.6	59.6 ± 15.9	51.8 ± 15.1	41.8 ± 5.6	42.2 ± 10.5	40.8 ± 10.4	43.0 ± 12.0

Heading numbers represent time as follow: *1*, 5 minutes after initiation of the extracorporeal circulation; *2*, when rectal temperature reached 20°C; *3*, 60 minutes after initiation of SCP; *4*, 120 minutes after initiation of SCP; *5*, when rectal temperature reached 24°C; *6*, when rectal temperature reached 28°C; *7*, when rectal temperature reached 32°C; and *8*, when rectal temperature reached 36°C.

lation was started. A 19-gauge detaining needle was inserted into the right brachial artery for measurement of blood pressure. A 4F catheter was inserted into the left maxillary vein in a retrograde fashion for venous blood gas analysis and for lactate measurement. An additional dose of pentobarbital sodium (15 mg/kg) was given before the beginning of rewarming.

CPB

After median sternotomy and full heparinization (300 U/kg), an arterial cannula was inserted into the ascending aorta, and 2 venous cannulas were inserted into the superior and inferior venae cavae to institute CPB. The perfusion system, consisting of a roller pump and a membrane oxygenator (Senkoika Corp, Tokyo, Japan) was primed with lactated Ringer's solution. Alpha-stat management was used in this experiment. A second dose of heparin (150 U/kg) was added before the beginning of rewarming.

Experimental Protocol

Deep hypothermia and SCP with extracorporeal circulation were performed in 14 mongrel dogs (infarct group, n = 7; control group, n = 7). After hematocrit levels in the extracorporeal circuit became stable, the first blood sample was obtained, and cooling was started. Pump flow was maintained at approximately 50 to 80 $mL \cdot kg^{-1} \cdot min^{-1}$ in accordance with the amount of venous return. When rectal temperature reached 20°C, SCP was initiated at a flow rate of 10 $mL \cdot kg^{-1} \cdot min^{-1}$ by clamping the proximal ascending aorta, the left subclavian artery, and the descending aorta. The lower half of the body was not perfused during SCP. After SCP was maintained for 120 minutes, rewarming up to 36°C was performed. Differences between rectal and arterial temperatures were always kept within 10°C in both the cooling and rewarming phases. Blood gas analysis (Blood Gas Analyzer Bayer 860, Bayer Diagnostics Corp, Walpole, Mass) and lactate measurement (Lactate Pro; Kyoto Daiichi Kagaku Corp, Kyoto, Japan) from the arterial cannula and maxillary vein were performed on the following 8 occasions: (1) 5 minutes after initiation of extracorporeal circulation; (2) when rectal temperature reached 20°C; (3) 60 minutes after initiation of SCP; (4) 120 minutes after initiation of SCP; (5) when rectal temperature reached 24°C; (6) when rectal temperature reached 28°C; (7) when rectal temperature reached 32°C; and (8) when rectal temperature reached 36°C. Blood samples for measurement of serum glutamate were obtained from venous cannula on occasion 1 and occasion 8. A blood sample for glutamate analysis was centrifuged, and protein was extracted from the serum. Then glutamate measurement for this serum was performed by means of a column packed with reverse-phase support with a special device (PICO·TAG, Waters Corporation, Milford, Mass).

Arteriovenous difference of oxygen ($AVDO_2$) and venous-arterial difference of lactate (VADL) were calculated by the following formulas:

$$AVDO_2\ (\mu mol/mL) = (1.34 \cdot Hgb \cdot Sao_2 + 0.0031 \cdot Pao_2)/2.24 - (1.34 \cdot Hgb \cdot Smvo_2 + 0.0031 \cdot Pmvo_2)/2.24 \quad (1)$$

$$VADL\ (\mu mol/mL) = Lmv\ (\mu mol/mL) - La\ (\mu mol/mL) \quad (2)$$

where Hgb is hemoglobin, Sao_2 is the arterial saturation of oxygen, $Smvo_2$ is the maxillary vein saturation of oxygen, $Pmvo_2$ is the partial pressure of maxillary venous oxygen, Lmv is maxillary venous lactate, and La is arterial lactate.

After the last blood sample was obtained, Evans Blue dye (2%, 20 mL) was injected into the extracorporeal circuit, and CPB was continued for another 30 minutes. Then, 500 mL of 10% formalin was then injected into the carotid arteries before the brain was extracted. After immersion in 10% formalin for a week, the brains were sectioned in the coronal plane and were examined for extravasation of Evans Blue dye in nonstained and hematoxylin and eosin–stained sections. For the histologic confirmation of old cerebral infarction, immunohistochemical study with antibodies against glial fibrillary acidic protein (DAKO Corporation, Carpinteria, Calif) was done to verify the presence of gliosis, which appears in the chronic phase.

Statistical Analysis

Values are expressed as means ± 1 SD. Statistical analysis was performed with the Mann-Whitney *U* test.

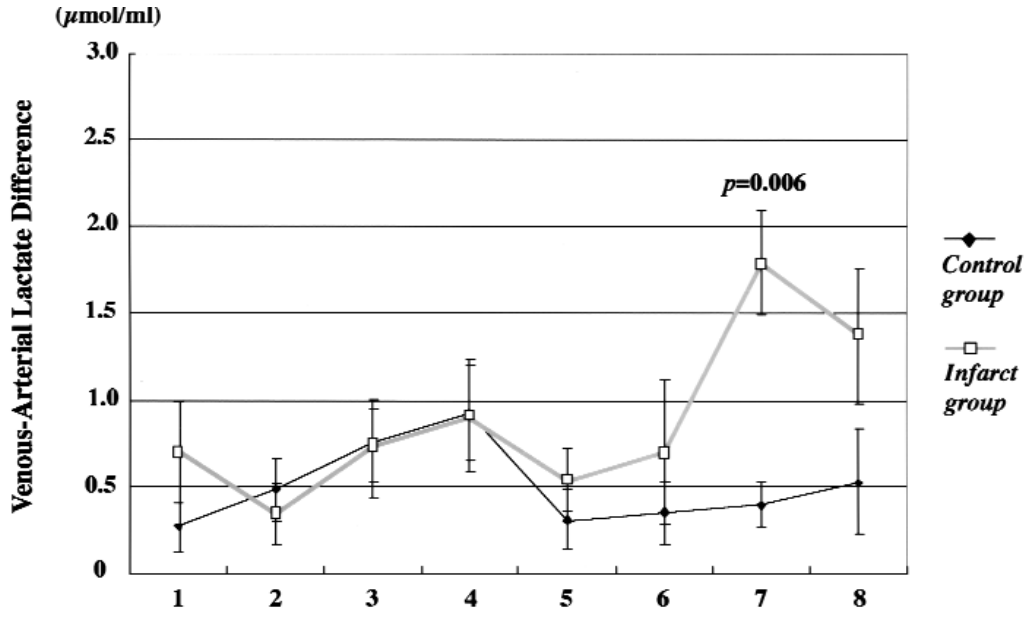

Figure 2. Levels of venous-arterial lactate difference. Levels in the infarct group at 32°C are significantly higher than those in the control group ($P < .01$). *Error bars* indicate SEs. Numbers along the *horizontal axis* are defined as follows: *1*, 5 minutes after initiation of extracorporeal circulation; *2*, when rectal temperature reached 20°C; *3*, 60 minutes after initiation of SCP; *4*, 120 minutes after initiation of SCP; *5*, when rectal temperature reached 24°C; *6*, when rectal temperature reached 28°C; *7*, when rectal temperature reached 32°C; and *8*, when rectal temperature reached 36°C.

Results

Old Cerebral Infarct Model and Physiologic Variables

When we evaluated the 12 dogs on the day after the injection of cylindrical silicone embolus, 3 dogs had neurologic deficit scores of 1, 3 had scores of 2, 5 had scores of 3, and 1 had a score of 4. The incidence of acute neurologic deficits of score 2 or 3 was 66.7% (8 dogs). Seven of these 8 dogs survived for 4 weeks or more. The final incidence of old cerebral infarction was 58.3% (7 dogs). The average duration between injection of embolus and experimental perfusion study was 32.9 ± 5.9 days.

There were no significant differences in terms of average body weight of the animals (12.0 ± 2.6 kg vs 11.0 ± 1.8 kg) and preoperative (38.7% ± 3.2% vs 40.0% ± 6.0%) and intraoperative hematocrit levels (25.6% ± 1.5% vs 22.6% ± 5.4%) between the control and infarct groups. Table 1 shows intraoperative blood gas and blood pressure data. Almost similar values for these parameters were found during CPB in both groups. The time required for rewarming was 64.6 ± 10.3 minutes in the infarct group and 59.0 ± 7.8 minutes in the control group ($P = .36$).

Maxillary Vein Saturation of Oxygen, Arteriovenous Difference of Oxygen, VADL, and Serum Glutamate Measurement

Changes in maxillary vein saturation of oxygen, arteriovenous difference of oxygen, and VADL values during CPB were almost similar in both groups, except for those in the rewarming phase. Differences between the 2 groups were particularly obvious at 32°C. In the infarct group maxillary vein saturation of oxygen had a tendency to decrease ($P = .06$) and arteriovenous difference of oxygen had a tendency to increase ($P = .34$) in comparison with the respective values in the control group, but these differences were not statistically significant. VADL (Figure 2) in the infarct group was significantly higher than that in the control group ($P = .006$).

Figure 3 shows the values of serum glutamate concentrations before cooling and after rewarming in each group. Although precooling concentrations of serum glutamate were similar in both groups, the values at the end of rewarming in the infarct group were significantly higher than those in the control group ($P = .046$). The postrewarming-precooling serum glutamate difference was also significantly higher in the infarct group ($P = .01$).

Histologic Examination and Reassessment of the Old Cerebral Infarct Model

On histologic examination, new cerebral infarction caused by intraoperative embolism or hypoperfusion was not found in any group. Because extravasation of Evans Blue dye was also not seen in any group, no obvious destruction of the blood-brain barrier after CPB was supposed to have occurred, even in the infarct group.

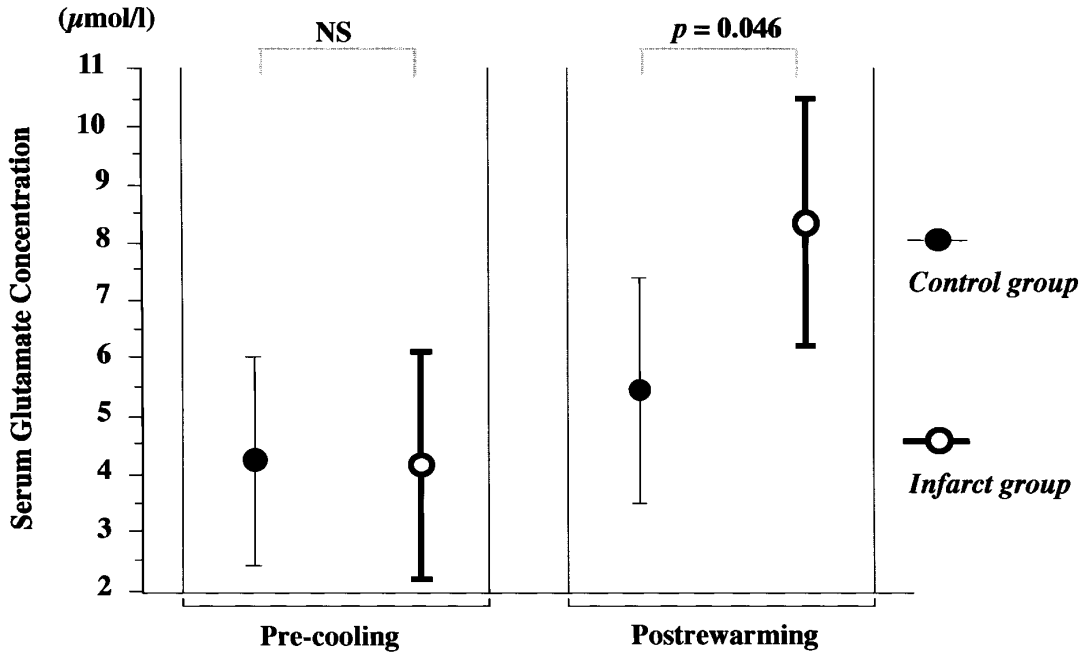

Figure 3. Levels of precooling and postrewarming serum glutamate in the 2 groups. In the postrewarming phase levels in the infarct group were significantly higher than those in the control group (*P* = .03). *Bars* show 95% confidence intervals. Blood samples for measurement of serum glutamate were obtained from the venous cannula on occasion 1 and occasion 8, as defined in the legend for Figure 2.

Although 6 animals in the infarct group had infarcts in the basal ganglia as a result of occlusion of the proximal MCA (Figure 4), the remaining animal had an extended infarct in the frontal region because of occlusion of the anterior cerebral artery and the MCA. On immunohistochemical study with antibodies against glial fibrillary acidic protein, the region of gliosis around the infarct was found (Figure 5), indicating that the cerebral infarction was old.

Discussion

In this experimental study we examined the effect of aortic arch operations with SCP on the canine brain with old cerebral infarction. We observed that VADL and serum glutamate concentrations significantly increased in the infarct group. These results indicate that an increase in anaerobic metabolism with an associated extracellular glutamate release occurs in the brain with old infarction because of cerebral ischemia during the operation.

We created cerebral infarction in mongrel dogs by injecting silicone cylinder emboli without craniectomy, as described by Molinari,[8,9] with some modification. Because we used longer (15 mm) emboli than those used by Molinari to occlude all perforating arteries, the possibility of cerebral infarction increased. Cerebral angiography clearly showed the occlusion of the MCA in our study. Furthermore, we used only those dogs that survived for about 1 month after the induction of neurologic deficits. In fact, histologic examination in our model revealed that the necrotic elements usually found in the acute phase of infarction disappeared and that gliosis persisted around the infarct area, indicating chronic state.[12] Therefore, our model can be considered a suitable representation of old cerebral infarction.

The effect of old cerebral infarction on VADL and serum glutamate concentration could not be a consequence of a difference in physiologic variables because blood gases, brachial artery pressures, anesthesia, and surgical procedures were carefully controlled. Rather, the increase in VADL and serum glutamate concentration possibly resulted from the pathologic factors in the brain with old cerebral infarction.

The increased VADL in the infarct group means an accelerated anaerobic glycolysis in the brain tissue and can be caused by cerebral ischemia. On the other hand, it has been reported that extracellular glutamate release from the neurons is increased by anoxia[13,14] or ischemia.[15] Castillo and colleagues[16] reported that early neurologic deterioration in patients with acute ischemic stroke is associated with a high concentration of glutamate in blood and cerebrospinal fluid. The increased serum glutamate concentration in the infarct group can therefore be caused by acute cerebral ischemia. Taken together, the increase in VADL and serum glutamate concentration in the infarct group can be considered as a manifestation of cerebral ischemia during the operation.

The mechanism of cerebral ischemia in the infarct group is unknown. However, there can be some possible explana-

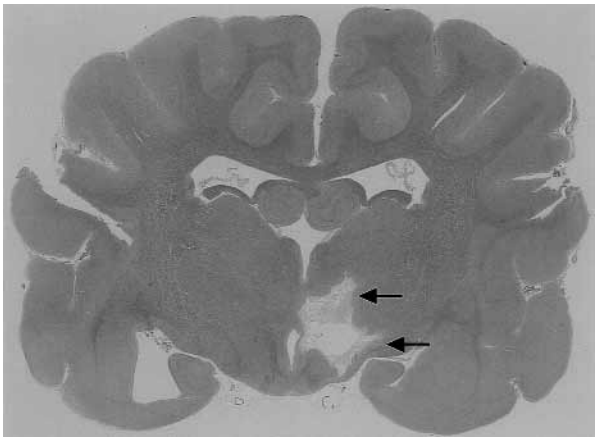

Figure 4. Coronal section of brain in the infarct group showing the infarction in the left basal nuclei on hematoxylin and eosin staining. No extravasation of Evans Blue dye is seen.

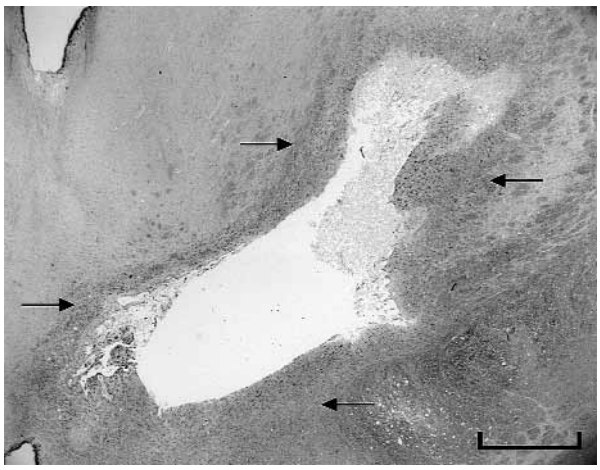

Figure 5. Immunohistochemical staining with antibodies against glial fibrillary acidic protein showing gliosis around the old infarct. *Bar* = 1 mm.

tions. First, the animals in the infarct group had regions around the old infarct in which the basal cerebral blood flow was low. Such regions are known as chronic penumbra. Because these regions are supplied by collateral circulation, autoregulation is disturbed,[17,18] and therefore cerebral blood flow becomes easily vulnerable to a passive decrease in these regions when cerebral perfusion pressure decreases. Watanabe and colleagues[19] described that low-flow perfusion at 20 mm Hg provided cerebral vasorelaxation and aerobic metabolism at 20°C. During SCP, we maintained a cerebral perfusion flow of 10 mL · kg^{-1} · min^{-1}, which is our practice in the clinical situation. Therefore, the resulting brachial artery pressure was at a higher level than that recommended by Watanabe and colleagues. In any case the most optimal perfusion pressure and flow in brains with old cerebral infarction are unknown. Although we think that patients with normal brains have a wider safety margin for cerebral ischemia, stricter management of CPB should be done in high-risk patients (ie, those with old cerebral infarction). However, appropriate management for CPB in hypothermia for high-risk patients has not yet been sufficiently understood because experimental studies with infarct models have not been performed. Local cerebral blood flow in the chronic penumbra may decrease below the ischemic level during SCP. Another possible explanation of cerebral ischemia in the infarct group is that air or atheromatous embolism may occur during the operation. However, it is not likely in this study because we used a method that does not require opening of the aorta and its branches. Even if such complications occur, their incidence should be equal in both groups because of the similarity in perfusion technique. In a clinical situation there are some techniques to minimize, such as embolic events. Ascending aortic or axillary artery cannulation, confirmation of absence of atheromatous lesion in the ascending aorta with epiaortic ultrasound scanning with 4-branched arch graft (allowing the exclusion of the origins of arch branches where atheromatous lesions are usually found), and insertion of SCP cannulas in the Trendelenburg position through arteriectomy of arch branches and not through the inside of the aortic lumen are important among them.[20] Although we do not think that our techniques of total arch replacement completely prevented embolic events, we assume that not only embolic events but also some other factors probably influence the postoperative neurologic outcomes in patients with old cerebral infarction.

With respect to the reason why the acceleration of anaerobic glycolysis was found at only 32°C, 2 reasons could be considered. First, pathologic mismatch between cerebral blood flow and cerebral metabolism increased during rewarming, and the mismatch might be maximized at a temperature of 32°C. Regarding the relationship of temperature to cerebral metabolism, some reports said that metabolism is progressively depressed when below 28°C.[21,22] Therefore, when below 28°C, a hypothermic effect may still work, even during rewarming. Second, oxygen debt might have occurred during prolonged SCP for 120 minutes in the infarct group. The oxygen debt might be manifested when the temperature was over 28°C. It was clearly unknown which reason (or both) was the cause of these results in this study. Irrespective of the mechanism of cerebral ischemia, the results of this experimental study were in keeping with our clinical results showing that old cerebral infarction was an independent predictor of postoperative neurologic dysfunction.[7] To reduce the incidence of neurologic complication, first of all, we have to examine whether a patient has a risk factor before performing an operation. As described by Ohmi and colleagues,[23] preoperative cerebral angiography is important in this regard. This is because the intracranial

arterial occlusion, and possibly the extent of collateral flow to a region, are best predicted by means of cerebral angiography in combination with computed tomography. Noninvasive examinations like magnetic resonance angiography or computed tomographic angiography should be recommended in patients with a history of cerebrovascular diseases before arch operations.

Several investigations about the optimal cerebral blood flow and perfusion pressure during deep hypothermia have been carried out since the initial report of Miyamoto and coworkers.[24] Tanaka and colleagues[25] described that regional cerebral blood flow depends more on perfusion flow than perfusion pressure and recommended half of the physiologic flow as optimum at a rectal temperature of 25°C. With regard to perfusion pressure, Tanaka and colleagues described that cerebral autoregulation is preserved under alpha-stat pH management at 20°C, when the perfusion pressure is more than 40 mm Hg. The data in these previous reports were obtained by using a normal brain model, and the most suitable perfusion method for patients with a cerebrovascular disease has not yet been established. An important next step would be to investigate this issue by using our infarct model.

A further implication of this study should be considered. Because we performed histologic examination immediately after the operation to confirm the presence of old cerebral infarction, whether the increase in VADL and serum glutamate concentration is related to the morphologic neuronal death remains unknown. However, the increase in these parameters results from cerebral ischemia and can be predictive of cerebral infarction. To establish the reliability of these examinations for sensitive prediction, further clinical and experimental investigations will be necessary.

Neuroprotective benefits of *N*-methyl-D-asparate antagonists against brain ischemia have been reported.[27] We think that *N*-methyl-D-asparate antagonists can also be expected to protect the chronic penumbra during arch operations.

In conclusion, in this study we observed that the dogs with old cerebral infarction and cerebral artery occlusion showed an increase in VADL and serum glutamate concentration during the rewarming phase of experimental SCP. This is caused by cerebral ischemia, which indicates that patients with old cerebrovascular diseases are at higher risk of adverse cerebrovascular events during operations. The old cerebral infarct model of our study is a suitable one for experimental studies on the effect of CPB on the diseased brain, and it is expected to contribute to the establishment of a more appropriate CPB management in patients with old cerebral infarction.

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