Comparison of pH management during antegrade selective cerebral perfusion in canine models with old cerebral infarction

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Objective: We sought to examine the influence on the brain, with or without old infarction, of pH management during antegrade selective cerebral perfusion in a canine model.

Methods: A cerebral infarct canine model was created by injecting a cylindrical silicone embolus. Dogs that had obvious neurologic deficits and had survived for 4 weeks or more were included in the model. Deep hypothermia with antegrade selective cerebral perfusion was performed in intact mongrel dogs (alpha-stat: group A, n = 6; pH-stat: group B, n = 6) and mongrel dogs with infarctions (alpha-stat: group C, n = 6; pH-stat: group D, n = 6). Maxillary vein saturation of oxygen, venous-arterial lactate difference, and serum concentrations of malondialdehyde and glutamate were measured and central conduction times and amplitude in somatosensory evoked potentials were assessed during the operation.

Results: During the experimental procedure, the maxillary vein saturation of oxygen was significantly less ($P < .05$), whereas the venous-arterial lactate difference was significantly greater ($P < .05$) in the cooling phase to 28°C in group C than in the other groups. The pH-stat group showed significantly greater arterial $Paco_2$ and lower pH than the alpha-stat group during the period between the cooling to 28°C and the rewarming to 28°C ($P < .05$). Other intraoperative parameters did not show any difference among the groups. In group C the serum concentrations of malondialdehyde and glutamate significantly increased, as did the central conduction time, whereas in both groups C and D the amplitude ratio decreased significantly.

Conclusions: This experiment suggests that pH-stat management during antegrade selective cerebral perfusion provides more effective protection for a brain with old infarction than alpha-stat management.

Neurologic complications after aortic arch operations have remarkably decreased because of the improvements in the operative techniques and methods of cerebral protection.^{1,2} Antegrade selective cerebral perfusion (ASCP) has been found to be the safest method of brain protection with respect to energy metabolism and time limitation.^{3,4} Additionally, clinical practice has indicated that ASCP, compared with other methods for cerebral protection, including deep hypo-

thermic circulatory arrest (DHCA) with or without retrograde cerebral perfusion, can reduce cerebral injury during aortic operations more effectively.⁵

A history of cerebrovascular disease, however, has been shown to be an independent predictor of postoperative neurologic complications in coronary artery bypass grafting⁶ and in the aortic arch operations assisted with DHCA alone.⁷ Although our total arch operations assisted with ASCP have shown a lower rate of mortality and morbidity,⁸ a multivariable analysis of 220 patients revealed that a history of cerebral infarction should be regarded as an independent predictor of postoperative neurologic dysfunction.⁹

Although our hospital has opted for alpha-stat management during aortic arch replacement, it remains controversial which pH management during ASCP with DHCA should be adopted for patients with neurologic diseases because, to our knowledge, no comparative studies of the influence of pH management during ASCP have thus far been reported.

Therefore in the present study we seek to determine the effect of pH management during ASCP on brains with or without old cerebral infarction in a canine model.

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, received 1985) and the "Guidelines for Animal Experimentation" formulated by Hamamatsu University School of Medicine (published 1987, received 1991).

Infarct Model

Our technique for creating a cerebral infarct model has been described previously.¹⁰ Briefly, after induction of general anesthesia, the left common carotid artery, the left external carotid artery, and the left internal carotid artery were exposed. Then one cylindrical silicone embolus was injected into the left internal carotid artery through a small arteriotomy in the left common carotid artery. Nonvisualization of the left middle cerebral artery (MCA) in the angiogram after this treatment suggested that the embolus was located in the proximal portion of the left MCA. After 12 hours, the dogs were evaluated with a neurologic scoring system consisting of 5 grades (0, no neurologic deficit; 1, walks with a limp or circles to the side with the lesion; 2, walks poorly and stands but cannot support the body with a left limb held off the ground; 3, cannot stand without support; and 4, dead).¹¹ The dogs that had neurologic scores of 2 or 3 and had survived for 4 weeks or more were included in the cerebral infarct model. In our earlier study¹⁰ the histologic examination revealed that in this model MCA occlusion induces old infarction in the basal ganglia in 4 weeks.

Animal Preparation

After an intravenous injection of pentobarbital sodium (30 mg/kg), tracheal intubation was performed, and mechanical ventilation was started. A 19-gauge detaining needle was inserted into the right brachial artery for measurements of blood pressure. A 4F catheter was inserted into the right 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.

Cardiopulmonary Bypass

After a 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 cardiopulmonary bypass (CPB). The perfusion system, consisting of a roller pump and a membrane oxygenator (Senkoika Corp, Tokyo, Japan), was primed with lactated Ringer solution. A second dose of heparin (150 U/kg) was added before the beginning of rewarming.

Measurement of Somatosensory Evoked Potentials

One-channel recordings were obtained on a Nicolet Compact Four/CA 2000 (Nicolet JAPAN Corp, Tokyo, Japan). After shaving, needle electrodes were attached to the sagittal suture, approximately 2 cm dorsal from the coronal suture and in the upper right-hand side of the sternum, and a reference electrode was fixed to the right shoulder. The median nerve of the right forelimb was exposed and stimulated with a bipolar stimulator. The pulse duration was 100 μ s, and the strength of the current was 2 to 5 mA with a frequency of 5.1 Hz. The results of the 300 responses were averaged with automatic artifact rejection by setting the filter between approximately 5 and 1000 Hz. The central conduction time (CCT), calculated as an interpeak latency of N2 (the second negative wave) and N4 (the fourth negative wave), and the amplitude ratio of N4 to N1 (the first negative wave) were measured by using the cursor mode of a computer, and preoperative and postoperative values were compared.

Experimental Protocol

Deep hypothermia with ASCP was performed in 24 mongrel dogs separated into the following 4 groups: group A, intact alpha-stat group ($n = 6$); group B, intact pH-stat group ($n = 6$); group C, infarct alpha-stat group ($n = 6$); and group D, infarct pH-stat group ($n = 6$). Before CPB, the first somatosensory evoked potential (SEP) was recorded, and the first blood sample was obtained. After hematocrit levels in the extracorporeal circuit became stable, the second blood sample was obtained, and cooling was started. Pump flow was maintained at approximately 50 to 80 $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in accordance with the amount of venous return. For the pH-stat group, the oxygenator received 5% carbon dioxide in a balance of oxygen, and arterial pH and Paco_2 were maintained at constant values during hypothermia. For the alpha-stat group, the oxygenator received only oxygen, and arterial pH and Paco_2 , measured at 37°C, were kept at 7.40 and at 40 mm Hg, respectively. After cooling to 20°C rectal temperature, ASCP was initiated at a flow rate of 10 $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ by clamping the proximal ascending aorta, the left subclavian artery, and the descending aorta. The lower half of the body was not perfused during ASCP. After 120

TABLE 1. Preoperative physiologic variables

	Intact group		Infarct group		P value*
	Group A (alpha-stat)	Group B (pH-stat)	Group C (alpha-stat)	Group D (pH-stat)	
Age (mo)	13.7 ± 2.0	12.7 ± 4.0	15.7 ± 1.6	16.8 ± 2.0	.53
Body weight (kg)	14.8 ± 1.1	15.2 ± 1.9	15.0 ± 1.7	16.7 ± 2.5	.33
Duration after CI (mo)	None	None	3.8 ± 1.4	4.6 ± 1.4	.72
Hematocrit (%)	36.0 ± 1.9	35.0 ± 1.2	36.5 ± 1.6	33.5 ± 0.6	.46
BAP (mm Hg)	167.3 ± 9.2	158.3 ± 2.8	153.0 ± 7.6	166.7 ± 7.6	.46
Pao ₂ (mm Hg)	115.7 ± 7.4	115.2 ± 7.0	101.7 ± 9.0	122.7 ± 5.3	.26
Paco ₂ (mm Hg)	36.0 ± 9.2	29.2 ± 2.4	34.8 ± 5.2	31.9 ± 1.3	.10
Arterial pH	7.42 ± 0.02	7.47 ± 0.01	7.44 ± 0.02	7.46 ± 0.01	.10
Arterial lactate (mmol/L)	1.78 ± 0.56	1.15 ± 0.39	1.00 ± 0.35	1.57 ± 0.42	.57
Rectal temperature (°C)	36.5 ± 0.3	37.1 ± 0.2	36.3 ± 0.3	36.3 ± 0.2	.16

CI, Cerebral infarction; BAP, brachial artery pressure.

*One-way analysis of variance.

minutes of ASCP, CPB resumed at 50 to 80 mL · kg⁻¹ · min⁻¹. Then rewarming up to 36°C rectal temperature was performed. Differences between rectal and arterial temperatures were always kept within 5°C in both the cooling and rewarming phases. Blood gas analysis (STAT PROFILE PHOX; MC Medical, Tokyo, Japan) and lactate measurement (Lactate Pro; Kyoto Daiichi Kagaku Corp, Kyoto, Japan) from the right brachial artery and maxillary vein were performed on the following 8 occasions: (1) before the operation; (2) 5 minutes after the initiation of CPB; (3) on reaching 28°C rectal temperature in the cooling phase; (4) on reaching 20°C rectal temperature in the cooling phase; (5) 60 minutes after the initiation of ASCP; (6) 120 minutes after the initiation of ASCP; (7) on reaching 28°C rectal temperature in the rewarming phase; and (8) on reaching 36°C rectal temperature in the rewarming phase. A blood sample for serum malondialdehyde (MDA) and glutamate analysis was centrifuged, and protein was extracted from the serum. Then MDA measurement for this serum was performed by means of thiobarbituric acid fluorescence (FP-777; Nihon Bunko, Tokyo, Japan), according to the method by Ohkawa and colleagues.¹² The serum glutamate measurement was performed by means of a column packed with reverse-phase support with a special device (PICO-TAG; Waters Corp, Milford, Mass).

The arteriovenous difference of oxygen (AVDO₂) and venous-arterial lactate difference (VALD) were calculated by means of the following formulas:

$$\begin{aligned} \text{AVDO}_2 (\text{mmol/L}) &= (1.34 \cdot \text{Hgb} \cdot \text{Sao}_2 + 0.0031 \\ &\quad \cdot \text{PaO}_2)/2.24 - (1.34 \cdot \text{Hgb} \cdot \text{Smvo}_2 + 0.0031 \\ &\quad \cdot \text{Pmvo}_2)/2.24 \end{aligned} \quad (1)$$

$$\text{VALD (mmol/L)} = \text{Lmv} - \text{La} \quad (2)$$

where Hgb is defined as hemoglobin, Sao₂ is defined as arterial saturation of oxygen, Smvo₂ is defined as maxillary vein saturation of oxygen, Pmvo₂ is defined as partial pressure of maxillary venous oxygen, Lmv is defined as maxillary venous lactate, and La is defined as arterial lactate.

Statistical Analysis

The values are expressed as means ± SE. A 1-way analysis of variance was used for comparison among the groups. When the 1-way analysis of variance showed a significant difference, we compared the 2 groups with the help of the Tukey honestly significant difference test (HSD).

Results

Physiologic Variables

There were no significant differences in preoperative physiologic variables among the groups (Table 1). In group C (Table 2) Smvo₂ was significantly lower ($P < .05$) and VALD was significantly higher ($P < .05$, Figure 1) during the procedure than in the other groups at 28°C in the cooling phase. The pH-stat groups (groups B and D) showed significantly higher arterial Paco₂ values and lower pH than those in the alpha-stat group (groups A and C) during the period from the cooling to 28°C to the rewarming to 28°C ($P < .05$). Other parameters, including mean arterial pressure, Pao₂, AVDO₂, average hematocrit (group A, 28.1% ± 0.4%; group B, 27.7% ± 0.3%; group C, 27.6% ± 0.4%; group D, 28.2% ± 0.4%; $P = .65$), and the time required for the cooling (group A, 60.7 ± 5.9 minutes; group B, 52.2 ± 3.0 minutes; group C, 54.0 ± 2.2 minutes; group D, 54.2 ± 4.6 minutes; $P = .51$) and rewarming (group A, 63.2 ± 2.8 minutes; group B, 59.2 ± 2.0 minutes; group C, 55.0 ± 1.3 minutes; group D, 54.2 ± 3.2 minutes; $P = .58$) phases did not show any difference among the groups.

Serum MDA and Glutamate Concentrations

We examined the biochemical marker of ischemia during the procedure. The preoperative value of serum MDA, a marker of free radical production and lipid peroxidation of membrane polyunsaturated fatty acid,^{13,14} and serum glutamate did not show any difference among the groups. However, in group C the serum concentration of MDA signifi-

TABLE 2. Intraoperative physiologic variables

	Intact group		Infarct group		P value*
	Group A (alpha-stat)	Group B (pH-stat)	Group C (alpha-stat)	Group D (pH-stat)	
MAP (mm Hg)					
On CPB	76.3 ± 3.8	66.7 ± 3.8	73.7 ± 5.5	81.7 ± 5.5	.19
Cooling 28°C	70.5 ± 4.0	73.3 ± 3.8	69.7 ± 3.8	77.2 ± 4.7	.57
Cooling 20°C	59.7 ± 3.5	63.3 ± 1.7	57.7 ± 2.2	66.0 ± 3.5	.20
ASCP 60 min	71.0 ± 3.8	68.2 ± 2.5	68.2 ± 3.5	63.0 ± 1.9	.33
ASCP 120 min	74.7 ± 4.5	69.8 ± 2.5	65.2 ± 5.9	69.3 ± 3.8	.51
Rewarming 28°C	72.3 ± 3.6	73.7 ± 5.0	70.7 ± 4.7	73.7 ± 4.0	.96
Rewarming 36°C	78.7 ± 5.1	74.5 ± 2.3	77.0 ± 5.1	85.7 ± 5.1	.37
Pao ₂ (mm Hg)					
On CPB	192.5 ± 4.6	186.0 ± 3.7	179.1 ± 9.1	173.2 ± 16.2	.55
Cooling 28°C	305.4 ± 32.2	247.6 ± 17.1	241.0 ± 38.9	272.5 ± 25.4	.42
Cooling 20°C	701.5 ± 29.4	643.6 ± 30.2	566.2 ± 33.6	596.0 ± 72.3	.20
ASCP 60 min	670.5 ± 25.0	687.3 ± 19.3	763.0 ± 44.7	724.7 ± 12.0	.12
ASCP 120 min	689.2 ± 29.0	705.4 ± 23.6	757.4 ± 2.99	704.5 ± 23.2	.32
Rewarming 28°C	396.1 ± 48.3	425.3 ± 26.6	424.9 ± 59.6	317.5 ± 51.0	.36
Rewarming 36°C	149.7 ± 18.5	144.3 ± 15.3	141.6 ± 9.4	153.2 ± 17.1	.95
Arterial pH					
On CPB	7.38 ± 0.02	7.40 ± 0.02	7.41 ± 0.02	7.36 ± 0.01	.27
Cooling 28°C	7.33 ± 0.01	7.22 ± 0.03	7.35 ± 0.02	7.19 ± 0.02	<.05†
Cooling 20°C	7.36 ± 0.02	7.17 ± 0.03	7.34 ± 0.01	7.15 ± 0.01	<.001†
ASCP 60 min	7.39 ± 0.03	7.17 ± 0.03	7.35 ± 0.02	7.17 ± 0.01	<.001†
ASCP 120 min	7.39 ± 0.02	7.15 ± 0.02	7.35 ± 0.01	7.15 ± 3.8	<.001†
Rewarming 28°C	7.36 ± 0.02	7.24 ± 0.02	7.34 ± 0.01	7.21 ± 0.03	<.05†
Rewarming 36°C	7.35 ± 0.02	7.40 ± 0.02	7.34 ± 0.02	7.41 ± 0.02	.33
Paco ₂ (mm Hg)					
On CPB	37.5 ± 0.9	39.4 ± 0.6	37.5 ± 0.8	39.5 ± 0.3	.10
Cooling 28°C	41.8 ± 2.1	64.3 ± 1.0	41.2 ± 1.7	66.7 ± 1.9	<.001†
Cooling 20°C	41.5 ± 2.5	92.4 ± 1.4	42.8 ± 2.1	91.7 ± 2.4	<.001†
ASCP 60 min	37.2 ± 1.5	95.9 ± 2.8	39.7 ± 2.0	94.9 ± 3.7	<.001†
ASCP 120 min	36.4 ± 1.3	92.3 ± 1.9	37.7 ± 1.9	91.3 ± 3.5	<.001†
Rewarming 28°C	37.1 ± 1.7	63.2 ± 1.5	37.8 ± 3.4	72.4 ± 3.2	<.001†
Rewarming 36°C	37.1 ± 1.4	40.1 ± 1.3	37.5 ± 3.2	43.0 ± 1.0	.16
SmvO ₂ (%)					
On CPB	75.4 ± 2.80	78.2 ± 1.43	74.2 ± 1.21	76.8 ± 1.56	.48
Cooling 28°C	94.9 ± 1.08	97.0 ± 0.66	91.3 ± 2.36	95.9 ± 0.48	<.05‡
Cooling 20°C	98.5 ± 0.02	99.4 ± 0.22	96.0 ± 2.01	99.1 ± 0.72	.16
ASCP 60 min	99.0 ± 2.80	99.6 ± 0.23	99.5 ± 0.31	99.2 ± 0.66	.71
ASCP 120 min	98.4 ± 0.48	99.3 ± 0.34	99.4 ± 0.33	99.5 ± 0.41	.23
Rewarming 28°C	96.5 ± 0.93	98.4 ± 0.31	98.1 ± 0.64	96.5 ± 1.58	.37
Rewarming 36°C	87.0 ± 2.54	93.0 ± 0.89	87.6 ± 3.00	88.5 ± 2.42	.30

MAP, Mean artery pressure; CPB, cardiopulmonary bypass; ASCP, antegrade selective cerebral perfusion; SmvO₂, maxillary vein saturation of oxygen.

*One-way analysis of variance.

†Comparison with Tukey HSD method between alpha-stat group (groups A and C) and pH-stat group (groups B and D).

‡Comparison with Tukey HSD method between groups B and C.

cantly increased 120 minutes after the initiation of ASCP and continued so until the end of experiment (Figure 2), an early indication of brain ischemia. The serum concentration of glutamate, on the other hand, was significantly higher during the rewarming period at 28°C and 36°C (Figure 3), showing ischemia in the brain.^{15,16}

SEP

We tried to detect the functional impairment in the brain during the experimental procedure. In group C, CCT was

significantly prolonged after surgical intervention compared with the preoperative value (Figure 4), indicating a delayed transmission in the brain.¹⁷ In both groups C and D, the experimental procedure also decreased significantly the amplitude ratio of N4 to N1 compared with the preoperative value (Figure 5), suggesting that neuronal activity in the sensory cortex¹⁷ decreased.

Discussion

Our previous work has examined, in animal models, the effect of aortic arch operations with ASCP by using alpha-

Figure 1. Levels of VALD. The values are shown according to the time course (see in text). In group C VALD significantly increased at time course 3. * $P < .05$, different from groups A and B. Values are expressed as means $\pm$ SE.

Figure 2. Changes of serum MDA concentration. The percentages of preoperative value are shown according to the time course (see in text). In group C the value significantly increased from time course 6 to time course 8. * $P < .05$, different from groups A and B; # $P < .01$, different from groups A and B. Values are expressed as means $\pm$ SE.

stat pH management on brains with old infarction and pointed out that an accelerated anaerobic metabolism and an increased glutamate release in animals with cerebral infarction¹⁰ was consistent with our clinical data.

Recent studies¹⁸⁻²¹ have suggested that during hypothermic CPB, the management for blood pH influences the neurologic outcome after surgical intervention. In a neonatal animal model pH-stat management ensured less functional disability and less neuronal cell damage in the neocortex and hippocampal CA1 region after DHCA.¹⁸ In a previous study in infants, pH-stat management revealed a better recovery of the cerebral physiology after DHCA and

was associated with lower postoperative morbidity, fewer electroencephalographic seizures, and a faster recovery of electroencephalographic activity.¹⁹ By contrast, another randomized study suggested that alpha-stat management decreased the incidence of postoperative cerebral dysfunction in adult patients undergoing coronary artery bypass grafting operations,²⁰ especially prolonging CPB time.²¹ Additionally, alpha-stat management preserves cerebral blood flow autoregulation and optimizes cellular enzyme activity. Therefore in the present study we sought to determine the influences of pH management with ASCP on brains in a canine model with or without old cerebral infarction.

Figure 3. Changes of serum glutamate concentration. The percentages of preoperative value are shown according to the time course (see in text). The concentration significantly increased in group C after time course 7. * $P < .05$, different from groups A and B; # $P < .01$, different from groups A and B. Values are expressed as means $\pm$ SE.

Figure 4. Changes in CCT after surgical intervention. The percentages of preoperative CCT are shown. In group C, CCT was significantly prolonged after the operation. In group D, CCT tended to increase, but it did not reach a significant level. * $P < .05$, different from groups A and B. Values are expressed as means $\pm$ SE.

In the present study the animals in group C showed a remarkable increase in parameters, including serum MDA and serum glutamate concentrations. The increase of MDA reflects a free radical production and subsequent lipid peroxidation of membrane polyunsaturated fatty acid and is an early biochemical marker of ischemic brain injury.^{13,14} An extracellular glutamate release from the neurons increases in either anoxia¹⁵ or ischemia.¹⁶

We also observed a prolonged CCT and a decrease of the N4/N1 amplitude ratio in the animals with old cerebral infarction and the absence of any of these in the intact animals. Previous studies have revealed that an impairment of SEP was associated with a cerebral injury in permanent

ischemic animal models.²² The prolonged CCT showed a correlation with the size of the cerebral infarction²² and with the outcome in patients with a traumatic brain injury.²³

Taken together, the brain with old cerebral infarction showed a functional impairment caused by ischemia during ASCP, whereas the intact brain showed no sign of ischemic damage independent of the method for pH management.

pH-stat recovered SmvO₂ and VALD, decreased MDA and glutamate concentrations in the serum, and improved CCT in SEP examination in the animals with old cerebral infarction. The results, especially the latter 3, indicate that the management with pH-stat provides brain protection against ischemia during ASCP. Strictly speaking, such pro-

Figure 5. Changes in N4/N1 ratio after surgical intervention The percentages of the preoperative N4/N1 ratio are shown. In groups C and D the N4/N1 ratio significantly decreased after the operation. * $P < .05$, different from groups A and B. Values are expressed as means $\pm$ SE.

tection might not be complete because the N4/N1 ratio in SEP amplitude was still low, even in the animals with pH-stat management.

In our earlier study¹⁰ VALD in the infarct group showed a significant increase in the rewarming phase, whereas it was not evaluated in the cooling phase. However, in the current study the levels of VALD in group C significantly increased in the cooling phase but not in the rewarming phase. We presume one of the reasons why an accelerated anaerobic glycolysis did not occur in the rewarming phase of the present study was the maintenance of the difference between the rectal and arterial temperature within 5°C during experimental CPB.

In a brain with old infarction, cerebral ischemia can occur in the peri-infarct area, in which the collateral blood flow is insufficient to save the brain from ischemia (ie, chronic penumbra). It is essential to increase the cerebral blood flow to protect the brain against ischemia. It is conceivable that management with pH-stat might increase cerebral blood flow and provide neuroprotection in a brain with old infarction. Miyamoto and colleagues²⁴ have described how pH-stat management mediates the vasodilatation of cerebral arteries and increases cerebral blood flow, thus proving advantageous in perfusions of brains with old infarction. In a brain with old infarction, as already mentioned, pH-stat management might provide more effective protection against ischemia compared with alpha-stat management.

The reason why pH-stat management has not shown a clear advantage in the clinical data^{21,22} remains unclear. The fact is, however, that pH management during deep hypothermic CPB in an adult has not as yet been fully examined. The discrepancy between the clinical and experimental settings cannot be noticed. In the present study we examined

the effects of pH management in the animal with or without old cerebral infarction that had been induced by occluding the cerebral artery. Therefore the reactivity to hypercapnia can remain functional in the vessels providing collateral blood flow. On the other hand, in the patient with old cerebral infarction, systemic arteriosclerosis can impair CO₂ reactivity. Regional CO₂ reactivity in patients with cerebral artery or internal carotid artery occlusion was significantly reduced.²⁵ In some patients with cerebrovascular disease, pH-stat management might fail to increase cerebral blood flow in the ischemic area during cardiac surgery because of poor CO₂ reactivity. Consequently, the operative results might not be as good as those obtained from this experimental study.

On the basis of these results, we recommend that pH-stat management can be adopted during ASCP in those patients with old cerebral infarction in whom normal CO₂ reactivity is preserved. In the risky patients with a history of ischemic stroke, the examination with single photon emission tomography is useful to analyze CO₂ reactivity, and it might improve the results of cardiovascular surgery.

In conclusion, the present study has examined the influences of pH management with ASCP on canine brains with or without old cerebral infarction. Cerebral ischemia occurred during experimental CPB in the infarct group. pH-stat management during ASCP proved more neuroprotective against ischemia than alpha-stat management, whereas the influence of the pH management on the functional outcome remains to be established.

References

1. Di Eusano M, Schepens MAAM, Morshuis WJ, Di Bartolomeo R, Pierangeli A, Dossche KM. Antegrade selective cerebral perfusion

- during operations on the thoracic aorta: Factors influencing survival and neurologic outcome in 413 patients. *J Thorac Cardiovasc Surg.* 2002;124:1080-6.
2. Dossche KM, Schepens MAAM, Morshuis WJ, Muysoms FE, Lange-meijer JJ, Vermeulen FEE. Antegrade selective cerebral perfusion in operations on the proximal thoracic aorta. *Ann Thorac Surg.* 1999;67:1904-10.
 3. Swain JA, McDonald TJ, Griffith PK, Balaban RS, Clark RE, Ceckler T. Low-flow hypothermic CPB protects the brain. *J Thorac Cardiovasc Surg.* 1991;102:76-84.
 4. Sakurada T, Kazui T, Tanaka H, Komatsu S. Comparative experimental study of cerebral protection during aortic arch reconstruction. *Ann Thorac Surg.* 1996;61:1348-54.
 5. Hagl C, Ergin MA, Galla JD, Lansman SL, McCullough JN, Spielvogel D, et al. Neurologic outcome after ascending aorta-aortic arch operations: effect of brain protection technique in high-risk patients. *J Thorac Cardiovasc Surg.* 2001;121:1107-21.
 6. Roach GW, Kanchuger M, Mangano CM, Newman M, Nussmeier N, Wolman R, et al. Adverse cerebral outcomes after coronary bypass surgery. *N Engl J Med.* 1996;335:1857-63.
 7. Svensson LG, Crawford ES, Hess KR, Coselli JS, Raskin S, Shenaq SA, et al. Deep hypothermia with circulatory arrest: Determinants of stroke and early mortality in 656 patients. *J Thorac Cardiovasc Surg.* 1993;106:19-31.
 8. Kazui T, Washiyama N, Muhammad BAH, Terada H, Yamashita K, Takinami M. Improved results of atherosclerotic arch aneurysm operations with a refined technique. *J Thorac Cardiovasc Surg.* 2001;121:491-9.
 9. Kazui T, Washiyama N, Bashar AHM, Terada H, Yamashita K, Takinami M, et al. Total arch replacement using aortic arch branched grafts with the aid of antegrade selective cerebral perfusion. *Ann Thorac Surg.* 2000;70:3-9.
 10. Washiyama N, Kazui T, Takinami M, Yamashita K, Fujita S, Terada H, et al. Experimental study on the effect of antegrade cerebral perfusion on brains with old cerebral infarction. *J Thorac Cardiovasc Surg.* 2001;122:734-40.
 11. Smith AL, Hoff JT, Nielsen SL, Larson CP. Barbiturate protection in acute focal cerebral ischemia. *Stroke.* 1974;5:1-7.
 12. Ohkawa H, Ohnishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Anal Biochem.* 1979;95:351-8.
 13. Lantos J, Temes G, Roth R, Morvay G. Alterations in malondialdehyde concentration of jugular vein blood following transient brain ischemia: the effect of lactic acidosis. *Acta Physiol Hung.* 1994;82:229-36.
 14. Sakamoto A, Ohnishi ST, Ohnishi T, Ogawa R. Relationship between free radical production and lipid peroxidation during ischemia-reperfusion injury in the rat brain. *Brain Res.* 1991;554:186-92.
 15. Hansen AJ. Effect of anoxia on ion distribution in the brain. *Physiol Rev.* 1985;65:101-48.
 16. Takagi K, Ginsberg MD, Globus MYT, Dietrich WD, Martinez E, Kraydieh S, et al. Changes in amino acid neurotransmitters and cerebral blood flow in the ischemic penumbral region following middle cerebral artery occlusion in the rat: correlation with histopathology. *J Cereb Blood Flow Metab.* 1993;13:575-85.
 17. Vanderzant CW, Schott RJ, Natale JA, Pondo CA, D'Alecy LG. Somatosensory evoked potentials of the dog: recording techniques and normal values. *J Neurosci Methods.* 1989;27:253-63.
 18. Priestley MA, Golden JA, O'Hara IB, McCann J, Kurth CD. Comparison of neurologic outcome after deep hypothermic circulatory arrest with alpha-stat and pH-stat cardiopulmonary bypass in newborn pigs. *J Thorac Cardiovasc Surg.* 2001;121:336-43.
 19. du Plessis AJ, Jonas RA, Wypij D, Hickey PR, Riviello J, Wessel DL, et al. Perioperative effects of alpha-stat versus pH-stat strategies for deep hypothermic cardiopulmonary bypass in infants. *J Thorac Cardiovasc Surg.* 1997;114:991-1001.
 20. Patel RL, Turtle MR, Chambers DJ, James DN, Newman S, Venn GE. Alpha-stat acid-base regulation during cardiopulmonary bypass improves neurophysiologic outcome in patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 1996;111:1267-79.
 21. Murkin JM, Martzke JS, Buchan AM, Bentley C, Wong CJ. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. II. Neurologic and cognitive outcomes. *J Thorac Cardiovasc Surg.* 1995;110:349-62.
 22. Meyer KL, Dempsey RJ, Roy MW, Donaldson DL. Somatosensory evoked potentials as a measure of experimental cerebral ischemia. *J Neurosurg.* 1985;62:269-75.
 23. Skeigh JW, Havill JH, Frith R, Kersel D, Marsh N, Ulyatt D. Somatosensory evoked potentials in severe traumatic brain injury: a blinded study. *J Neurosurg.* 1999;91:577-80.
 24. Miyamoto TA, Miyamoto KJ. Alpha-stat strategy: cause of ischemia in brains with old cerebral infarction despite selective cerebral hypothermic antegrade perfusion. *J Thorac Cardiovasc Surg.* 2002;124:1260-1.
 25. Ogasawara K, Ogawa A, Terasaki K, Shimizu H, Tominaga T, Yoshimoto T. Use of cerebrovascular reactivity in patients with symptomatic major cerebral artery occlusion to predict 5-year outcome: comparison of xenon-133 and iodine-123-IMP single-photon emission computed tomography. *J Cereb Blood Flow Metab.* 2002;22:1142-8.

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