

Antegrade Selective Cerebral Perfusion Combined with Deep Hypothermic Circulatory Arrest on Cerebral Circulation: Comparison between Pulsatile and Nonpulsatile Blood Flows

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Purpose: In aortic arch surgeries, antegrade selective cerebral perfusion (SCP) combined with deep hypothermic circulatory arrest (DHCA) has been recently widely used in institutions as one of the most reliable methods for cerebral protection. However, some studies reported a 3.7–9.3% incidence of postoperative cerebral complications. To perform antegrade SCP more safely, we sought to examine the impact of pulsatile flow perfusion during DHCA on cerebral tissue metabolism, focusing on physiological effects of pulsatile flow perfusion.

Materials and Methods: Sixteen pigs were divided into 2 groups. In each group, antegrade SCP combined with DHCA was conducted. During circulatory arrest, for SCP, a pulsatile flow (group P) and a nonpulsatile flow (group N) were used. We compared results between group P and group N. Jugular venous oxygen saturation (SjO₂) and cerebral tissue oxygen partial pressure (PtO₂) were measured at baseline, and continuously throughout the extracorporeal circulation. Hematocrit (Ht), and concentrations of S-100 protein and CK-BB in blood and the cerebrospinal fluid (CSF) were measured at baseline (before the beginning of extracorporeal circulation), following SCP, and after rewarming. Following rewarming, each brain under perfused fixation was removed, and histopathological examinations were conducted using Kluver-Barrera and Tunnel staining methods, electron micrograph.

Results: SjO₂ was found to be within normal ranges until after SCP, but decreased with rewarming in both groups. In Group N, changes in SjO₂ were significant, with a decrease to ≤50%. In Group N, concentrations of S-100 protein and CK-BB in CSF after SCP and after rewarming were significantly higher than those in Group P. The time needed for rewarming to 36°C in Group P was shorter than that in Group N.

Conclusion: Our results suggest that the pulsatile flow circulation method shows cerebral protection effects with increasing blood flow in small cerebral tissues. In addition, it is effective for improving the imbalance between oxygen supply and demand, especially in the process of rewarming from hypothermic conditions. This method seems to be useful as an adjunct in hypothermic circulatory arrest procedures. (*Ann Thorac Cardiovasc Surg* 2007; 13: 93–101)

Key words: selective cerebral perfusion, pulsatile perfusion, deep hypothermic circulatory arrest

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Introduction

In aortic arch surgeries, antegrade selective cerebral perfusion (SCP) has recently been widely used as one of the most reliable methods for cerebral protection.¹⁾ However, some studies reported a 3.7–9.3% incidence of postoperative cerebral complications.^{1–3)} Generally, perfusion

in antegrade SCP is conducted using a nonpulsatile flow. However, it has been shown that perfusion with a more physiological pulsatile flow could act in peripheral arterioles, and improve blood flow in small tissues.⁴⁾ In addition, such perfusion has been reported to be effective for main organs under normal temperature.⁵⁻⁷⁾ In the present study, we examined effects of pulsatile flow circulation in hypothermic circulatory arrest procedures on cerebral tissue metabolism.

Materials and Methods

Sixteen male pigs were used in this study (group P: n=8, 41.2±0.6 kg, group N: n=8, 40.8±0.3 kg). Pentobarbital (20 mg/kg) and ketamine hydrochloride (10 mg/kg) were used intramuscularly for preanesthesia. Subsequently, general anesthesia was maintained with intravenous injection of ketamine hydrochloride (1 mg/kg/h). Musculax (0.5 mg/kg) was injected intravenously in pigs fixed in the supine position, and endotracheal intubation was conducted (TRACHELON 6 mm, Terumo Co., Ltd., Japan). Ventilation was conducted using an artificial ventilator with 40% oxygen, a ventilation frequency of 14/min, and a tidal volume of 12 ml/kg (Servo Ventilator 900D, Siemens-Elcoma AB, Stockholm, Sweden). After exposing the right femoral artery and the left axillary artery, arterial pressures were measured using catheters inserted into arteries. Exposure of the right half side of cranial bones, production of a hole of about 1 cm in diameter at the parietal region, and cannulization into the procelia (lateral cerebral ventricle) were conducted to ensure for a cerebrospinal fluid (CSF) sampling line. From the same hole, a temperature probe (Thermocouple Probe, Anritu Meter Co., Ltd., Japan) and a cerebral tissue oxygen partial pressure (PtO₂)-measuring probe (LICOX, GMS Co., Ltd., Kiel, Germany) were inserted into the cerebral tissue, and were fixed at the head area. Using thoracotomy by median sternotomy, Jugular venous oxygen saturation (SjO₂) was measured with a 5 Fr Swan-Ganz catheter (Edwards Lifesciences, CA, USA) inserted from the superior vena cava, and the tip of the catheter was fixed to the bulb of the jugular vein. Following systemic heparinization of 300 IU/kg, extracorporeal circulation was established with blood removal from the right atrium using a venous cannula (Dual Drainage Venous Cannula, MERA Co., Ltd., Japan), and blood flow into ascending aorta using arterial cannula (Large Flow Aortic Perfusion Cannula, MERA Co., Ltd., Japan). For pumping of blood flow, the centrifugal pump (GYRO PUMP JP0005,

Medtronic Inc., NW, USA) and a roller pump (BIO-PUMP PULS BPX-80, Medtronic Inc., NW, USA) were used for nonpulsatile and pulsatile flows, respectively. Each pump system was connected to artificial lungs (HPO-20RHF-C, MERA Co., Ltd., Japan). Cardiopulmonary bypass (CPB) with 70 mL/kg/min was started. Simultaneously, core cooling was started with blood flow temperature set at 5°C, using a heat exchanger (HHC-51, MERA Co., Ltd., Japan). After Vf (ventricular fibrillation) occurred, the aorta was clamped and a root cannula (Medtronic Inc., NW, USA) inserted into the base of the aorta. Cardiac arrest was established by injecting 15 mL/kg/min of cardioplegia (Myotector, Mochida Pharmaceutical Co., Ltd., Tokyo, Japan). Circulatory arrest was established by stopping extracorporeal circulation when cerebral temperature reached 20°C. Using cannula (Mera ballon, MERA Co. Ltd., Japan) into two carotid arteries, antegrade SCP for 60 min was conducted with 10 mL/kg/min, and at 20°C. After 60-min perfusion, the cannulas were removed, followed by rewarming to 36°C with thermoregulation, to achieve a within 5°C temperature gap between blood flow temperature and the deep body temperature. SjO₂ and cerebral PtO₂ were measured throughout the study (including measurement at baseline and at completion of the examination). Jugular blood flow during extracorporeal circulation was measured by a flow meter probe (Medical Volume Flowmeters HT107/HT207 series, TRANSONIC Co., Ltd., USA) used for a carotid artery. Simultaneously, measured axillary arterial pressure (AAP) was divided by blood flow. In addition, the value derived from the division was used to estimate cerebrovascular resistance (CVR).

$$\begin{aligned} \text{Estimate CVR (mmHg/mL/100 g/min)} \\ = \text{mean AAP/blood flow} \end{aligned}$$

The CVR and StO₂ ratios were determined in relation to the baselines. Using blood and CSF samples collected before extracorporeal circulation, after SCP, and after rewarming, Ht, S-100 protein, and CK-BB were measured. Completion of the examination was set at the time of rewarming to 36°C, and brains were removed after perfused fixation by injecting 10 L PFA (PFA; Paraformaldehyde in 0.1 mol Sorensen PB, pH 7.4) from the carotid arteries using a head drop. Following fixation of brain tissues for a week, histopathological examinations were conducted using Kluver-Barrera staining and Tunnel staining and studied with electron microscopy.

All animals received humane care in accordance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research, as well as

Table 1. Experimental and metabolic data

	Baseline	Cooling	SCP	30 min after the start of rewarming
MAAP (mmHg)				
N	116±5	60±4	59±6	63±8
P	123±8	58±2	55±7	62±5
CPB flow (L/min)				
N		2.8±0.5		2.7±0.3
P		2.7±0.1		2.8±0.4
SCP flow (L/min)				
N			0.43±0.06	
P			0.38±0.15	
Pulse pressure (mmHg)				
N	–	–	0	–
P	–	28±7	18±5	22±8
Brain temp (°C)				
N	36.6±0.7	19.8±0.5	18.8±0.9	24.6±0.6
P	36.1±0.6	19.4±0.8	19.2±0.9	28.1±0.7
Hematocrit (%)				
N	28.6±1.3	22.1±0.9	21.5±1.5	26.3±2.3
P	29.1±2.5	23.0±0.2	22.4±0.8	24.7±0.6
PaCO ₂ (mmHg)				
N	38.4±2.6	41.8±2.8	46.0±0.7	34.6±0.9
P	38.0±2.7	46.1±2.6	44.5±3.8	40.1±4.4

MAAP, mean axillary artery pressure; CPB, cardiopulmonary bypass; SCP, selective cerebral perfusion; NS, not significant.

with the “Guide for the Care and Use of Laboratory Animal Resources” and published by the National Institute of Health (NIH publication 86–23, revised, 1996).

Data analysis

Statistical analysis was performed using Stat View 5.0 (SAS Inc., USA). The Mann-Whitney U test used to assess the distribution of variables between study groups. Values of *P* less than or equal to 0.05 were accepted as significant.

Results

Experimental data and metabolic data

The target pump flow was set at 2.7 L/min, and the pump flow was controlled to achieve an axillary arterial pressure of 60–80 mmHg. It was possible to achieve an axillary arterial pulse pressure of approximately 30 mmHg during systemic circulation, but only approximately 20 mmHg during SCP in Group P. There were no significant differences between the two groups in mean axillary arterial pressure during systemic circulation and SCP. Due to diluted extracorporeal circulation, Ht values were de-

creased after extracorporeal circulation, but there were no significant differences between the two groups in Ht values measured at 4 time points; i.e., before and after circulation, after SCP, and after rewarming (Table 1).

SjO₂

In both groups, SjO₂ increased from the beginning of extracorporeal circulation, to above 90%, and then gradually decreased with rewarming after SCP. In group N, SjO₂ began to decrease more drastically from 30°C, compared to group P. Some cases in group N showed <50% of SjO₂ at 35°C (Fig. 1).

PtO₂

With continuous measurements of PtO₂ using a probe inserted intracerebrally, PtO₂ in both groups was shown to gradually increase from the beginning of extracorporeal circulation, and subsequently decreased with rewarming after SCP. In group N, PtO₂ began to decrease more drastically from about 30°C compared to group P. A significant difference in PtO₂ value was seen between the two groups, especially at 35°C (Fig. 2).

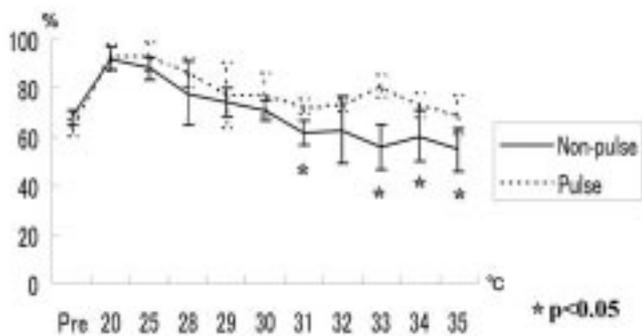


Fig. 1. Time course changes in jugular venous oxygen saturation (SjO₂) during the study.

Significant differences in SjO₂ were observed between the two groups at rewarming time.

S-100 proteins and CK-BB

Using CSF and blood samples in the procelia collected at 3 time points, i.e., before extracorporeal circulation, after selective cerebral perfusion, and after rewarming, CSF and blood S-100 protein and CK-BB concentrations were measured, and levels of cerebral tissue damage in the two groups were compared. Blood S-100 and CK-BB concentrations did not significantly increase from pre-CPB to post-CPB, and no significant difference between the two groups was shown. It was shown that S-100 protein and CK-BB concentrations in CSF at post-CPB were significantly increased compared to those at pre-CPB, and this increasing trend was significantly inhibited in group P (Figs. 3 and 4).

Estimated values of cerebrovascular resistance

Estimated CVR values began to increase with the start of extracorporeal circulation, and with cooling. Comparison between the two groups showed that there was a more significant increase in resistance in group N, and a lower CVR was maintained in group P (Fig. 5).

Rewarming time

In both groups, rewarming from 20 to 36°C was achieved when <5°C temperature gap was maintained between blood flow and the deep part, in order to avoid rapid increase in temperature. In group P, rewarming was achieved about 30 min faster than in group N (Fig. 6).

Pathological examinations

The perfused fixed brains were immediately removed after rewarming, and were stained with Kluver-Barrera

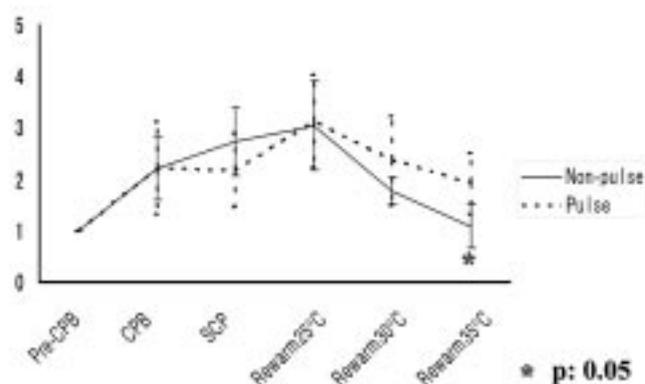


Fig. 2. Time course changes in brain tissue oxygen pressure index (PtO₂I) during the study.

Significant differences in PtO₂I were observed between the two groups at rewarming time. CPB, cardiopulmonary bypass; SCP, selective cerebral perfusion.

staining and Tunnel staining. Pathological examination of each brain tissue was then conducted. Comparison between the two groups was mainly conducted for the hippocampus (especially for the CA1 area) that has been considered to be susceptible to ischemia because of its location near the peripheral end of the cerebrovascular system. Kluver-Barrera staining revealed some atypical cells with deformed cellular nuclei, and the chromatin was strongly stained in group N compared to group P. Tunnel staining revealed few TUNNEL-positive cells in both groups, and apoptosis was not seen. Electron microscopical examinations showed that in group N, there were more damaged cells in which cell substrates were deeply stained and chromatin agglutination was present than in group P. No significant effect of pulsatile flow-mediated pressure overload on cerebral cells was seen (Fig. 7).

Discussion

The occurrence of cerebral complications in aortic arch surgery has been recognized as a serious problem, resulting in poor patient prognosis. Affecting factors for cerebral complications at surgery are divided into two groups: ischemic and embolic. Embolic complications correlate with patients' vascular characteristics, and are caused by poor surgical techniques. To prevent embolic complications, many physicians currently perform preventive actions including strict preoperative evaluation, echographic evaluation of calcification during operation, careful attention to surgical procedures, and avoidance of embolism using a retrograde cerebral perfusion method.^{8,9)} In

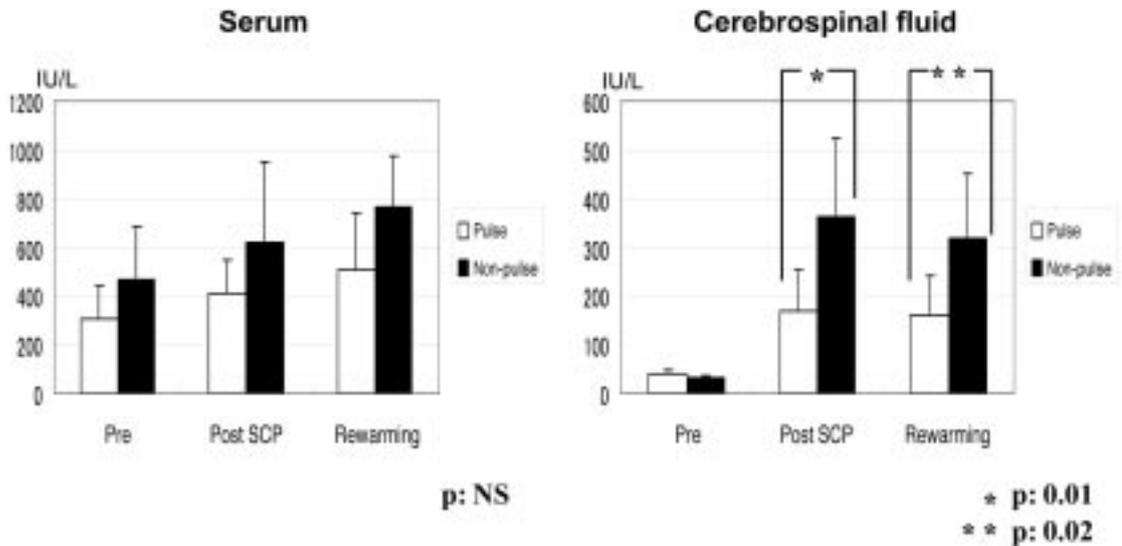


Fig. 3. CK-BB concentration in plasma and cerebrospinal fluid during this study. There was no significant difference in plasma, but significant difference in cerebrospinal fluid.

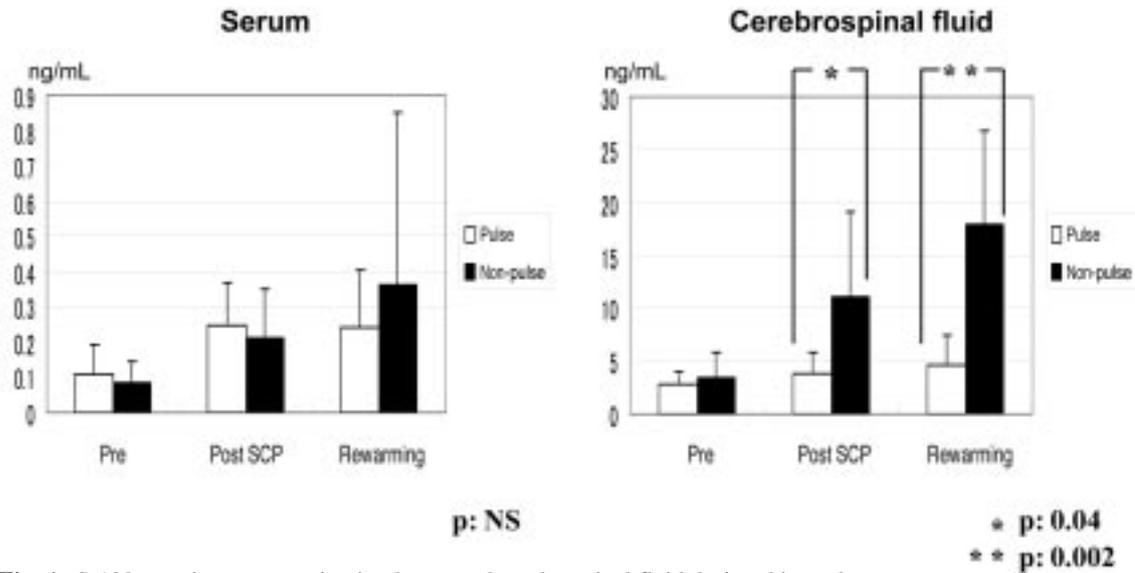


Fig. 4. S-100 protein concentration in plasma and cerebrospinal fluid during this study. There was no significant difference in plasma, but in cerebrospinal fluid.

contrast, ischemic cerebral complications are caused by a decrease in local cerebrovascular blood flow, decrease of oxygen supply, and oxygen consumption under non-physiological circulation dynamics conditions with hypothermia; and changes in blood pressure, hemodilution, and stationary flow under conditions of extracorporeal circulation. The extracorporeal circulation technique has improved, and its safety has now been established. Generally, intermittent extracorporeal circulation used in surgeries including open heart surgery has been conducted

using a nonpulsatile flow. However, pulsatile blood flow has been considered to be a more physiological blood flow procedure for the living body. Recently, the usefulness of pulsatile flow has been suggested, and its experimental effectiveness for organism has also been reported in some studies.⁵⁻⁷⁾ In addition, the pulsatile flow procedure has been clinically used for cardiac assisting circulation, such as left ventricular assisting device^{10,11)} or in high risk patients with carotid arteriosclerosis, with favorable results.

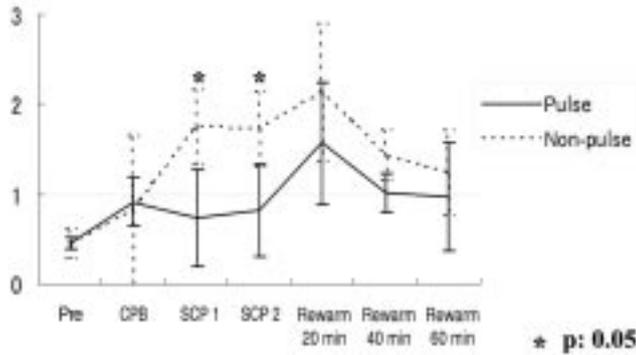


Fig. 5. Time course changes in cerebrovascular resistance index (CVRI) during the study. Significant differences in CVRI were observed between the two groups.

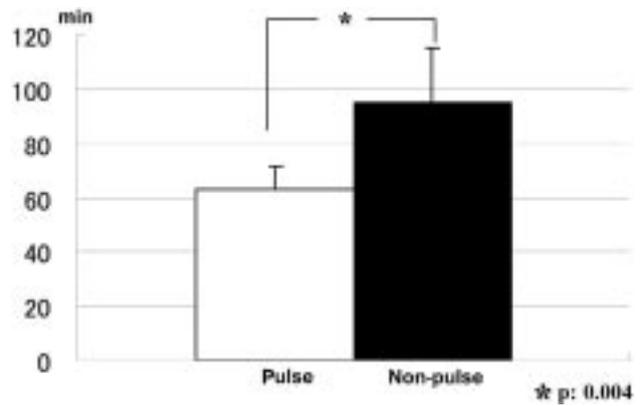


Fig. 6. The graph is rewarming time from 20 to 36°C at brain temperature. Significant differences in rewarming time were observed between the two groups.

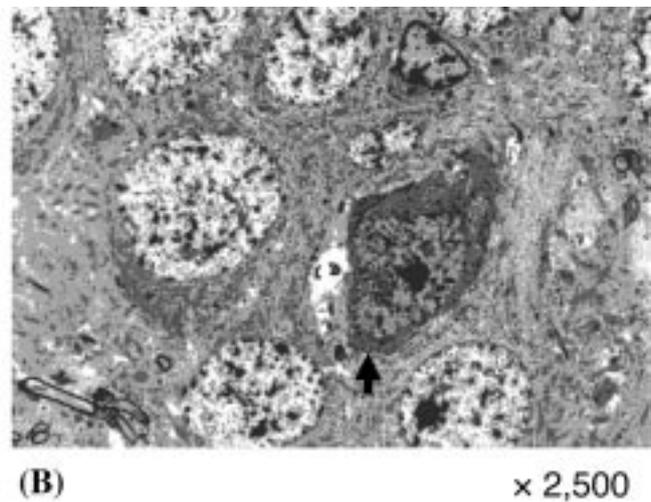
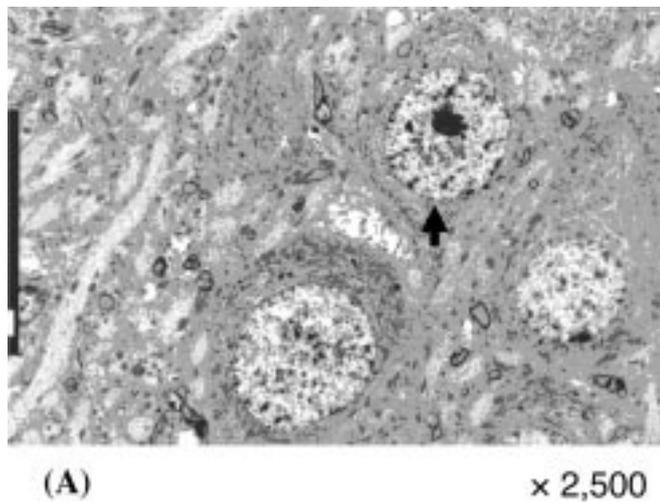


Fig. 7. Brain tissue (hippocampus CA1 area) showed by electro microscopic scanning. In group N (B), there were more damaged cells in which cell substrates were deeply stained and chromatin agglutination was present than in group P (A).

Such pulsatile flow is considered to have positive effects in improving acidosis and metabolism. It also increases oxygen supply by maintaining good peripheral circulation promoted by reduced peripheral vascular resistance via the baroreceptor reflex, catecholamine and renin-angiotensin systems, and a higher kinetic energy.^{4,12)} There are many experimental reports suggesting that pulsatile flow may have organ protective effects.⁵⁻⁷⁾ Notably, results of the present study suggest that use of the pulsatile flow in highly invasive procedures including deep hypothermic circulatory arrest (DHCA) and SCP might prevent cerebral damage.

With regard to cooling methods, it has been suggested

that there was no disadvantage with rapid cooling from the point of view of organ protection, and rapid cooling was favorable for the organism. Cerebral protective effects with hypothermic procedures including inhibition of neuron excitation, and discharge of excitable amino acids, and thereby, prevention of an increase in intercellular calcium ions, hyperoxidation of lipids in cell membranes, and free radical production, have been reported in previous studies.¹³⁾ As a result of these cerebral protective actions, cell membranes are stabilized, and cellular and cerebral edema caused by increased permeability in the blood-brain barrier are inhibited. In addition, by reducing oxygen requirements in brain tissues, cerebral

functional disorders can be prevented even in hypoxic conditions.

However, previous reports on cerebral hypothermic therapy in CPA patients have suggested that rewarming from hypothermic conditions should be conducted as slowly as possible.¹⁴⁻¹⁶⁾ During deep hypothermic procedures, rewarming of the body temperature should generally be conducted without excessive increase of blood flow temperature even under time pressure of extracorporeal circulation with thermoregulation, to achieve a target gap temperature between the deep part and blood flow of 5–10°C. The reasons why such a rewarming process should be followed may include prevention of cerebral edema caused by increased cerebrovascular volume resulting from sudden increase of cerebral blood flow due to decreased cerebrovascular resistance with rapid rewarming. As reported by Kono et al., pulsatile flow seems to decrease cerebral peripheral vascular resistance according to physiological conditions, and safer rewarming can be achieved by providing sufficient oxygen for metabolic actions in small tissues during rewarming using a pulsatile flow.¹⁷⁾ In addition, beside such a direct protective effect, it is suggested that the pulsatile blood flow technique may reduce the time needed for rewarming from hypothermia to normal temperature conditions by increasing organ blood flow, and may be effective in protecting organs indirectly by reducing the pump time, as demonstrated in the present study.

In this study, we measured levels of S-100 protein and CK-BB as indicators of cerebral damage. It is considered that both of these factors are found in cerebral tissues, and are usually not found outside cerebral cells, but are found outside cells with cerebral damage. It has been recently reported that the amount of S-100 protein may increase with cerebral damage, and reflects patient's prognosis.¹⁸⁾ In the field of cardiac surgery, there are many reports on S-100 protein measured after extracorporeal circulation.¹⁹⁻²¹⁾ These reports focused on S-100 concentration in blood. It is suggested that S-100 protein concentration in CSF may increase earlier after occurrence of damage than that in blood. In this study, in the nonpulsatile group, it was shown that the increase in S-100 protein concentration in CSF was significantly higher than that in blood. In fact, Kuniyama et al. reported that, when they measured S-100 protein concentration in CSF collected through catheters for CSF drainage during surgical procedures for the treatment of thoracoabdominal aortic aneurysm, there was a positive correlation between S-100 protein concentration and incidence of neuropathy.^{22,23)} Early detection of neuropathy may result in early detection of irreversible disorders and early treatment.

thy.^{22,23)} Early detection of neuropathy may result in early detection of irreversible disorders and early treatment.

In this study, S_jO₂ and PtO₂ were used to evaluate oxygenation during DHCA, and antegrade SCP. S_jO₂ was used as an indicator of difference between oxygen demand and supply in cerebral tissues. High values of S_jO₂ were shown during hypothermic conditions due to less oxygen consumption. However, S_jO₂ gradually decreased with rewarming. These results are in accordance with those reported by Kiziltan et al.²⁴⁾ In our study, the decreasing rate of S_jO₂ was minimal in group P. In addition, PtO₂ also decreased with rewarming, and the decreasing rate in group N was significantly higher than that in group P.

With regard to DHCA, Griep et al, applied this method in surgical operations in aortic arches to establish intermittent systemic and cerebral circulation arrest by cooling rectal temperature to approximately 15°C.²⁵⁾ However, time allowed to arrest cerebral circulation is limited. Some investigators have reported that brain protective effects may be maximized using DHCA in combination with SCP.¹⁻³⁾ In Japan, many physicians currently use this combination procedure.²⁶⁾ There are 2 methods in blood transmission: antegrade and retrograde. Many reports suggested favorable usefulness of these 2 methods.^{1-3,8,9,26)} but at present, there is no conclusive information on which of these methods is superior. To clarify this matter, further investigations are required.

Carbon dioxide (CO₂) is considered to be one of the factors affecting cerebral blood flow during hypothermic extracorporeal circulation. Elevated levels of CO₂ in blood may cause cerebrovascular dilation. For this reason, some physicians use a method to improve cerebral oxygenation by providing CO₂ during rewarming from hypothermic conditions.²⁷⁾ In addition, levels of PaCO₂ in arterial blood are primarily responsible for regulation of pH.

To regulate pH during hypothermic extracorporeal circulation, two methods are available: using alfa-stat or pH-stat. It has been suggested that the latter method, i.e., using pH-stat, might increase cerebral blood flow by maintaining pH by adding CO₂.²⁸⁾ However, in clinical practice, the former method, i.e., using alfa-stat, has been widely used. The efficacy of the pH-stat method has not been clearly established yet. In our experimental study, the alfa-stat method was used in both groups. On the other hand, further investigations are needed to examine the usefulness of the pH-stat method.

In this study, pathological comparisons were conducted using each brain removed after SCP with pulsatile or

nonpulsatile flow. Kluver-Barrera staining showed that abnormal cells with heteromorphous alteration of cellular nuclei were dominant in the group N, whereas Tunnel staining showed that almost all cells in both groups were not apoptotic. These results suggested that bad effects of nonpulsatile flow on cerebral cells might be intermittent, and this flow might not cause irreversible alteration of cells. However, such an intermittent ischemic alteration, in combination with other risk factors that might invasively affect the organism, may cause postoperatively irreversible nervous disorders. Even though such an ischemic alteration may be intermittent, it should be resolved. However, in the present study, we conducted a pathological examination on brains removed immediately after rewarming. Further investigations are required to clarify pathological alterations for long term period after rewarming.

Conclusion

It is suggested that, in hypothermic circulatory arrest combined with SCP, extracorporeal circulation with pulsatile flow is effective for cerebral tissue metabolism. This effect may appear most significant during the process of rewarming from hypothermic conditions.

Acknowledgments

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