Optimal temperature for selective cerebral perfusion

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Objective: Although combinations of hypothermic circulatory arrest and antegrade selective cerebral perfusion are used for cerebral protection during arch surgery, there is no consensus regarding the optimal temperature during selective cerebral perfusion. This study explored the effect of different temperatures during selective cerebral perfusion on cerebral metabolism and neurologic outcome.

Methods: In this blinded study, 40 pigs (19-21 kg) were randomized into 4 groups after 30 minutes of hypothermic circulatory arrest at 20°C. During a 60-minute interval of selective cerebral perfusion, with flow regulated to maintain a perfusion pressure of 50 mm Hg, pigs were perfused at 10°C, 15°C, 20°C, and 25°C. Fluorescent microspheres enabled calculation of cerebral blood flow during perfusion and recovery. Hemodynamics, intracranial pressure, cerebrovascular resistance, and oxygen consumption were also monitored. Behavioral scores were obtained for 7 days after surgery.

Results: Cerebral blood flow decreased significantly ($P < .002$) during cooling in all groups: it was significantly higher throughout selective cerebral perfusion in the 20°C to 25°C versus the 10°C to 15°C group ($P = .0001$) and remained higher during recovery ($P = .0001$). Oxygen consumption decreased significantly with cooling ($P = .0001$), remained low during perfusion, and rebounded with rewarming but was significantly lower at 10°C to 15°C than at 20°C to 25°C throughout selective cerebral perfusion ($P = .003$) and after CPB was discontinued ($P = .001$). Postoperative behavioral scores were significantly better after selective cerebral perfusion at 10°C to 15°C than at 20°C to 25°C ($P = .001$).

Conclusions: This study suggests that selective cerebral perfusion at 10°C to 15°C provides better cerebral protection than selective cerebral perfusion at 20°C to 25°C, even though oxygen consumption remains low for hours after selective cerebral perfusion at 10°C to 15°C. Prompt return of metabolism to baseline levels after hypothermic circulatory arrest/selective cerebral perfusion does not necessarily predict superior behavioral outcome.

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Cerebral injury after aortic arch surgery has 2 major causes. Embolic stroke, when it occurs, is likely to result in a permanent focal deficit; although it has become less common with increasing experience, it is still a disastrous and sometimes fatal form of cerebral insult. A more frequent problem after aortic surgery is mild global cerebral injury. Such injury is clinically apparent as the syndrome known as transient neurologic dysfunction. Transient neurologic dysfunction

tion is thought to be a consequence of inadequate cerebral protection during the mandatory interval of interrupted antegrade cerebral perfusion. In rare instances, a very prolonged operation may cause an irreversible global ischemic insult.¹ Various strategies have been used to improve protection of the brain during the mandatory interruption of normal antegrade perfusion required for aortic arch surgery, with the hope of decreasing the morbidity and mortality of these operations. Hypothermic circulatory arrest (HCA) and hypothermic selective cerebral perfusion (SCP) are among the most successful strategies and are frequently used in combination.

The demonstration that operation on the aortic arch could be undertaken without obvious neurologic sequelae with HCA first permitted consideration of routine surgery for aortic arch aneurysms.² However, experimental studies showed that, even at low temperatures, brain metabolism still remains as high as 40% of baseline levels. Because the occurrence of postoperative cognitive dysfunction has been correlated with prolonged HCA in a number of studies, techniques such as antegrade SCP were introduced to shorten arrest times, with the hope of reducing the incidence of subtle cerebral injury.^{3,4}

The combination of HCA with SCP allows the surgeon to establish antegrade flow to the brachiocephalic vessels with minimal risk of atheroembolization during a brief interval of circulatory arrest and then provide adequate protection to the brain by using SCP throughout the remaining operation. Currently, HCA and SCP are both used clinically, both separately and in combination.⁵⁻⁸ However, the physiology of SCP after HCA is only beginning to be investigated. In an earlier study, we were surprised to discover that cerebral oxygen consumption and cerebral blood flow (CBF) were higher with SCP at 20°C than with hypothermic cardiopulmonary bypass (CPB) at the same temperature.⁹

This study was undertaken in a chronic animal model to investigate how temperature during SCP preceded by HCA affects not only CBF and metabolism, but also behavioral recovery.

Materials and Methods

Study Design

Forty female juvenile Yorkshire pigs 2 to 3 months old and weighing 19 to 21 kg were used for this experiment. All animals had a period of HCA at 20°C and were randomized thereafter to 1 of 4 study groups (10 animals were analyzed in each study group):

1. SCP 60 minutes at 10°C
2. SCP 60 minutes at 15°C
3. SCP 60 minutes at 20°C
4. SCP 60 minutes at 25°C

A randomization scheme was developed before the start of the protocol by an independent member of the Department of Bi-

omathematics and was revised after half of the animals had been studied.

Perioperative Management and Anesthesia

After pretreatment with intramuscular ketamine (15 mg/kg) and atropine (0.03 mg/kg) to induce anesthesia, animals were anesthetized with intravenous sodium thiopental (20 mg/kg). Endotracheal intubation was performed, and the pigs were ventilated with a fraction of inspired oxygen of 0.5 and isoflurane 1% to 2% to maintain sufficient anesthesia. Paralysis was achieved with intravenous pancuronium (0.1 mg/kg). The ventilator rate and the tidal volume were adjusted to maintain the arterial carbon dioxide tension at approximately 35 to 40 mm Hg. End-expiratory carbon dioxide and inspiratory and expiratory isoflurane were monitored continuously (model 2010-200 R; PPG Biomedical Systems, Lenexa, Kan). Arterial oxygen tension was maintained greater than 100 mm Hg. A bladder catheter (Foley 8F-10F) was inserted for measurement of urine output, and temperature probes were placed in the esophagus, rectum, and brain (via a burr hole in the skull). The brain temperature was monitored with a so-called deep brain temperature probe, a thermal fine-needle probe positioned in the gray matter of the brain (IT-18; Physitemp Instruments Inc, Clifton, NJ). An arterial line was placed in the right axillary artery for pressure monitoring and blood sampling (Blood Gas Analyzer; Ciba Corning 865; Chiron Diagnostics, Norwood, Mass).

Intracranial Pressure

Before cannulation for CPB, the sagittal sinus was cannulated. A midline scalp incision was made, and the underlying periosteum was removed to facilitate exposure of the coronal and sagittal sutures. Under 2.5× magnification, a 3-mm cutting burr was used to remove the bone over the sinus. A 24-gauge catheter was inserted into the sagittal sinus to permit both sampling of cerebral venous blood and monitoring of cerebral venous pressure. An intracranial pressure (ICP) pressure probe was connected to a transducer (Codman ICP Express; Johnson & Johnson Professional Inc, Raynham, Mass).

Operative Technique

The chest was opened via a left thoracotomy in the fourth intercostal space. After heparinization (300 IU/kg), a 16F cannula was inserted in the aortic arch, and a single-stage 26F cannula was inserted in the right atrium. Nonpulsatile CPB, using alpha-stat pH management, was initiated at a flow rate of 80 to 100 mL · kg⁻¹ · min⁻¹. To avoid distention of the left ventricle during CPB and as an injection port for fluorescent microspheres, a 10F vent catheter was inserted into the left atrium.

A heat exchanger (Hemotherm Cooler/Heater; Cincinnati Sub-Zero, Cincinnati, Ohio) was used for core cooling, and surface cooling was achieved with a cooling blanket. The CPB circuit was primed with a bloodless solution consisting of 1000 mL 0.9% NaCl, furosemide (1 mg/kg), heparin (5000 IU), and KCl (1.5 mg/kg). The pH was maintained at 7.40 with an arterial Pco₂ of 35 to 40 mm Hg (uncorrected for temperature), and hematocrit was maintained between 23% and 28%. After initiation, CPB was continued for 30 minutes to reach a brain temperature of 20°C, to guarantee thorough cooling, and to avoid an upward drift of the temperature during circulatory arrest. In all animals, myocardial

Figure 1. Protocol of the experiment, showing the time points when measurements cited in the tables and figures were taken. Details are in the text. The 4 groups differed beginning with time point 3: 60 minutes of SCP at 10°C, 60 minutes of SCP at 15°C, 60 minutes of SCP at 20°C, and 60 minutes of SCP at 25°C.

protection was afforded by applying iced saline (approximately 4°C) topically in the pericardium during HCA and SCP.

To initiate antegrade SCP, the ascending and descending aorta directly beyond the subclavian artery were clamped to allow the perfusate to flow only to the brachiocephalic trunk and the left subclavian artery. The lower body was not perfused during SCP. We began with a pump flow rate of 10 to 12 mL · kg⁻¹ · min⁻¹; the flow rate was adjusted to maintain a mean arterial pressure of 45 to 50 mm Hg for the period of SCP.

After HCA and selective perfusion, total body perfusion was reinstituted in all groups; core and surface rewarming were initiated and continued to an esophageal temperature of 35°C to 36°C. Care was taken to avoid a difference of more than 10°C between the perfusate and core temperature.

Cerebral Blood Flow

CBF was measured with fluorescent microspheres as previously described.¹⁰ In brief, approximately 2 million microspheres, 15 ± 0.5 μm in diameter, in 7 different colors, were injected and flushed with 5 mL of saline solution into a left ventricular catheter before and after CPB and into the aortic cannula during SCP or CPB.

Before injection, the fluorescently labeled microspheres, suspended in 10% dextran with 0.05% polyoxyethylenesorbitan monooleate (Tween 80) were mixed, sonicated, and vortexed. To allow calculation of absolute blood flow rates, a reference blood sample was taken from the brachial artery at 2.9 mL/min with a Harvard withdrawal pump (Harvard Bioscience, Inc, Holliston, Mass). Withdrawal of blood started 10 seconds before injection of the microspheres and was continued for 110 seconds after microsphere injection.^{10,11}

In all animals, the brain was removed, the 2 hemispheres were cut in the middle, and the specimens were weighed. Tissue samples (1-3 g) from 4 different regions—neocortex (gyrus precentralis), cerebellum, hippocampus, and brain stem—were taken for

microsphere count. The microspheres were recovered from brain tissue by sedimentation and from the blood by a commercial protocol (NuFlow Extraction protocol 9507.2; Interactive Medical Technologies Ltd, Irvine, Calif).

CBF was calculated from fluorescence in blood and tissue samples with the following formula:

$$\text{CBF (mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}) = (R \times I_T) / (I_R \times \text{Wt}),$$

where R was the rate at which the reference blood sample was withdrawn (2.9 mL/min), I_T was the fluorescence intensity of the tissue sample, I_R was the fluorescence intensity of the blood sample, and Wt was the weight of the tissue sample (in grams).

Cerebral Metabolism

Cerebral sagittal sinus and arterial samples were obtained simultaneously for calculation of cerebral oxygen extraction (arteriovenous oxygen content difference), sagittal sinus oxygen saturation, and cerebral oxygen saturation extraction (arteriovenous oxygen saturation difference). Cerebral vascular resistance (CVR) was calculated by using the equation

$$\text{CVR (mm Hg} \cdot \text{mL}^{-1} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}) = \text{MAP} - \text{MSSP} / \text{CBF},$$

where MAP indicates mean arterial pressure, and MSSP indicates mean sagittal sinus pressure.

The cerebral metabolic rate of oxygen (CMRO₂) was determined as follows:

$$\text{CMRO}_2 (\text{mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}) = \text{CBF} \times (\text{arterial O}_2 \text{ content} - \text{sagittal sinus O}_2 \text{ content}) / 100$$

Arterial and venous blood pH, oxygen tension, carbon dioxide tension, hematocrit, oxygen saturation, and oxygen content, as well as glucose and lactate, were measured with a Ciba Corning Diagnostics Corporation Analyzer.

TABLE 1. Temperature, hemodynamic variables, and blood gases

Variable	Baseline	Cooling	15 min of perfusion	60 min of perfusion	15 min after CPB	120 min after CPB
Brain temperature (°C)						
10°C	34.9 ± 0.5	20.0 ± 0.1	14.1 ± 0.4	11.8 ± 0.6	35.3 ± 0.8	33.9 ± 1.3
15°C	34.9 ± 0.5	20.0 ± 0.1	17.8 ± 0.5	16.0 ± 0.4	34.9 ± 0.7	34.2 ± 0.9
20°C	35.8 ± 1.3	19.9 ± 0.1	19.9 ± 0.1	19.9 ± 0.5	33.4 ± 1.1	33.5 ± 0.8
25°C	35.4 ± 0.5	19.9 ± 0.1	22.1 ± 1.0	24.3 ± 0.5	34.8 ± 0.5	34.9 ± 1.1
MAP (mm Hg)						
10°C	56.6 ± 3.3	48.9 ± 4.2	44.9 ± 1.9	46.4 ± 2.7	49.6 ± 4.2	50.9 ± 5.5
15°C	56.6 ± 4.1	47.5 ± 2.6	45.3 ± 2.1	45.8 ± 1.8	47.0 ± 4.1	48.2 ± 4.1
20°C	57.2 ± 3.1	47.3 ± 2.1	46.9 ± 1.7	47.1 ± 2.1	44.9 ± 2.5	45.7 ± 4.9
25°C	56.5 ± 5.6	48.2 ± 4.3	45.7 ± 1.6	46.1 ± 1.2	47.0 ± 5.7	50.3 ± 5.1
Hematocrit (%)						
10°C	30.9 ± 2.6	26.5 ± 2.9	25.9 ± 2.4	26.2 ± 2.4	32.8 ± 4.1	34.1 ± 2.8
15°C	30.5 ± 3.2	26.0 ± 3.3	25.1 ± 3.7	25.2 ± 3.9	30.8 ± 3.9	32.6 ± 3.0
20°C	29.5 ± 3.0	25.1 ± 2.8	24.1 ± 2.4	24.4 ± 2.4	30.5 ± 3.0	31.9 ± 3.1
25°C	29.3 ± 1.9	24.8 ± 3.8	24.0 ± 3.8	23.8 ± 3.6	29.6 ± 3.3	31.3 ± 3.4
Oxygen saturation SS (%)						
10°C	73.7 ± 3.5	84.5 ± 2.9	88.4 ± 2.8	94.7 ± 2.3	71.9 ± 2.7	68.8 ± 5.2
15°C	73.2 ± 3.5	82.7 ± 1.7	83.2 ± 3.6	87.7 ± 5.4	68.1 ± 7.6	66.6 ± 3.4
20°C	74.9 ± 3.0	85.8 ± 4.6	79.1 ± 4.7	82.5 ± 2.6	67.2 ± 5.9	65.5 ± 6.6
25°C	74.6 ± 2.1	85.3 ± 3.1	76.2 ± 3.3	78.2 ± 3.2	63.1 ± 7.9	65.0 ± 7.8
Pco ₂ (mm Hg)						
10°C	39.1 ± 4.1	42.7 ± 1.5	39.2 ± 3.1	37.8 ± 3.2	43.5 ± 4.5	43.9 ± 3.4
15°C	35.5 ± 3.2	40.1 ± 3.5	39.5 ± 2.0	37.6 ± 2.4	41.0 ± 5.0	45.0 ± 3.9
20°C	36.1 ± 3.7	39.5 ± 3.4	39.8 ± 2.0	37.7 ± 2.2	43.0 ± 3.6	45.7 ± 3.0
25°C	39.3 ± 2.4	39.8 ± 1.5	38.5 ± 4.5	39.2 ± 3.7	41.9 ± 2.9	42.0 ± 3.0
pH						
10°C	7.54 ± 0.04	7.43 ± 0.02	7.44 ± 0.03	7.43 ± 0.03	7.38 ± 0.05	7.39 ± 0.07
15°C	7.56 ± 0.03	7.45 ± 0.05	7.43 ± 0.02	7.42 ± 0.03	7.39 ± 0.05	7.38 ± 0.06
20°C	7.52 ± 0.02	7.42 ± 0.07	7.44 ± 0.05	7.42 ± 0.03	7.38 ± 0.04	7.42 ± 0.05
25°C	7.52 ± 0.02	7.43 ± 0.08	7.44 ± 0.06	7.41 ± 0.04	7.38 ± 0.04	7.43 ± 0.05
Lactate (mmol/L)						
10°C	0.9 ± 0.4	2.7 ± 0.9	3.1 ± 0.5	4.4 ± 1.0	5.2 ± 1.6	6.0 ± 3.4
15°C	0.9 ± 0.3	2.7 ± 1.0	4.1 ± 1.0	5.4 ± 1.7	7.2 ± 1.5	7.3 ± 2.5
20°C	1.3 ± 0.5	2.5 ± 0.8	3.8 ± 1.1	5.6 ± 1.5	7.5 ± 3.2	7.4 ± 1.6
25°C	0.9 ± 0.1	2.4 ± 1.0	3.5 ± 0.6	4.7 ± 0.6	6.5 ± 1.5	5.0 ± 2.3

All values are mean ± SD. Values for arterial oxygen saturation are not shown because they were all consistently ≥99.6%. MAP, Mean arterial pressure; SS, sagittal sinus; CPB, cardiopulmonary bypass.

Study Protocol

CBF, CVR, and CMRO₂ were determined at 6 time points throughout the experiment by microsphere injection. Simultaneously, hemodynamic parameters, ICP, and sagittal sinus pressures were recorded, and arterial and venous blood samples were obtained. The experimental protocol is shown in Figure 1, and the time points are listed below.

1. At baseline, at a rectal temperature of 36°C, before cooling.
2. After 30 minutes of cooling, at a brain temperature of 20°C.
3. At 15 minutes after the initiation of SCP at the determined brain temperature.
4. At 60 minutes after the initiation of SCP at the determined brain temperature.
5. At normothermia (approximately 36°C), 15 minutes after discontinuation of CPB.
6. At normothermia (approximately 36°C), 120 minutes after discontinuation of CPB.

Behavior and Postoperative Neurologic Outcome

An independent veterinarian not aware of the protocol evaluated the animals at the same time each day, scoring mental status, movement, and appetite, as described in previous reports.¹² The scale allows a maximum of 12 points for the behavior of a healthy pig and allows sensitive grading of impairment of consciousness, motor function, and coordination. Previous studies have validated the correlation of this behavioral index with histologic evidence of brain injury.¹³

Statistical Analysis

The animals were randomized into 4 study groups by an independent party. The group assignment was revealed immediately after the second time point. Before the statistical analysis of outcome data (CBF, CVR, CMRO₂, ICP, oxygen extraction, lactate, and

TABLE 2. Cerebral blood flow (CBF), cerebral vascular resistance (CVR), and cerebral metabolism

Variable	Baseline	Cooling	15 min of perfusion	60 min of perfusion	15 min after CPB	120 min after CPB
CBF (mL · min ⁻¹ · 100 g ⁻¹)						
10°C	43.3 ± 6.7	35.8 ± 2.9	20.8 ± 6.0	21.8 ± 4.5	23.4 ± 6.1	22.8 ± 3.9
15°C	45.2 ± 4.2	35.9 ± 4.7	29.4 ± 3.4	26.7 ± 2.1	29.44 ± 4.6	26.6 ± 4.3
20°C	44.2 ± 1.9	35.8 ± 2.7	44.3 ± 4.4	36.8 ± 4.4	37.7 ± 4.3	38.5 ± 1.7
25°C	43.3 ± 6.9	35.4 ± 3.9	41.7 ± 2.1	33.4 ± 4.1	34.2 ± 3.5	38.5 ± 1.7
CVR (mm Hg/mL · min ⁻¹ · 100 g ⁻¹)						
10°C	1.17 ± 0.21	1.26 ± 0.14	2.14 ± 0.82	2.03 ± 0.43	1.95 ± 0.46	2.06 ± 0.58
15°C	1.13 ± 0.13	1.22 ± 0.18	1.44 ± 0.15	1.61 ± 0.13	1.44 ± 0.25	1.56 ± 0.24
20°C	1.15 ± 0.11	1.22 ± 0.14	1.00 ± 0.09	1.21 ± 0.15	1.11 ± 0.20	1.06 ± 0.17
25°C	1.18 ± 0.16	1.23 ± 0.21	1.01 ± 0.07	1.31 ± 0.19	1.17 ± 0.20	1.11 ± 0.14
CMRO ₂ (mL · min ⁻¹ · 100 g ⁻¹)						
10°C	2.06 ± 0.6	0.98 ± 0.34	0.45 ± 0.24	0.29 ± 0.10	1.12 ± 0.28	1.27 ± 0.28
15°C	2.23 ± 0.43	1.01 ± 0.27	0.78 ± 0.16	0.67 ± 0.29	1.71 ± 0.47	1.65 ± 0.31
20°C	2.47 ± 0.33	0.90 ± 0.15	1.34 ± 0.26	1.05 ± 0.22	2.27 ± 0.24	2.31 ± 0.31
25°C	1.86 ± 0.31	1.01 ± 0.24	1.45 ± 0.46	1.08 ± 0.25	2.29 ± 0.34	2.57 ± 0.25

All values are mean ± SD. CMRO₂, Cerebral metabolic rate of oxygen; CPB, cardiopulmonary bypass.

sagittal sinus pressure), baseline values were compared by 1-way analysis of variance (ANOVA) or Kruskal-Wallis test, as appropriate. Small differences between groups were found for baseline measurements of CMRO₂, lactate, pH, Pco₂, and temperature; thus, changes from baseline were used for further comparisons of all the variables. Measurements during SCP and CPB and off bypass were analyzed by 2-way ANOVA, including tests for mean differences between groups and between time points and for changes of differences between groups throughout the experiment (interaction effects).

The α level for all sets of tests was set at .05. To increase the power of the analysis and simplify interpretation of the results, statistical analyses were performed comparing the results of the 10°C and 15°C groups combined with those of the 20°C and 25°C groups combined, as indicated on the figures. Statistical analysis was performed with SAS (SAS Institute, Cary, NC) on a personal computer.

Results

Comparability of Experimental Groups

As intended by the design of the study, no significant differences (1-way ANOVA: $P > .2$) in basic data, such as animal weight or hemodynamic parameters, were seen between groups at baseline. Table 1 shows the values of measured variables for each group at subsequent time points; arterial oxygen saturations were uniformly at least 99.6% and have therefore not been included. Significant differences were seen between groups at baseline for arterial lactate, pH, Pco₂, temperature, and CMRO₂ (Table 2; Kruskal-Wallis test), although these differences were small enough that they were unlikely to have had any clinical effect. Nevertheless, for further statistical analysis, changes from baseline at each measurement time point were used.

Physiologic temperatures were achieved within 45 minutes after the beginning of rewarming. Discontinuation of CPB was accompanied by a downward drift of temperature of approximately 1.0°C to 1.5°C in all groups, so the temperature at the last time point was, as documented in Table 1, lower than the preceding measurement and, with a mean of 33°C to 34°C, also lower than baseline.

Hematocrit levels, also seen in Table 1, although not significantly different between groups, did change during the course of the experiments. By installing the CPB circuit, the hematocrit decreased in all groups during the cooling period and was, with values ranging from 23.8% to 26.2%, comparably low for all groups during SCP (Table 1). After discontinuation of bypass, hematocrit was above baseline in all groups.

Mortality

Two 10°C animals, two 20°C animals, and two 25°C animals did not reach the final measurement time; none showed evidence of neurologic injury. Three of the pigs that died showed signs of left ventricular failure, 1 could not be defibrillated, and 1 had pulmonary edema. There was no mortality among the 15°C animals. To allow reliable statistical analysis, animals that died before completing the protocol were replaced in a rerandomized fashion.

CBF

At baseline, CBF ranged between 43.3 and 45.2 mL · min⁻¹ · 100 g⁻¹ and did not differ among groups. Cooling to 20°C resulted in a significant decrease ($P = .0001$) of CBF to values approximately 20% below baseline

Figure 2. Percentage changes from baseline for CBF during the entire experiment. All values are shown as mean $\pm$ SE. *Change from baseline differs significantly ($P < .05$) in the 10°C to 15°C group from the corresponding change in the 20°C to 25°C group.

in all 4 groups (Table 2; Figure 2). Fifteen minutes after the start of SCP, the 10°C and 15°C groups showed a further decrease in CBF, with values differing significantly ($P = .002$) from baseline: CBF was reduced to approximately 50% of baseline at 10°C and to 37% at 15°C (Figure 2). Values in the 20°C and 25°C groups were only slightly diminished from baseline. A relatively constant low level of CBF continued during the entire period of SCP at 10°C and 15°C, whereas the warmer temperature groups showed a gradual diminution in CBF during SCP. After 60 minutes of SCP, CBF was significantly higher ($P = .003$) at 20°C to 25°C than at 10°C to 15°C.

After rewarming, CBF increased slightly in the groups perfused at the higher temperatures but stayed approximately 10% below baseline. In contrast, the pigs that underwent SCP at 10°C to 15°C had markedly diminished CBF throughout the 2-hour postbypass period. Two hours after discontinuation of bypass, CBF had not reached baseline in any of the study groups, perhaps in part because of continuing mild hypothermia, but CBF remained significantly lower ($P = .003$) in the 10°C to 15°C pigs—42% below baseline—than in the 20°C to 25°C pigs (Table 2; Figure 2).

CVR

No differences in CVR at baseline were found among groups. CVR was essentially unchanged during cooling to 20°C in all groups, but it increased rapidly—within 15 minutes—after the start of SCP in the animals with SCP at 10°C: these animals showed a dramatic increase in CVR to values approximately 80% above baseline (Table 2; Figure 3). CVR was increased less markedly in the group with SCP at 15°C and declined to less than baseline in the 20°C to 25°C groups. With continuing SCP, CVR increased to values greater than baseline in all groups but decreased to less

Figure 3. Percentage changes from baseline for CVR during the entire experiment. All values are shown as mean $\pm$ SE.

than baseline after rewarming and until the end of the experiment in the 20°C to 25°C group (Table 2; Figure 3). Neither of the 10°C to 15°C groups showed significant recovery of CVR toward baseline as late as 2 hours after discontinuation of CPB.

Cerebral Metabolism

Cerebral oxygen consumption decreased with cooling, as expected, with no differences between groups. During SCP, animals in the 20°C to 25°C groups showed an increase in $CMRO_2$, versus a decrease in the 10°C to 15°C group, although oxygen consumption remained significantly below baseline in all groups (MEANS procedure*; $P < .0001$; Table 2; Figure 4). With ongoing SCP, there was a progressive decline in oxygen consumption in the 20°C to 25°C group but not in the 10°C to 15°C group: changes from baseline differed significantly at both SCP time points between the 10°C to 15°C group and the 20°C to 25°C group.

After rewarming, $CMRO_2$ increased promptly in all 4 groups. However, even 2 hours after CPB was discontinued, $CMRO_2$ remained less than baseline in the 10°C to 15°C group, in contrast to the 20°C to 25°C group, in which $CMRO_2$ was higher than baseline: the difference between the 2 temperature groups was significant ($P = .001$; Table 2; Figure 4).

CBF/ $CMRO_2$ and Sagittal Sinus Oxygen Saturation

The ratio of CBF to cerebral oxygen consumption at baseline can be considered to represent physiologic autoregulation and, thus, to demonstrate the ideal relationship between oxygen supply and metabolic demand of the brain (Figure 5). This ideal level of perfusion, and variations from it, are reflected by the extent of oxygen extraction and, therefore, by the sagittal sinus oxygen concentration.

At baseline, CBF/ $CMRO_2$ showed no significant differences between groups. Cooling resulted in a reduction in

*Significantly below baseline in all groups for the entire experiment.

Figure 4. Percentage changes from baseline for CMRO₂ at different time points during the experiment. All values are shown as mean $\pm$ SE. *Change from baseline differs significantly ($P < .05$) in the 10°C to 15°C group from the corresponding change in the 20°C to 25°C group.

Figure 5. Ratio of CBF and CMRO₂ during the entire experiment.

both CBF and CMRO₂, but the ratio clearly increased in all groups, as did the sagittal sinus oxygen saturation (Table 1). This likely represents blood flow in excess of demand, or luxury perfusion, although it should be borne in mind that hematocrit is lower during hypothermic perfusion, and therefore some increase in blood flow is required to maintain oxygen delivery. With SCP at 10°C to 15°C, but especially with SCP at 10°C, the CBF/CMRO₂ ratio increased dramatically, suggesting marked luxury perfusion and loss of cerebral autoregulation. In contrast, in the 20°C to 25°C group, no significant change in CBF/CMRO₂ was apparent during SCP. The presence of luxury perfusion was reflected by a very high sagittal sinus oxygen saturation in the 10°C group after 60 minutes of SCP.

After rewarming, CBF/CMRO₂ rapidly decreased in all groups and returned to levels slightly lower than, but not significantly different from, baseline. Sagittal sinus oxygen concentrations reflected the decrease in CBF relative to oxygen demand (Table 1).

Figure 6. Behavioral scores (mean $\pm$ SE) for the 4 different groups. A score of 12 indicates complete recovery to normal, and 0 means coma or death. *Change from baseline differs significantly ($P < .05$) in the 10°C to 15°C group from the corresponding change in the 20°C to 25°C group. POD, Postoperative day.

Lactate Levels

As seen in Table 1, lactate levels increased during cooling in all groups and continued to increase throughout SCP and during recovery. There were no significant differences between groups at any of the time points during perfusion or recovery.

ICP

Cooling to 20°C resulted in a clear decrease in ICP. After the start of perfusion, all animals showed a further decrease of ICP to values significantly less than baseline and then showed an increase in pressure to greater than baseline values during recovery.

Neurologic Outcome and Postoperative Behavior

Differences were observed in the rapidity and completeness of postoperative behavioral recovery, as seen in Figure 6. In comparison to the other groups, the 10°C animals recovered faster and more completely during the 7-day observation period: they consistently reached higher scores and achieved a full score on postoperative day 6. The 15°C animals seemed to recover more slowly during the initial 48 hours, but they did as well as the 10°C group thereafter. Postoperative behavioral scores (Table 3) were significantly higher after SCP at 10°C to 15°C than at 20°C to 25°C ($P = .001$) for postoperative days 4, 5, and 6.

Discussion

Optimal safeguarding of the brain requires (1) avoidance of embolization of atherosclerotic debris to prevent stroke and (2) assurance of adequate cerebral protection during the phase of surgery that requires arrest of normal antegrade cerebral flow.^{14,15} One approach is to cannulate the cerebral vessels without HCA so that the entire operation can be

TABLE 3. Behavioral scoring

Group	POD 1	POD 2	POD 3	POD 4	POD 5	POD 6	POD 7
10°C	8.2 ± 1.9	8.8 ± 1.7	9.9 ± 1.5	11.1 ± 1.5	11.8 ± 0.6	12.0 ± 0	12.0 ± 0
15°C	5.8 ± 1.2	7.8 ± 1.0	9.3 ± 1.1	10.9 ± 0.7	11.3 ± 0.6	11.7 ± 0.5	11.8 ± 0.4
20°C	7.2 ± 1.8	7.9 ± 0.9	8.7 ± 0.5	9.2 ± 0.4	10.1 ± 0.7	10.7 ± 0.9	11.6 ± 1.0
25°C	6.1 ± 0.3	7.2 ± 0.4	8.5 ± 0.5	8.9 ± 0.3	9.7 ± 0.7	10.0 ± 0.7	10.9 ± 0.6

All values are mean ± SD. POD, Postoperative day.

performed with antegrade SCP.^{3,4} This approach has the theoretical advantage of avoiding HCA altogether, but it requires blind insertion of cannulae into the cerebral vessels and the risk of embolization.¹⁶ An earlier study demonstrated that a clinical technique that combines a short interval of HCA with SCP provides excellent global cerebral protection in a chronic porcine model.^{2,17}

Although agreement regarding the general principle that some combination of HCA and SCP should be used during aortic arch surgery has been achieved, there is no consensus regarding many of the details of implementation of SCP, including the ideal temperature. A colder temperature takes longer to achieve and may be complicated by coagulopathy, but a warmer temperature may not provide as secure a degree of cerebral protection and may result in a more severe ischemic insult to the lower body during lengthy repairs.^{18,19} This study was therefore undertaken to try to determine the optimal temperature for use of SCP after HCA by assessing the effect of different temperatures during SCP on cerebral physiology and behavioral outcome.

This study suggests that lower temperatures during SCP—10°C to 15°C versus 20°C to 25°C—result in a better neurologic outcome. This conclusion is based on the more rapid and complete behavioral recovery of animals perfused at the lower temperatures according to a score that, in earlier studies of HCA and alternate cerebral protection strategies, has been validated by correlation with better recovery of neurophysiologic measurements, lower ICP, and fewer histopathologic lesions²⁰ in animals with higher scores. Although no significant differences in ICP were noted between groups, ICPs were low, which, on the basis of previous studies, is consistent with a good outcome.²¹

The faster behavioral recovery at colder temperatures is accompanied by greater suppression of cerebral metabolism during SCP and by a marked reduction in CBF. Although CBF is greatly reduced during profoundly hypothermic SCP, the CBF/CMRO₂ ratio and the sagittal sinus saturation indicate that this flow nevertheless provides ample perfusion because of the even more profound metabolic suppression. The provision of excellent cerebral protection at such a low absolute blood flow would seem to be a significant advantage of profoundly hypothermic SCP because clinically it would reduce exposure to embolization from the

often severely atherosclerotic aortas seen in patients with arch aneurysms.

It is interesting that the recovery of cerebral metabolism is slower in the deeply hypothermic SCP groups than in those undergoing SCP at higher temperatures, despite the eventual better neurologic recovery in the colder group. It is also consistent with previous studies which have suggested that a period of cold reperfusion after HCA/CPB may protect the brain from reperfusion injury.²²

This study confirms previous work which has shown that a derangement in autoregulation is produced by cold. At 10°C, there is a marked loss of autoregulation, resulting in luxury perfusion during SCP, albeit at very low absolute flow rates. In all groups there was clearly an inappropriate vasoconstrictive response after HCA and hypothermic perfusion, which in this experiment lasted at least 2 hours after surgery but which in earlier studies was seen for as long as 8 hours.^{23,24} This is a reminder that optimal neurologic recovery in patients subjected to deep hypothermia depends on hemodynamic stability for many hours after surgery. The posthypothermic cerebral vasoconstrictive response is not nearly as marked with SCP at 20°C to 25°C. Taking the influence of hematocrit on blood flow into consideration, one may speculate that there was no effect on cerebral metabolism, because hematocrit levels were comparable for all 4 groups during SCP.

It is interesting that no obvious morbidity seemed to result as a consequence of failure to perfuse the lower part of the body during the 90 minutes of circulatory arrest at any of the temperatures used in this study. Lactate levels were increased in all groups and had not yet started to diminish at the conclusion of the acute experiment. No animals had postoperative renal failure or spinal cord dysfunction, thus suggesting that the initial level of hypothermia required for HCA was adequate protection for organs other than the brain during SCP, regardless of SCP temperature.

In this study, SCP was preceded by a 30-minute interval of HCA because we believe that the ideal method for anastomosis of the cerebral vessels requires HCA and because many previous studies suggest that 30 minutes is the longest duration for safe arrest of cerebral circulation without perfusion. A short interval of HCA is essential for any

SCP protocol, but some surgeons introduce catheters into the cerebral vessels during a much briefer arrest period. Whether our findings regarding the optimal temperature for SCP can readily be extrapolated to SCP with minimal prior HCA is an interesting question, because SCP without HCA is often performed at higher temperatures. It should be noted that CBF declined over time during SCP at 20°C to 25°C in our study, but not during SCP at lower temperatures. It should also be noted that if less-thorough systemic cooling had been performed before SCP, it is likely that lactate levels after SCP at the higher temperatures would have been greater, and lower body ischemic consequences might have occurred.

In conclusion, this study suggests that SCP at 10°C to 15°C after HCA results in profound metabolic suppression lasting several hours after SCP, thus permitting faster neurologic recovery at a lower CBF than SCP at higher temperatures. In addition to providing better global cerebral protection, SCP at a lower temperature, by reducing CBF, also minimizes the risk of cerebral injury from embolization during arch surgery.

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