Effect of pressure management during hypothermic selective cerebral perfusion on cerebral hemodynamics and metabolism in pigs

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Objective: The effect of perfusion pressure on cerebral hemodynamics and metabolism during selective cerebral perfusion in patients undergoing aortic surgery is still unknown. This study explored cerebral blood flow, metabolic rate, and intracranial pressure at different pressure rates.

Methods: Twenty-five pigs (32–38 kg) were cooled during cardiopulmonary bypass to 25°C. After 10 minutes of hypothermic circulatory arrest, the animals were randomized to 60 minutes of selective cerebral perfusion at 3 different perfusion pressures: group I (n = 8), 40 mm Hg; group II (n = 9), 60 mm Hg; and group III (n = 8), 80 mm Hg. Microspheres were injected at baseline, the coolest temperature, and 5, 15, 25, and 60 minutes of selective cerebral perfusion, respectively, to calculate cerebral hemodynamics.

Results: Cerebral blood flow decreased during cooling to 54% of baseline value (50 mL/min per 100 g) and recovered in all groups during the first 15 minutes of selective cerebral perfusion. In groups I and II it reached 110% to 113% of baseline values, whereas group III animals showed significantly higher values ($P_{25\text{min}} = .003$) during the first 25 minutes of selective cerebral perfusion (360%; 153 mL/min per 100 g). Cerebral blood flow decreased in all groups over the following 35 minutes of selective cerebral perfusion to 57% of baseline value. Cooling to 25°C decreased the intracranial pressure to 10 mm Hg (93%). During selective cerebral perfusion, groups I and II showed a further intracranial pressure decrease to 45% and 82%, respectively, whereas group III, with 15 mm Hg (128%), had significantly higher intracranial pressure values at the end of selective cerebral perfusion ($P_{25\text{min}} = .03$ and $P_{60\text{min}} = .02$). The metabolic rate decreased to 30% of the baseline value during cooling, reaching 34% to 38% after 60 minutes of selective cerebral perfusion, with no significant differences between groups.

Conclusion: High-pressure perfusion provides no benefit during long-term selective cerebral perfusion at 25°C. Higher cerebral blood flow during the initial 25 minutes of selective cerebral perfusion leads to cerebral edema, with no alteration in metabolic rate. (J Thorac Cardiovasc Surg 2010;139:1623-31)

Surgical treatment of ascending aorta and aortic arch aneurysms requires cerebral protection during the ischemic period. Hypothermic circulatory arrest (HCA) is a simple, routinely used method to prevent cerebral injury but has limitations regarding the maximal safe duration, optimal depth of cooling, and reperfusion injury. Antegrade selective cerebral perfusion (SCP) is a neuroprotective technique that has gained widespread popularity. It offers the opportunity to carry out complex surgical procedures without strict time limitations because of the maintenance of cerebral blood flow (CBF) during most parts of the operation. Despite potential risks, such as embolization and vessel damage, during the cannulation procedure, there is clinical and experimental evidence of improved neurologic outcome with SCP rather

than HCA alone when prolonged cerebral protection is required.^{1,2} The combination of HCA with SCP provides the advantage of both hypothermic protection and antegrade continuous flow through the brachiocephalic vessels after a brief interval of HCA to reduce the risk of embolization and cerebral ischemia.³

Crittenden and colleagues⁴ were the first to experimentally demonstrate the superiority of SCP over other methods of cerebral protection by showing in a sheep model that hypothermic low-flow SCP preserved intracellular pH and energy stores. The mechanisms of brain injury caused by cerebral edema and warm reperfusion damage are not fully understood, and little is known about CBF and cerebral metabolism during prolonged SCP. In a previous study³ we showed differences in regional blood flow (RBF) and metabolic rate at a stable nonpulsatile pump flow, a stable mean arterial pressure (MAP), and a constant temperature. Less is known about regional changes in blood flow during SCP at different perfusion pressure levels.

We undertook this study in pigs to investigate how a short, clinically relevant interval of HCA followed by SCP at different perfusion pressure levels affects the RBF, cerebral oxygen metabolism (CMRO₂), cerebral vascular resistance (CVR), and intracranial pressure (ICP) changes.

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Abbreviations and Acronyms

CBP	= cardiopulmonary bypass
CMRO ₂	= cerebral metabolic rate of oxygen
CVR	= cerebral vascular resistance
HCA	= hypothermic circulatory arrest
ICP	= intracranial pressure
MAP	= mean arterial pressure
RBF	= regional blood flow
SCP	= selective cerebral perfusion

MATERIALS AND METHODS

Twenty-three female juvenile pigs, approximately 3.5 months of age with a weight of 32 to 38 kg, were used for this experiment. After cooling during cardiopulmonary bypass (CPB) to 25°C, the animals were randomized to one of the 3 study groups: group I, 10 minutes of HCA followed by 60 minutes of SCP at 40 mm Hg (n = 8); group II, 10 minutes of HCA followed by 60 minutes of SCP at 60 mm Hg (n = 9); and group III, 10 minutes of HCA followed by 60 minutes of SCP at 80 mm Hg (n = 8).

Perioperative Management and Anesthesia

All animals received preoperative humane care in compliance with the guidelines of the North Rhine–Westphalian Chamber of Agriculture. The protocol for the experiment was approved by the German Research Society (Deutsche Forschungsgesellschaft).

After pretreatment with intramuscular azaperone (2 mg/kg) and ketamine (15–20 mg/kg) to induce deep sedation, animals were anesthetized with intravenous propofol 1% (1–2 mg/kg), fentanyl (25 µg · kg⁻¹ · h⁻¹), and midazolam (0.2 mg · kg⁻¹ · h⁻¹). After endotracheal intubation, the pigs were ventilated mechanically with a fraction of inspired oxygen of 0.5. Paralysis was achieved with intravenous pancuronium (0.2 mg · kg⁻¹ · h⁻¹). The ventilation rate and tidal volume were adjusted (Fabius, Dräger, Germany) to maintain the arterial carbon dioxide tension at about 35 to 40 mm Hg. Arterial oxygen tension was maintained at greater than 100 mm Hg.

A bladder catheter (Foley 10F) was inserted for online measurement of urine output, and temperature probes were placed in the rectum and the brain through a small burr hole in the skull. A 14-gauge arterial line was placed in the right brachial artery for pressure monitoring and arterial blood sampling (Blood Gas Analyzer; ABL Radiometer, Copenhagen, Denmark).

Intracranial Pressure

Sagittal sinus cannulation was performed before cannulation and heparinization for CPB. A midline scalp incision was made, and the underlying periosteum was removed to facilitate identification of the coronal and sagittal sutures. A 5-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. The ICP pressure probe was connected to a transducer (Codman ICP Express; Johnson and Johnson, Inc, Raynham, Mass).

Operative Technique

The chest was opened through a small left thoracotomy in the fourth intercostal space. After opening the pericardium, the heart and great vessels were exposed. The ascending and descending aortas were dissected, and vessel loops were placed to define future levels of clamping. After heparinization (300 IU/kg), the distal ascending aorta was cannulated with a 16F

arterial cannula, and the right atrium was cannulated with a single 26F cannula. Nonpulsatile CPB, using alpha-stat pH management, was initiated at a flow rate of 80 to 100 mL · kg⁻¹ · min⁻¹ and then adjusted to maintain a minimum MAP of 50 mm Hg. To avoid distension of the left ventricle during CPB and as an injection port for fluorescent microsphere injection, a 10F vent catheter was inserted through the left atrium. After initiation of CPB, the lungs were allowed to collapse. A heat exchanger was used for core cooling.

The CPB circuit included roller pumps (Stöckert Instruments, Munich, Germany), a cardiomy reservoir, and a membrane oxygenator (VPCML Plus; Cobe Cardiovascular, Inc, Arvada, Colo), which was primed with previous citrate-treated blood from an animal donor, and heparin (5000 IU). The pH was maintained by means of alpha-stat principles at 7.40 with an arterial PCO₂ of 35 to 40 mm Hg and uncorrected for temperature. The hemoglobin level was maintained between 8 and 10 g/dL.

Once stable CPB was established, cooling for approximately 45 to 60 minutes to a brain temperature of 25°C was undertaken (heat exchanger; Biomedicus, Medtronic, Minneapolis, Minn), and the operating room temperature was maintained at 22°C to prevent an upward temperature drift.

Diastolic cardiac arrest was achieved by clamping the ascending aorta and adding 1 mEq/kg potassium chloride through a 14F cardioplegic cannula into the aortic root. Myocardial protection was afforded by applying iced saline (approximately 4°C) topically in the pericardium during the 70-minute interval of combined HCA and SCP.

After the previously described cannulation of the aortic arch and cross-clamping of the ascending aorta for cardioplegia, SCP was installed after 10 minutes of HCA by clamping the descending aorta. Isolation of the aortic arch permitted SCP through the brachiocephalic trunk and the left subclavian artery. In this concept the subclavian arteries were included in the SCP circuit for arterial pressure monitoring (upper limb) and reference blood sample withdrawal for microsphere flow calculation (Figure 1).

After 10 minutes of HCA and 60 minutes of SCP, CPB was reinstituted by releasing the clamp in the descending aorta. Core and surface rewarming were begun and continued to a brain temperature of approximately 35°C to 36°C. Care was taken to avoid a temperature difference between the perfusate and core temperature of greater than 10°C. During weaning from CPB, administration of 3 to 5 mg · kg⁻¹ · min⁻¹ dobutamine was frequently used. When necessary, cardiac defibrillation was performed after administration of lidocaine (1 mg/kg). After decannulation, protamine sulfate (5 mg/kg) was administered to antagonize heparin.

Cerebral Blood Flow

CBF was measured with fluorescent microspheres, as described in previous studies.⁵ In brief, approximately 2 million microspheres, 15 ± 0.5 µm in diameter in 6 different colors, were injected and flushed with 5 mL of saline solution into a left ventricular catheter before CPB and into the aortic cannula during SCP.

Before injection, the fluorescently labeled microspheres, suspended in 10% dextran with 0.05% polyoxyethylene sorbitan mono-oleate (Tween 80), were mixed, sonicated, and vortexed. A reference blood sample was taken from the brachial artery (upper right limb) at a rate of 2.9 mL/min with a Harvard Withdraw Pump (Harvard Bioscience, Inc, Holliston, Mass) to allow calculation of absolute blood flow rates. The withdrawal of blood started 10 seconds before injection of the microspheres and continued for 110 seconds after the microsphere injection.

Microspheres of 15 µm were selected to avoid nonentrapment, which is a risk when using smaller microspheres, and to avoid streaming and hemodynamic sequelae from occlusion of larger than capillary vessels, which is a risk when using larger microspheres.⁶

The animals were killed 60 minutes after aortic decannulation with an intravenous injection of sodium pentobarbital (30 mg/kg) and saturated potassium chloride (6 mEq/kg).

FIGURE 1. Cardiopulmonary bypass assessment. *P*, Arterial pressure measurement/reference microsphere withdrawal; *SCP*, selective cerebral perfusion; *PO*, microsphere injection; *Ao*, aorta; *RA*, right atrium; *Res*, reservoir; *LV*, left ventricle; *LV vent*, left ventricular vent cannulation; *Ox*, oxygenator.

In all animals the brain was removed, the 2 hemispheres were cut in the middle, and the specimens were weighed. Tissue samples (0.6–1.2 g) from 4 different regions (neocortex, cerebellum, hippocampus, and brain stem) were taken for microsphere counts. Thereafter, the microspheres were recovered from the brain tissue by means of sedimentation and from the blood by using a commercial protocol (NuFlow Extraction protocol 9507.2; Interactive Medical Technologies Ltd, Irvine, Calif). Fluorescence analysis was carried out by the same company.

Regional cerebral blood flow was then calculated from the intensity of fluorescence microspheres in blood and tissue samples by using the following formula:

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

where *R* is the rate at which the reference blood sample was withdrawn (2.9 ml/min), *IT* is the fluorescence intensity of the tissue sample, *IR* is the fluorescence intensity of the blood sample, and *Wt* is 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). CVR was calculated by using the following equation, where *MSSP* is defined as mean sagittal sinus pressure:

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

The cerebral metabolic rate of oxygen ($CMRO_2$) was determined as follows:

$$CMRO_2 \text{ (mL} \times 100\text{g}^{-1} \times \text{min}^{-1}) = CBF \times (\text{Arterial O}_2 \text{ content} - \text{Sagittal sinus O}_2 \text{ content})/100$$

Arterial and venous blood pH, oxygen tension, carbon dioxide tension, hemoglobin level, oxygen saturation, and oxygen content, as well as glucose and lactate levels in the sagittal sinus, were measured by using the same blood gas analyzer (ABL Radiometer Copenhagen).

Study Protocol

Hemodynamics, such as heart rate, central venous pressure, MAP, sagittal sinus pressure, and core and brain temperature were monitored continuously (Omnicare 24C; Hewlett Packard, Böblingen, Germany). Additionally, ICP, arterial blood gases, and hemoglobin, glucose, and lactate values were recorded at all 7 time points, as shown in Figure 2. Regional and total cerebral CBF, CVR, and $CMRO_2$ were calculated at the first 6 measurement time points (marked with asterisks in Figure 2): at baseline, after reaching the temperature of 25°C, and at 5, 15, 25, and 60 minutes of SCP.

Statistical Methods

Randomization was carried out by an independent party, with individual group allocation revealed at the onset of SCP. Groups were compared separately at baseline, during CPB, and during SCP. The *t* test or the Mann–Whitney test, as appropriate, was used for comparisons at baseline. When the data were consistent with normality and equal variance assumptions, the measurements during CPB and SCP were compared by using repeated measures, with tests for average differences between groups and for group–time interactions (change in the difference between groups over time). Otherwise, the groups were compared separately at each time point by using the Mann–Whitney or Fisher's exact tests. We report *P* values unadjusted for multiple testing: their purpose is not for an exact global assessment but rather to be used as a guide to help interpret the pattern of differences between groups at different times. Analyses were implemented with SPSS software (SPSS, Inc, Chicago, Ill).

RESULTS

Comparability of Experimental Groups

All animals reached the final measurement time point of 30 minutes off CPB. A comparison of preoperative animal weights (37.7 ± 10 , 32.5 ± 8.9 , and 34.2 ± 3.4 kg for groups I–III, respectively) showed no differences between groups.

As intended by the design of the study, hemodynamic data showed no significantly relevant differences between groups in heart rate, MAP, or central venous pressure. There were also no significant differences in rectal or brain temperatures between the groups.

Global and Regional CBF

The values for the global CBF at the 6 different time points for each group are shown in Table 1. There were no significant differences for CBF at baseline (49.8, 45.6, and 51.6 mL/min per 100 g for groups I–III, respectively). CBF decreased to 54% of the baseline value during cooling to 25°C with CPB, showing no differences between the groups. After 5 minutes of SCP, a rapid return to baseline

TABLE 1. Global cerebral blood flow, cerebral vascular resistance, and cerebral oxygen metabolism

Variable	Baseline	Coollest T = 25°C	5 min SCP	15 min SCP	25 min SCP	60 min SCP
CBF (mL/min/100 g)						
Group I	49.8 ± 7.7	26.3 ± 8.7	54.9 ± 15.4	49.3 ± 15.7	27.0 ± 6.2	23.6 ± 9.7
Group II	45.6 ± 9.0	28.0 ± 18.3	51.8 ± 14.8	57.7 ± 17.1	57.9 ± 4.7	26.3 ± 14.1
Group III	51.6 ± 9.6	22.4 ± 2.3	187.7 ± 44.9	158.4 ± 54.6	113.4 ± 44.0	30.7 ± 3.5
CVR (mm Hg/mL/min/100 g)						
Group I	1.3 ± 0.3	2.1 ± 0.7	0.6 ± 0.2	0.8 ± 0.4	1.3 ± 0.4	1.6 ± 0.9
Group II	1.3 ± 0.3	2.3 ± 1.3	0.9 ± 0.4	0.8 ± 0.3	0.7 ± 0.1	2.0 ± 0.9
Group III	1.6 ± 0.5	2.4 ± 0.2	0.4 ± 0.1	0.5 ± 0.2	0.7 ± 0.2	2.2 ± 0.3
CMRO ₂ (mL/min/100 g)						
Group I	2.9 ± 1.1	1.1 ± 0.5	2.1 ± 0.3	1.3 ± 0.4	1.2 ± 0.4	1.1 ± 0.4
Group II	3.5 ± 0.6	0.9 ± 0.6	2.1 ± 0.3	1.5 ± 0.7	1.8 ± 0.4	1.2 ± 0.6
Group III	2.9 ± 0.8	0.7 ± 0.3	2.7 ± 1.5	1.8 ± 0.7	1.7 ± 0.5	1.0 ± 0.4
O ₂ extraction (mL/dL)						
Group I	5.7 ± 2.7	3.9 ± 0.7	3.9 ± 1.2	2.6 ± 0.9	4.0 ± 0.9	4.8 ± 2.1
Group II	7.6 ± 0.9	3.3 ± 0.8	4.1 ± 1.1	2.9 ± 1.4	3.5 ± 1.3	4.8 ± 2.4
Group III	5.6 ± 1.1	3.3 ± 1.1	1.4 ± 0.6*	1.2 ± 0.4*	1.6 ± 0.5*	3.3 ± 1.6
O ₂ sat SS (%)						
Group I	63.8 ± 13.1	73.6 ± 7.8	74.3 ± 9.6	84.3 ± 8.7	74.6 ± 5.5	66.9 ± 13.6
Group II	48.9 ± 8.6	78.2 ± 13.7	69.6 ± 16.5	82.5 ± 17.0	75.4 ± 14.3	62.9 ± 19.7
Group III	62.9 ± 8.1	80.8 ± 9.5	94.6 ± 4.3	97.1 ± 4.2	93.8 ± 4.2	80.1 ± 14.5

All values are shown as mean ± standard deviation. CBF, cerebral blood flow; CVR, cerebrovascular resistance; CMRO₂, cerebral metabolic rate of oxygen; O₂ extraction, arteriovenous oxygen content difference; O₂ sat SS, sagittal sinus oxygen saturation. *Significant differences between groups with $P \leq .05$.

values could be seen in groups I and II, with a dramatic increase in CBF during SCP at 80 mm Hg in group III. At 5, 15, and 25 minutes of SCP at both the absolute flow values, the change from baseline showed statistically significant differences between the groups during multivariate testing ($P_{5\text{min}} = .005$, $P_{15\text{min}} = .003$, $P_{25\text{min}} = .003$, $P_{45\text{min}} =$

.009, $P_{45\text{min}} = 0.005$, and $P_{45\text{min}} = .007$). CBF persisted at significantly higher flow levels at 80 mm Hg over the first 25 minutes of SCP (220% of baseline value) compared with perfusion at 60 mm Hg (126%) or 40 mm Hg (54%), as the pairwise comparison revealed (5 minutes: $P_{80/40} = .003$ and $P_{80/60} = .001$; 15 minutes: $P_{80/40} = .003$ and $P_{80/60} = .024$;

FIGURE 2. Study protocol, showing time points at which measurements cited in the table and figures were taken. Microsphere injections are marked with asterisks. Details are listed in the text. The 3 groups differ, beginning with time point 3 (5 minutes of SCP). MAP, Mean arterial pressure; CPB, cardiopulmonary bypass; SCP, selective cerebral perfusion; HCA, hypothermic circulatory arrest; T, temperature.

FIGURE 3. Time course of global cerebral blood flow (CBF) over the entire experiment. Values are shown as mean values $\pm$ standard errors. *Significant differences between groups at a time point value (*p*). **Significant differences in change from baseline (*p*_Δ). SCP, Selective cerebral perfusion; T, temperature.

and 25 minutes: $P_{80/40} < .0001$ and $P_{80/60} = .003$). Over the last 35 minutes, CBF decreased in all groups, reaching 47% (group I), 58% (group II), and 59% (group III) of the respective baseline values at the final measurement (Figure 3).

This trend of global CBF values was reproducible among all regions of the brain, certainly at different baseline levels, with the highest mean levels in the cerebellum (58.6 ± 11 mL/min per 100 g) and neocortex (56.4 ± 14.5 mL/min per 100 g) followed by the pons region (44.1 ± 12.2 mL/min

per 100 g) and the lowest CBF in the hippocampus (34.9 ± 9 mL/min per 100 g). The values for RBF for the 6 time points listed for the 4 separate regions are shown in Figure 4.

In the neocortex cooling to 25°C reduced the RBF to 50% of the initial baseline value, from 56.4 to 27.9 mL/100 mg per minute. After beginning SCP at different pressure levels, we found significant differences between groups during the first 5 minutes ($P_{5min} = .005$), with a slow decrease in RBF at 40 mm Hg (49% of baseline value), a moderate increase at 60 mmHg (75% of baseline value), and a dramatic increase at 80 mm Hg (220% of baseline value). Continuing with SCP, the RBF decreased in all 3 groups, maintaining significantly higher levels at 80 mm Hg perfusion ($P_{15min} = .003$ and $P_{25min} = .003$, respectively, in deviation from baseline: $P_{Δ5min} = .009$, $P_{Δ15min} = .005$, and $P_{Δ25min} = .007$). After 60 minutes of SCP, the RBF was 29% (group I), 28% (group II), and 37% (group III), respectively, of the initial baseline value. Even at high-pressure SCP (80 mm Hg), there was no return to baseline values.

The RBF of the cerebellum did show a slightly higher baseline level compared with the neocortex RBF (58.6 ± 11 vs 56.4 ± 14.5 mL/100 mg per minute). It decreased during cooling, reaching a mean value of 30.8 ± 17.8 mL/100 mg per minute at 25°C, and returned to baseline values during the first 20 minutes of SCP at 40 and 60 mm Hg,

FIGURE 4. Time course of regional cerebral blood flow (RBF) in the neocortex, cerebellum, pons, and the hippocampus region. Values are shown as mean values. *Significant differences between groups at a time point. SCP, Selective cerebral perfusion.

FIGURE 5. Time course of cerebral metabolic rate ($CMRO_2$) over the entire experiment. Values are shown as means $\pm$ standard errors. *SCP*, Selective cerebral perfusion; *T*, temperature.

respectively, showing significantly higher levels at 80 mm Hg ($P_{5min} = .006$, $P_{15min} = .004$, and $P_{25min} = .004$, respectively, in deviation from baseline: $P_{\Delta 5min} = .008$, $P_{\Delta 15min} = .008$, and $P_{\Delta 25min} = .012$). After 60 minutes of SCP, the perfusion pressure no longer had an effect on the RBF of the cerebellum: RBF decreased in all animals to 50% of the initial baseline value, showing no difference between the groups.

The pons region had a lower baseline RBF (44.1 ± 12.2 mL/100 mg per minute) compared with the neocortex and the cerebellum. During cooling, it decreased further to 31.1 ± 16.4 mL/100 mg per minute. During SCP, it rapidly returned, greatly exceeding the baseline values after 5 minutes, and decreased slowly during the rest of SCP, with significant differences between the groups ($P_{5min} = .004$, $P_{15min} = .004$, and $P_{25min} = .004$, respectively, in deviation from baseline: $P_{\Delta 5min} = .006$, $P_{\Delta 15min} = .009$, and $P_{\Delta 25min} = .009$). After 60 minutes of SCP, the RBF of the pons area reached baseline levels in all 3 groups.

The hippocampus region was the area with the lowest baseline RBF (34.9 ± 9 mL/min per 100 g). The RBF changes showed a similar pattern as in the cerebellum. After a decrease at cooling, the RBF returned close to baseline values during the first 20 minutes of SCP. After 25 minutes of SCP, the RBF slightly decreased to 24.8 ± 5.9 mL/min per 100 g at 40 mm Hg but stayed stable at 34.2 ± 5.9 mL/min per 100 g at 60 mm Hg. In the same period RBF exceeded normal values significantly at 80 mm Hg (238%–403% of baseline values; $P_{5min} = .002$, $P_{15min} = .006$, and $P_{25min} = .005$, respectively, in deviation from baseline: $P_{\Delta 5min} = .003$, $P_{\Delta 15min} = .008$, and $P_{\Delta 25min} = .008$).

Cerebral Vascular Resistance

CVR did not show significant differences between the groups at baseline (1.3 ± 0.3 vs 1.3 ± 0.3 vs 1.6 ± 0.5 mm Hg $\cdot$ mL $^{-1} \cdot$ min $^{-1}$ per 100 g), increasing in all animals during cooling to 25°C (Table 1). After starting SCP, CVR increased after 5, 15, and 25 minutes, exceeding the baseline

FIGURE 6. Time course of intracerebral pressure (*ICP*) over the entire experiment. Values are shown as means $\pm$ standard errors. *Significant differences between groups at a time point value (*p*). *SCP*, Selective cerebral perfusion; *T*, temperature.

value at 60 minutes of SCP in all 3 groups (123% of baseline at 40 mm Hg, 162% of baseline at 60 mm Hg, and 138% of baseline at 80 mm Hg). Although all 3 groups showed a continuous increase in CVR during SCP, with the highest levels at 80 mm Hg ($2.2 \pm 0.3 \text{ mm Hg} \cdot \text{mL}^{-1} \cdot \text{min}^{-1}$ per 100 g), followed by 60 mm Hg ($2.0 \pm 0.9 \text{ mm Hg} \cdot \text{mL}^{-1} \cdot \text{min}^{-1}$ per 100 g) and 40 mm Hg ($1.6 \pm 0.9 \text{ mm Hg} \cdot \text{mL}^{-1} \cdot \text{min}^{-1}$ per 100 g), the only significant differences between groups were found at the beginning of SCP ($P_{5\text{min}} = .008$).

Cerebral Oxygen Metabolism

CMRO₂ data are displayed in Table 1. Cooling to 25°C on CPB increased sagittal sinus oxygen saturation but showed no significant differences between the study groups. During SCP, oxygen saturation increased in all 3 groups, exceeding the baseline at 5, 15, and 25 minutes of SCP, with the highest oxygen saturation level in group III. After 60 minutes of SCP, the oxygen saturation returned to initial values in group I (70%) and group II (63%) but still exceeded the baseline value in group III (80%). No significant differences were seen between groups.

Oxygen extraction (arteriovenous oxygen content difference) was significantly ($P = .01$) reduced in all groups during cooling to 25°C, which was associated with a decrease to approximately 40% to 70% of baseline values. At 5, 15, and 25 minutes of SCP, the oxygen extraction was significantly higher at 40 and 60 mm Hg compared with that seen after SCP at 80 mm Hg ($P_{5\text{min}} = .005$, $P_{15\text{min}} = .008$, and $P_{25\text{min}} = .003$). After 60 minutes of SCP, the oxygen extraction increased slowly to 84% of the baseline value in group I and to 63% in group II but remained low at 59% of the initial value in group III.

The cerebral metabolic rate, calculated for each time point, showed in all groups a significant decrease to 30% of the baseline value during cooling to 25°C (Figure 5). After starting SCP, the CMRO₂ increased to 72% (group I), 60% (group II), and 93% (group III) of the baseline value, followed by a second decrease to 43% to 62% of the baseline value for all groups after 15 minutes of SCP. After 60 minutes of SCP, the CMRO₂ reached 38% of the baseline values in group I and only 34% in groups II and III. At 25 and 60 minutes of SCP, the CMRO₂ increased slowly, reaching 35% of the baseline value in groups I and II but only 31% in group III. CMRO₂ values and changes from baseline showed no significant differences between groups at any time point.

Intracerebral Pressure

At baseline, ICP showed no significant differences between groups, although it was slightly lower in group II animals (Figure 6). During cooling to 25°C, it decreased moderately in all 3 groups to 87% to 96% of the initial values. Differences between groups could be seen only after starting SCP at different pressure levels: whereas the ICP

decreased slowly to 45% of the baseline value during the first 25 minutes of SCP in group I (40 mm Hg), it remained almost unchanged in group II (60 mm Hg) and showed a sudden increase to 123% during the first 5 minutes of SCP in group III (80 mm Hg). Even though the ICP level in group III animals returned to baseline levels after 25 minutes of SCP, this time point measurement still revealed significant differences between the groups in absolute values ($P_{25\text{min}} = .03$), as well as in change from baseline ($P_{\Delta 25\text{min}} = .015$). During the last 35 minutes of SCP, the ICP increased in all animals, exceeding the initial baseline values in groups II (115%) and III (128%) but reaching only 55% of the baseline value in group I ($P_{\Delta 60\text{min}} = .021$).

DISCUSSION

For the surgical treatment of aortic arch disease, special neuroprotective strategies are required to prevent cerebral ischemia. The combination of a short period of HCA followed by an extended interval of SCP offers an increased safety interval.^{5,7} Although clinical studies have reported that SCP under nonpulsatile circumstances is useful and “safe,”^{7,8} there is still uncertainty about the ideal cerebral perfusion pressure (CPP) at which SCP should be performed. Global hypoperfusion of the brain caused by a low perfusion pressure during SCP can cause ischemic damage with neurologic injury. Especially in elderly patients with pre-existing arterial hypertension, a higher CPP would provide better cerebral perfusion with adequate oxygen delivery to the brain. However, this patient cohort also often manifests advanced atherosclerosis, increasing the risk of embolic damage during high-pressure SCP, especially if the autoregulation mechanism of the cerebral vessels is altered under hypothermic conditions.

CBF is a function of CPP, representing the difference between MAP and ICP, and the CVR. Under normothermic physiologic circumstances the autonomous vasomotility regulation maintains a constant CBF, which is mostly MAP independent if this ranges from 50 to 150 mm Hg.⁹ During surgical aortic arch repair, this relationship might be altered by anesthesia, CPB, hypothermia, pH management, blood viscosity, cerebrovascular comorbidities, and cerebral embolization and edema.¹⁰ Furthermore, the use of SCP with circulatory arrest to the lower body might influence the integrity of cerebral autoregulation. Earlier experimental¹¹ and clinical¹² data described a preserved cerebral autoregulation during CPB, even under hypothermic conditions. In contrast, more recent studies revealed instead a disturbed autoregulation on hypothermic CPB, in which CBF is determined by the perfusion pressure.^{13,14}

The aim of this study was to find the ideal CPP during SCP after HCA. Furthermore, it is the first study to report not only the global hemodynamic effect of different CPP levels but also to show the regional CBF changes in 4 different brain regions before and during SCP. As expected, there

was a reduction in global CBF at 25°C after 45 minutes of cooling. This is in accord with theoretic predictions and the experimental work of others.^{15,16} Comparing CBF at the 3 different CPP levels, we found initially a substantial increase in CBF at 80 mm Hg compared with that seen at 60 and 40 mm Hg. However, this effect lasted only 25 minutes, after which the high CPP did not improve the CBF in the 80 mm Hg group anymore, so that all groups demonstrated a lower CBF after 60 minutes of SCP compared with the initial baseline value. Concomitant with the decrease in CBF during prolonged SCP, there was a significant increase in ICP after 25 minutes of high-pressure SCP in the 80 mm Hg group, which suggests onset of substantial cerebral edema, a fact that is associated with an adverse neurologic outcome.¹⁷

Analyzing the regional CBF, we found some differences between the brain areas. At baseline, the highest RBF was seen in the cerebellum and neocortex, followed by the pons region and finally the hippocampus area. All regions showed a decrease in RBF during cooling to 25°C, with a substantial decrease to almost 50% of the baseline value. At the beginning of SCP, the RBF increased dramatically in the cerebellum and the pons and less in the hippocampus, staying most stable in the neocortex. After the initial 5 minutes of SCP, it decreased continuously in all brain regions, reaching baseline levels in the pons and hippocampus area but only 30% of the baseline value in the cerebellum and only 50% of the baseline value in the neocortex. This tremendous, perfusion pressure-independent decrease of neocortex RBF beyond the 25-minute benchmark of SCP might explain some of the neurologic dysfunction seen in clinical practice after aortic arch surgery with prolonged SCP.

The CVR decreased in all animals at the beginning of SCP but increased constantly during the SCP period, reaching higher levels than the initial baseline value after 60 minutes of SCP in all groups. These changes are similar to the findings of earlier experimental studies.¹⁸ Surprisingly significant differences between groups in CVR could be seen only at the onset (5 minutes of SCP) but not during the rest of the SCP period. In the first 5 minutes of SCP, the moderate perfusion pressure group (60 mm Hg), the closest to physiologic values, appears to have a relatively higher CVR than the groups with a lower or higher perfusion pressure, even if this mean value is still less than the initial baseline CVR. The final increase in CVR after 25 minutes of SCP, which was mostly seen under high-pressure conditions (group III), could probably be caused by the previously described cerebral edema.

The mechanisms for reduced CBF after a prolonged period of SCP, even at high-pressure levels (80 mm Hg), as well as the development of a cerebral edema beyond the 25-minute benchmark, are not totally clear. It seems likely that the continuously high hydrostatic pressure in combination with a variable colloid osmotic pressure and a stimula-

tion of acute-phase reactants caused by a prolonged CPB time are responsible for a substantial capillary leak syndrome. This is also accentuated by the ischemic membrane damage during the HCA period. The leakage of fluid into the extravascular space increases ICP, compressing the small cerebral vessels and decreasing CBF.

An interesting observation was the change in CMRO₂ during the SCP period. Although there was a significantly higher oxygen extraction at 5, 15, and 25 minutes of SCP at 40 and 60 mm Hg compared with that seen after SCP at 80 mm Hg, no significant differences between groups at any time point could be seen in the absolute CMRO₂ value, as well as in its percentage change from baseline over time. Even if the oxygen delivery to the irrigated tissue during early SCP was higher at 80 mm Hg, the CMRO₂ data revealed that this led only to a "luxury perfusion" of the perhaps sufficiently protected brain, with no significant benefit in cerebral metabolism suppression.

CONCLUSIONS

Our results indicate that prolonged high-pressure (80 mm Hg) hypothermic SCP does not improve regional and global CBF when compared with low-pressure (40 mm Hg) or moderate-pressure (60 mm Hg) SCP. When provided for more than 25 minutes, it increases CVR, producing substantial cerebral edema without showing better cerebral metabolic suppression. High-flow SCP with a resulting MAP of greater than 60 mm Hg in the upper body should be avoided.

Calculation of RBF showed that, under identical hypothermic conditions, different regions of the brain appeared to have their own characteristics for vasoconstriction and arterial irrigation. The acknowledgement of these dynamics could be highly relevant for different clinical strategies of perfusion and should be investigated further in the future.

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