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Selective cerebral perfusion at 28 °C — is the spinal cord safe?☆

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Abstract

Objective: To shorten cooling/rewarming associated with hypothermic neuroprotection strategies during complex aortic arch surgery, selective cerebral perfusion (SCP) at 28 °C has recently been advocated, although its safe limits — especially with regard to the ischaemic tolerance of the spinal cord — have not been systematically examined. **Methods:** Twenty juvenile Yorkshire pigs (30.3 ± 2.8 kg) were randomly allocated to undergo circulatory arrest and SCP at 28 °C for 90 min (group A; $N = 12$) or 120 min (group B; $N = 8$) at 50 mmHg using alpha-stat pH management. Spinal cord blood flow (SCBF) was assessed using fluorescent microspheres at baseline (prior to SCP); at 5 and 80 min during SCP, and at 1, 5 and 48 h after cardiopulmonary bypass (CPB). A modified Tarlov score was used to evaluate neurobehavioural recovery in all survivors blindly from videotapes for 5 days postoperatively. Histological ischaemic spinal cord injury was scored after sacrifice. **Results:** All pigs could be weaned from CPB and ventilation, but seven pigs (58%) in group A and five (63%) in group B developed multi-organ failure and died within 24 h. SCBF diminished immediately after initiation of SCP and was absent throughout SCP in all segments below T8/9, recovering to baseline 1 h after SCP at all cord levels. All survivors suffered moderate-to-severe histological lumbar spinal cord damage, more severe in group B ($p \leq 0.049$). Three of five group A pigs recovered normal function, but two suffered paraparesis. Group B survivors had a worse neurologic outcome ($p < 0.0001$): all suffered paraplegia (one immediate, and two on day 2, after initial recovery). **Conclusion:** SCP provides insufficient SCBF below T8/9 to sustain cord viability. At 28 °C, the ischaemic tolerance of the cord may be exceeded enough by 90 min to impair function; by 120 min, SCP at 28 °C invariably results in paraplegia.

Keywords: Selective cerebral perfusion; Spinal cord perfusion/protection; Paraplegia; Aortic arch aneurysm repair

1. Introduction

Antegrade selective cerebral perfusion (SCP) during lower body circulatory arrest (LBCA) in deep hypothermia has achieved widespread acceptance as a neuroprotective technique in aortic arch surgery [1—8]. The desire to avoid deep hypothermia and thereby shorten cooling and rewarming periods on cardiopulmonary bypass (CPB) has recently encouraged a gradual increase of body temperature during SCP in many centres: while the advocates of this trend point out its avoidance of potential deep-hypothermia-associated coagulation disorders and reduction of inflammatory substances generated by prolonged CPB, they seem to underestimate the risk of severe ischaemic injury to the visceral organs and the spinal cord.

Previous experimental studies from our laboratory have allowed us to generate an estimate of the time—temperature relationship for injury to spinal cord, which suggests that prolonged LBCA at moderate hypothermia may expose the spinal cord to ischaemic injury [9,10]. Despite the absence of experimental data suggesting the contrary, selective upper body perfusion during LBCA has been clinically implemented at core temperatures as high as 28 °C, and is already being used by an increasing number of surgeons [11—13], although the tolerance to relatively warm ischaemia of the spinal cord and the visceral organs is as yet unknown.

In 2007, the Hannover group was the first to report on the dangers of prolonged LBCA with only moderate hypothermia: a subgroup analysis revealed a mortality of 27% and a paraplegia rate of 18% in patients with LBCA for more than 60 min at 28 °C [14].

During moderate hypothermic LBCA, the spinal cord becomes the most vulnerable organ, so its viability should arguably dictate the safety margins for selective upper body perfusion. Since there have been no clinical or experimental studies assessing the safe limits of prolonged LBCA and SCP at

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moderate hypothermia with regard to spinal cord recovery, we sought to compare the outcomes of different durations of LBCA and SCP at a core body temperature of 28 °C in the same porcine survival model that has been used in the previous studies to explore other aspects of cerebral physiology during SCP in our laboratory [9,10,15–19]. The durations chosen were ones that were suggested to be safe versus unsafe according to a time–temperature graph drawn from the previous studies following aortic cross-clamping at different temperatures.

2. Materials and methods

2.1. Study design

Twenty female juvenile Yorkshire pigs (Animal Biotech Industries, Allentown, NJ, USA), 4–5 months of age, weighing 30.3 ± 2.8 kg, were randomly allocated to undergo circulatory arrest and SCP at 28 °C for 90 min (group A; $N = 12$) or 120 min (group B; $N = 8$) at 50 mmHg using alpha-stat pH management. Fluorescent microspheres enabled segmental measurement of spinal cord blood flow (SCBF) along the entire spinal cord at baseline (prior to SCP); at 5 and 80 min during SCP and 1, 5, 24 and 48 h after CPB. A modified Tarlov score was used to evaluate neurobehavioural recovery in all survivors blindly from videotapes for 5 days postoperatively. Histological ischaemic spinal cord injury was scored after sacrifice. This experimental model technically – except for temperature management – closely simulates the procedure used clinically for resection of transverse aortic arch aneurysms at our institution.

As previously described, the anatomy of the pig differs from that of humans in having 13 thoracic (as well as five lumbar) segmental arteries, which arise together from the descending (abdominal) aorta and subsequently divide [20,21]. Previous studies suggest that the subclavian arteries and the median sacral arteries play a major role in the perfusion of the paraspinous collateral vascular network in both species, although the iliac arteries may provide a greater proportion to direct the blood supply in humans than in pigs [20]. Previous experiments with this model have also demonstrated that the spinal cord perfusion pressure and collateral flow in the pig behave in ways very similar to what is observed under comparable circumstances clinically in humans [22–24].

2.2. Perioperative management and anaesthesia

All animals received humane care in compliance with the guidelines of 'Principles of Laboratory Animal Care' formulated by the National Society for Medical Research and the 'Guide for the Care and Use of Laboratory Animals' published by the National Institute of Health (NIH Publication No. 88-23, revised 1996). The Mount Sinai Institutional Animal Care and Use Committee approved the protocols for all experiments.

After pre-treatment with intramuscular ketamine (15 mg kg^{-1}) and atropine (0.03 mg kg^{-1}), an endotracheal tube was placed. The animals were then transferred to the operating room and were mechanically ventilated with a FiO_2 of 0.5, and a minute volume adequate for maintenance of a normal pCO_2 (35–40 mmHg). Anaesthesia was induced through the bolus intravenous administration of propofol (1 mg kg^{-1}) and fentanyl (50 μg kg^{-1}) and was maintained with infusions of ketamine (15 mg kg^{-1} h^{-1}), propofol (7 mg kg^{-1} h^{-1}) and fentanyl (5 μg kg^{-1} h^{-1}). This anaesthetic regimen has been described previously [25]. Paralysis for intubation was achieved with intravenous pancuronium (0.1 mg kg^{-1}).

The ventilator rate and the tidal volume were adjusted to maintain the arterial carbon dioxide tension at 35–40 mmHg. End-expiratory carbon dioxide (PPG Biomedical Systems, Model 2010-200 R, Lenexa, KS, USA) was monitored continuously. Arterial oxygen tension was maintained >90 mmHg. A bladder catheter (Foley 8–10F) was inserted for online measurement of urine output. Electrocardiographic measurements are recorded continuously. An arterial line was placed in the right brachial artery for pressure monitoring and blood sampling (pH, oxygen tension, carbon dioxide tension, oxygen saturation, base excess, haematocrit (HCT), haemoglobin, glucose and lactate, (Blood Gas Analyzer, Ciba Corning 865, Chiron Diagnostics, Norwood, MA, USA).

2.3. Operative technique and selective cerebral perfusion

The chest was opened through a small left thoracotomy in the fourth intercostal space. The pericardium was opened and the heart and great vessels were identified. After heparinisation (300 IU kg^{-1}), the right atrium was cannulated with a 26F single-stage cannula, and the aortic arch with a 16F arterial cannula. CPB was initiated at a flow rate of 80–100 ml kg^{-1} min^{-1} and thereafter adjusted to produce a minimum mean arterial pressure of 45 mmHg. A 10F left atrial cannula was inserted for venting the left heart. A left atrial catheter was inserted through a pulmonary vein to enable fluorescent microsphere injections.

The CPB circuit consisted of non-pulsatile roller heads, a membrane oxygenator (VPCML Plus; Cobe Cardiovascular, Arvada, CO, USA) and heat exchanger (Hemotherm Cooler/Heater; Cincinnati Sub-Zero, Cincinnati, OH, USA); cardiotomy suction was used. The circuit was rinsed with 1800 ml 0.9% saline and 4000 IU heparin; no donor blood priming was used. Once stable CPB was established, cooling to 28 °C was undertaken (alpha-stat pH management [6]). CPB was continued for a minimum of 10 min after initiation to ensure thorough cooling to the rectal target temperature of 28 °C.

Just before the commencement of SCP, diastolic cardiac arrest was achieved by adding 1 mEq kg^{-1} potassium chloride to the venous reservoir.

Then, clamps were placed across the ascending aorta and the proximal descending aorta to isolate the arch, and antegrade selective upper body perfusion was started and maintained at a mean pressure of 50 mmHg using α-stat pH management. Myocardial protection was supplemented by irrigation of the pericardium with iced saline (~4 °C). After the 90- or 120-min interval, the clamps were removed and CPB with whole-body perfusion re-instituted. Rewarming with CPB was undertaken, supplemented with a heating blanket and carried through to a rectal temperature of 35 °C. Cardiac defibrillation was achieved electrically without the need for pharmacologic adjuncts in all animals.

2.4. Monitoring of intra- and postoperative systemic perfusion pressure (MAP)

Two arterial pressure lines were placed: one in the right brachial artery to monitor intra-operatively, and another in the descending aorta, for direct postoperative aortic pressure monitoring and – in the animals that underwent microsphere measurements – for postoperative reference sampling. These lines enabled systemic perfusion pressure monitoring, blood sampling (pH, oxygen tension, carbon dioxide tension, oxygen saturation, base excess, HCT, haemoglobin, glucose and lactate (Blood Gas Analyzer, Ciba Corning 865, Chiron Diagnostics, Norwood, MA, USA) as well as reference sampling for microsphere measurements prior to, during and after SCP.

2.5. Intracranial pressure

Before cannulation for CPB, the sagittal sinus was cannulated as previously described [9]: a midline scalp incision was made, and the underlying periosteum was removed to facilitate exposure of the coronal and sagittal sutures. A 3-mm cutting burr was used to remove the bone over the sinus. A 24-G catheter was inserted into the sagittal sinus to permit monitoring of cerebral venous pressure. An intracranial pressure (ICP) pressure probe was connected to a transducer (Codman ICP Express; Johnson & Johnson Professional Inc., Raynham, MA, USA).

2.6. Neurobehavioural assessment

All animals were videotaped at the same time daily, and a neuroscientist, blinded to the intra-operative course of events, used the coded videotapes to carry out neurological scoring using a modification of the Tarlov score. The modified Tarlov score is scaled as follows: no voluntary movements (0); perceptible movements at joints (1); good movements at joints but inability to stand (2); ability to get up and stand with assistance $<$1 min (3); ability to get up with assistance and stand unassisted $<$1 min (4); ability to get up with assistance and stand unassisted $>$1 min (5); ability to get up and stand unassisted $>$1 min (6); ability to walk $<$1 min (7); ability to walk $>$1 min (8) and complete recovery (9).

2.7. Regional blood flow assessment (microspheres)

Our regional blood flow assessment strategy involves the use of microspheres – 15 μm polystyrene beads – which fluoresce under ultraviolet light. Use of different colours (yellow, pink, purple and coral, each of which is available in low, medium and high varieties), enables multiple measurements in the same tissue; sampling technicalities limit this to about 8 per tissue.

The microsphere bolus consisted of 2.5 million spheres, which were administered centrally, into a left heart chamber, or into the CPB inflow during CPB and SCP. At the same time as the injection was made, a reference sample of blood was withdrawn from an artery 'downstream' in the arterial tree from the injection site. This was withdrawn using a specialised pump at a precise rate; in our experiments, 2.91 ml min^{-1}. This basically allows a ratio calculation: the ratio of microspheres in a given piece of tissue to those in the blood reference sample is the same as the ratio of their blood flows. The reference samples were placed in tubes with EDTA anticoagulant. Multiple injections of different colours were made at relevant stages of the surgical protocol.

At the end of the experiment, the pig was sacrificed by exsanguination under anaesthesia and the tissues were harvested for blood flow determination, histological analysis or both. The spinal cord was removed from the animal through a midline dorsal incision which runs from the skull to the sacrum. The paraspinal muscles were dissected off the vertebral column and the spinal canal was then entered through bilateral laminectomies down the length of the back, exposing the spinal cord, which was then removed. The anatomical levels can be identified through the origins of the spinal nerves and the appropriate divisions made for analysis.

The blood and tissue samples were then analysed at Interactive Medical Technologies (IMT) Ltd, Irvine, California, USA. The samples were analysed in a flow cytometer (fluorescent spectrophotometer) which measured the fluorescence at the various wavelengths. Spinal cord blood flow was determined from the fluorescent intensities (counts) of the tissue and blood reference samples using the formula:

$$\mathrm{SCBF}\,(\mathrm{ml\,min^{-1}\,g^{-1}}) = \{(R \times I_t)/(I_{br} \times \mathrm{Wt})\}$$

where R is the blood reference withdrawal rate (2.91 ml min^{-1}), I_t and I_{br} are the tissue and blood reference samples' fluorescent intensities or counts, and Wt is the weight of the tissue sample (g).

Due to the high cost of microsphere measurements, systematic blood flow studies were limited to group A animals, in whom a better outcome was expected, enabling postoperative as well as intra-operative blood flow measurements. Although one group B pig had blood flow studies, only blood flow data from group A animals were included in the analysis of SCBF.

2.8. Histopathological evaluation

Portions of the spinal cord not used for microsphere analysis were fixed in 10% formalin solution, embedded in paraffin and then sectioned transverse to the craniocaudal axis, with samples at 0.5-cm intervals. Sections 6 μm in thickness were stained with haematoxylin and eosin, examined and scored blindly by an experienced neuropathologist according to a schematic grading system which was developed to classify the ischaemic spinal cord damage (ISCD) at each segmental level: 1 = necrosis of single (motor) neurons only; 2 = necrosis of one posterior horn only; 3 = necrosis of both posterior horns only; 4 = necrosis of both posterior horns + surrounding white matter; 5 = necrosis of both anterior horns only; 6 = central necrosis involving posterior and anterior horns + parts of white matter; 7 = complete necrosis of gray matter only; 8 = complete necrosis of the whole section (Fig. 1).

2.9. Data analysis

Data are presented as mean ± SD. Fisher's exact test was used for comparisons of paraplegia and death rates between the two groups. For blood flow data, to avoid confounding

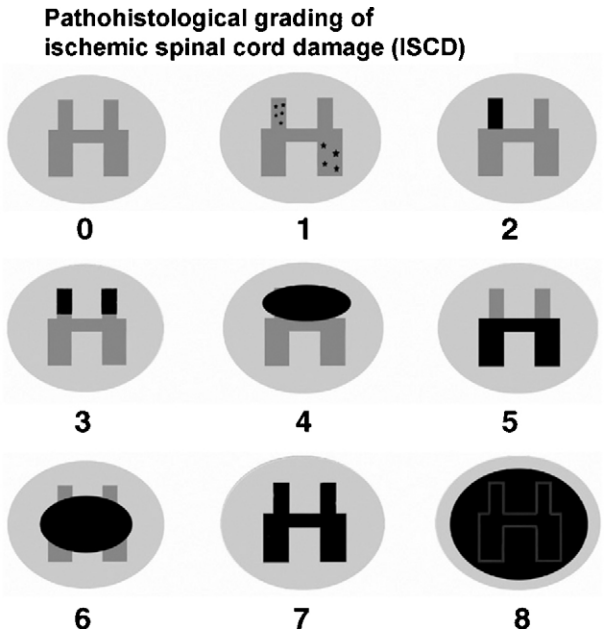

Fig. 1. Kleinman's schematic grading system – as previously described – was developed to classify the ischaemic damage at each segmental level of the spinal cord: 1 = necrosis of single (motor) neurons only; 2 = necrosis of one posterior horn only; 3 = necrosis of both posterior horns only; 4 = necrosis of both posterior horns + surrounding white matter; 5 = necrosis of both anterior horns only; 6 = central necrosis involving posterior and anterior horns + parts of white matter; 7 = complete necrosis of gray matter only; 8 = complete necrosis of the whole section.

from group effect, only pigs from group A were analysed (because SCBF was only analysed in one pig, as explained above). Because there are only five pigs, to avoid overfitting a model, the spinal cord was divided into three regions (C1–T3, T4–T13, and L1–S) according to the expected flow during SCP. Subsequently, within each region, the average baseline blood flow at 28 °C was compared to the average blood flow at 10 and 80 min on SCP, and then compared to the flow at 1, 5 and 48 h after SCP, separately. Mixed effects models – with time being the fixed effect and pigs and spinal segments within the area being the random effects – were fit to account for serially correlated data within a pig. For the histology and Tarlov scores, repeated measurement analyses were performed; group-specific heterogeneous compound symmetry structure was specified to model the serially correlated data within a pig.

For comparisons of physiologic and haemodynamic parameters between the groups A and B survivors and non-survivors, and paraplegic versus non-paraplegic animals, the Wilcoxon rank-sum tests were performed to avoid the requirement of the normality assumption.

3. Results

3.1. Comparability of experimental groups

All animals were examined daily by a veterinary team and found to be in normal health prior to surgery.

The results of this experiment were analysed by comparing two groups: group A, SCP at 28 °C for 90 min ($N = 12$), and group B, SCP at 28 °C for 120 min ($N = 8$). The preoperative weights of the animals in the two groups were similar (group A: 31 ± 3 kg, group B: 29 ± 2 kg, $p = 0.11$). The intra-operative target mean aortic pressure was 50 mmHg on CPB and SCP. Only volume infusions but no pharmaceuticals were used to maintain aortic pressures. The haemodynamic and CPB-related data are shown in Table 1.

As intended by the design of the study, there were no significant differences in intra-operative physiological parameters between groups A and B animals, survivors and non-survivors or paraplegic and neurologically recovered pigs with regard to cooling and rewarming times, rectal temperatures, mean arterial pressure, pH, pCO_2, pO_2, and HCT during SCP, as detailed below.

3.2. Cooling and rewarming on cardiopulmonary bypass

A core body temperature (rectal) below 30 °C was reached in all animals on average after 20 min on CPB, on average; the average cooling time on CPB to reach the rectal target temperature of 28 °C was 22 ± 7 min (group A: 23 ± 7 min; group B: 20 ± 7 min; $p = 0.26$). The animals were weaned from CPB at a mean rectal temperature of 35.1 ± 1.2 °C after an average rewarming time on pump of 71 ± 26 min (group A: 70 ± 30 min; group B: 72 ± 23 min; $p = 0.85$).

3.3. Selective cerebral perfusion (SCP) during lower body circulatory arrest (LCBA)

The core body temperature during LBCA and SCP was maintained at 28.1 ± 0.5 °C, rectally (mean ± SD); there was no significant difference between the two groups: 28.2 ± 0.7 °C in group A, and 28.0 ± 0.4 °C in group B ($p = 0.64$). The average HCT during LBCA and SCP was $20.3 \pm 2.5\%$; there was no significant difference between the groups: the mean HCT was $19.6 \pm 2.5\%$ in group A and $20.6 \pm 2.5\%$ in group B ($p = 0.54$). The mean flow rate during the period of SCP – to maintain 50 mmHg at all times – was 9.6 ± 4.6 cc min^{-1} kg^{-1}; there was no significant difference between the groups: 10.8 ± 5.8 cc min^{-1} kg^{-1} in group A and 9.1 ± 2.8 cc min^{-1} kg^{-1} in group B ($p = 0.58$). The sagittal sinus pressure during SCP was 11 ± 3 mmHg with no significant difference between the groups: 12 ± 3 mmHg in group A and 11 ± 3 mmHg in group B ($p = 0.49$).

However, the sagittal sinus pressures were slightly higher in paraplegic versus neurologically recovered animals (based on two-sample t-test ($p = 0.055$); the non-parametric Wilcoxon rank-sum test was also close to significant: $p = 0.085$).

All pigs could be weaned from CPB and ventilation, but seven pigs (58%) in group A and five pigs (63%) in group B developed multi-organ failure and died within 24–36 h (Table 2); there was no difference between the groups in terms of multi-organ failure and early death ($p = 0.99$).

3.4. Spinal cord blood flow (SCBF)

Five animals from group A underwent SCBF measurements prior to, during and after SCP at the following time points: at 28 °C prior to initiation of SCP (baseline), 5 min after initiation of SCP (SCP start), 10 min prior to the end of

Table 1
Haemodynamic, physiologic and metabolic parameters during SCP and rewarming.

Variable by group	SCP start	10 min SCP	30 min SCP	60 min SCP	90 min SCP	120 min SCP	10 min rewarming	30 min rewarming	60 min rewarming	p*=
Rectal temperature (°C)										
A	27.5 ± 0.6	27.8 ± 0.7	28.3 ± 0.7	28.5 ± 0.8	27.9 ± 0.7	–	30.6 ± 1.6	33.9 ± 1.2	35.1 ± 0.7	n.s.
B	27.6 ± 0.1	27.8 ± 0.2	28.2 ± 0.3	28.2 ± 0.5	28.0 ± 0.5	27.9 ± 0.5	30.5 ± 1.7	33.6 ± 1.6	35.2 ± 0.8	
Both groups	27.5 ± 0.4	27.8 ± 0.5	28. 2 ± 0.5	28.3 ± 0.6	28.0 ± 0.5	–	30.6 ± 1.6	33.8 ± 1.4	35.1 ± 0.7	
Blood pressure (mmHg)										
A	50 ± 0	50 ± 0	50 ± 0	50 ± 0	50 ± 1	–	49 ± 5	49 ± 6	50 ± 5	n.s.
B	50 ± 0	50 ± 0	53 ± 7	53 ± 5	54 ± 5	51 ± 4	49 ± 4	50 ± 4	52 ± 3	
Both groups	50 ± 0	50 ± 0	51 ± 5	51 ± 4	52 ± 3	–	49 ± 4	50 ± 5	51 ± 4	
Pump flow (cc min^{-1})										
A	476 ± 163	446 ± 180	325 ± 197	288 ± 179	295 ± 181	–	1741 ± 273	1828 ± 284	1924 ± 115	n.s.
B	550 ± 136	453 ± 82	240 ± 76	200 ± 56	203 ± 74	231 ± 122	1630 ± 184	1724 ± 261	1744 ± 243	
Both groups	509 ± 152	449 ± 143	291 ± 102	253 ± 147	256 ± 150	–	1694 ± 240	1779 ± 270	1826 ± 209	
Pump flow [cc min^{-1} kg^{-1}]										
A	15.7 ± 5.0	14.5 ± 5.6	10.5 ± 6.4	9.3 ± 5.8	8.9 ± 6.4	–	57.0 ± 7.6	61.0 ± 9.4	63.2 ± 7.2	n.s.
B	19.0 ± 4.4	15.7 ± 3.2	8.3 ± 2.7	7.0 ± 1.8	7.0 ± 2.3	7.9 ± 3.7	56.1 ± 2.9	59.5 ± 8.1	60.9 ± 11.1	
Both groups	17.2 ± 4.9	15.0 ± 4.7	9.6 ± 5.3	8.3 ± 4.7	8.1 ± 5.2	–	56.6 ± 6.0	60.3 ± 8.6	61.9 ± 9.2	
pCO_2 (mmHg)										
A	32 ± 6	35.3 ± 3.5	34.5 ± 5.6	33.9 ± 6.9	34.3 ± 7.8	–	36.9 ± 4.9	36.0 ± 4.2	37.5 ± 5.7	n.s.
B	39 ± 4	34.9 ± 3.8	37.1 ± 6.2	33.1 ± 2.4	35.3 ± 4.2	35.9 ± 3.9	35.0 ± 2.9	36.6 ± 3.1	35.9 ± 2.1	
Both groups	35 ± 6	35.2 ± 3.5	35.3 ± 5.7	33.6 ± 5.6	34.8 ± 6.3	–	36.1 ± 4.2	36.3 ± 3.6	36.6 ± 4.0	
pO_2 (mmHg)										
A	419 ± 54	383 ± 81	387 ± 44	378 ± 39	383 ± 58	–	312 ± 63	328 ± 69	342 ± 54	n.s.
B	380 ± 53	372 ± 43	379 ± 50	362 ± 42	354 ± 44	363 ± 46	365 ± 64	368 ± 30	360 ± 24	
Both groups	403 ± 56	379 ± 66	385 ± 44	372 ± 36	370 ± 52	–	335 ± 67	345 ± 58	351 ± 40	
Haematocrit (%)										
A	19 ± 3	19 ± 3	20 ± 2	20 ± 3	21 ± 3	–	19.9 ± 2.7	21.3 ± 2.8	21.4 ± 4.0	n.s.
B	20 ± 2	20 ± 2	19 ± 3	21 ± 2	22 ± 3	22 ± 3	20.9 ± 2.8	22.9 ± 3.3	24.3 ± 3.7	
Both groups	20 ± 3	20 ± 2	19 ± 2	20 ± 3	21 ± 3	–	20.3 ± 2.7	22.0 ± 3.0	23.0 ± 3.9	
Sagittal sinus pressure (mmHg)										
A	12 ± 2	12 ± 2	12 ± 3	12 ± 3	12 ± 3	–	–	–	–	n.s.
B	11 ± 5	12 ± 4	10 ± 4	10 ± 4	10 ± 2	9 ± 4	–	–	–	
Both groups	11 ± 3	12 ± 4	12 ± 3	11 ± 3	11 ± 3	–	–	–	–	
pH										
A	7.5 ± 0.07	7.44 ± 0.06	7.43 ± 0.04	7.40 ± 0.04	7.40 ± 0.08	–	7.38 ± 0.08	7.42 ± 0.05	7.41 ± 0.04	n.s.
B	7.44 ± 0.06	7.48 ± 0.03	7.41 ± 0.07	7.37 ± 0.07	7.38 ± 0.06	7.42 ± 0.05	7.42 ± 0.06	7.42 ± 0.04	7.43 ± 0.06	
Both groups	7.47 ± 0.07	7.45 ± 0.05	7.42 ± 0.05	7.39 ± 0.06	7.39 ± 0.07	–	7.39 ± 0.08	7.42 ± 0.05	7.41 ± 0.04	

Table 2
Mortality, morbidity and postoperative modified Tarlov score.

Pig # (modified)	Group	Mortality	Survival (days postoperative)	Respiratory failure	Tarlov score
1	B	•	–		
2	B	•	–	•	
3	B		6		1
4	B	•	–	•	
5	B		6		1
6	B		6		1
7	B	•	–	•	
8	B	•	1	•	
9	A	•	–	•	
10	A	•	–	•	
11	A	•	–		
12	A	•	1		
13	A		6		3
14	A		6		9
15	A	•	1		
16	A	•	–		
17	A	•	–	•	
18	A		6		6
19	A		6		9
20	A		6		9

Bullet symbol: event occurred.

SCP (SCP end), and 1 h, 5 h and 48 h postoperatively (normothermia, 37 °C).

Spinal cord blood flows are shown graphically in Fig. 2, but because of the small number of blood flow studies, adjacent segments were combined for statistical analysis, as in Fig. 3.

Blood flow to the spinal cord diminished immediately after initiation of SCP and was nearly absent throughout SCP below the T4–T13 region.

During lower body reperfusion, within 1 h after SCP, the cervical and thoracic SCBF exceeded baseline flow, but there was no significant increase in blood flow below segment L1 during reperfusion as compared to baseline (Fig. 3). Interestingly, all segments above the distal aortic cross clamp level (C1–T3) exhibited perfusion significantly higher than the segments below the level of the aortic cross clamp ($p = 0.008$) at 1 h after SCP. The lumbar spinal cord – where ischaemic damage was observed – does not exhibit as high a level of perfusion as the more cranial cord 1 h postSCP (Fig. 3). It should be borne in mind that during moderate hypothermia (baseline, 28 °C), SCBF is significantly lower than at normothermia (5 h or 48 h postoperatively; all $p \leq 0.01$) in all segments.

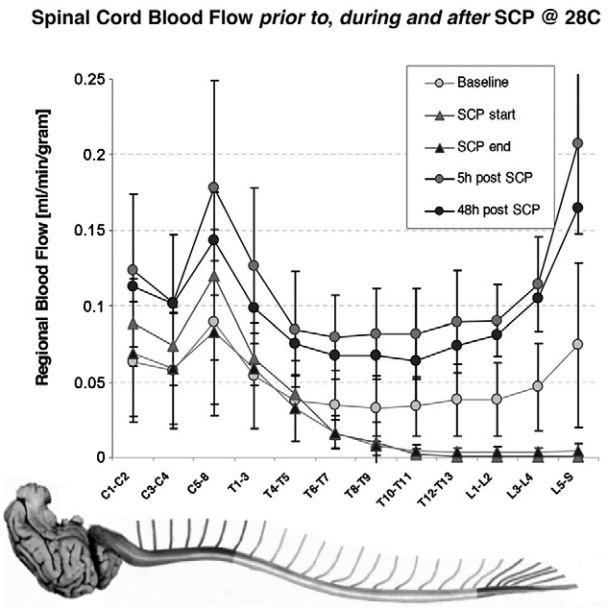

Fig. 2. Regional spinal cord blood flow measurements ($N = 5$ animals, using fluorescent microspheres as detailed in the text): baseline at 28 °C — prior to initiation of SCP, SCP start — 5′ after initiation of SCP, SCP end — 10′ prior to the end of SCP and, at 5 h and 48 h postoperatively.

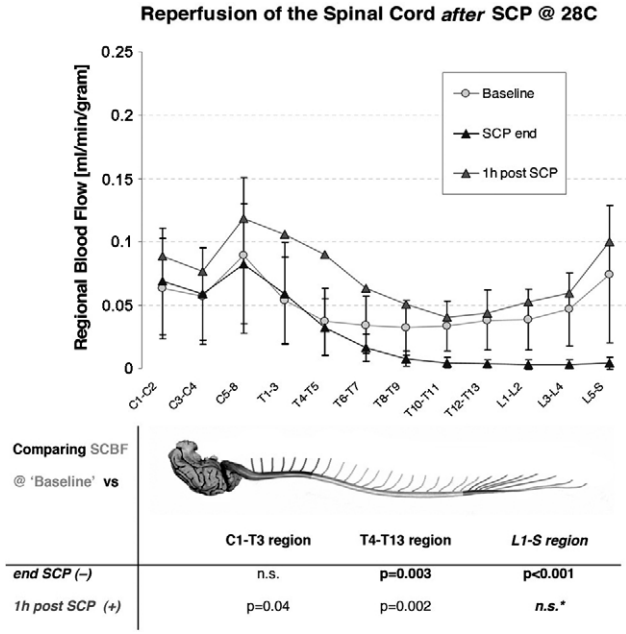

Fig. 3. The blood flow to the cervical and upper thoracic cord is not significantly reduced during SCP at 28 °C, whereas the lower thoracic and lumbar cord suffers significant ischaemia. Although blood flow returns quickly during early reperfusion to the cervical and upper thoracic cord, the return of blood flow to the lumbar region of the spinal cord during reperfusion is significantly delayed.

3.5. Histopathological findings — grading of ischaemic spinal cord damage

There was no evidence of necrosis in the cervical and thoracic segments in either paraplegic/paraparetic or

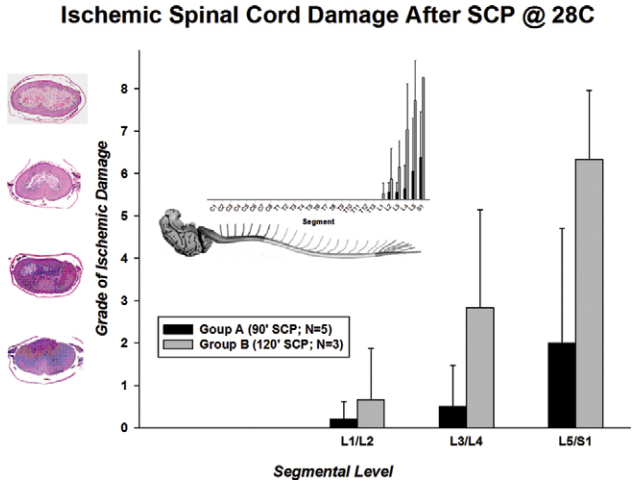

Fig. 4. Regional ischaemic damage of the spinal cord (ISCD) after SCP for 90- and 120-min at 28 °C: group A (black bars) versus group B (grey bars). The *y*-axis shows the grade of the ischaemic damage and a corresponding low power (2×) transverse section of the spinal cord, stained with haematoxylin and eosin, from group A versus group B survivors three days after SCP as examples. The cord segments from which the sections are taken are indicated on the *x*-axis. The inset illustrates the focus of damage in the lumbar spinal cord; the cervical and thoracic cord are unaffected by permanent ischaemic damage.

recovered animals to the level of L1 in any animal (Fig. 4). In the lumbar segments, however, paraparetic/paraplegic animals showed distinctive necrosis of the grey matter involving the posterior and anterior horns and surrounding white matter, sparing a thin peripheral rim of white matter below the pia. All survivors suffered moderate-to-severe ischaemic lumbar spinal cord damage, which was more severe in group B ($p = 0.03$). The entire cervical and thoracic cord was histologically intact in both groups. Even in the pigs that regained normal function, the spinal cord showed significant ischaemic damage of neurons at all lumbar levels at lower magnification.

Both group A and group B pigs suffered histologic damage in the lumbar spinal cord with a trend towards more severe damage distally: mean scores for L3, L4, L5 and S1 are 0.4, 0.6, 1.6 and 2.4 for group A ($p = 0.09$ for trend) and 1.8, 4.0, 5.7, and 7.2 for group B ($p = 0.001$), respectively.

There was no significant difference in histologic damage in the thoracic and proximal lumbar (—L3) spinal cord between groups A and B ($p = 0.17$), whereas in the mid-lumbar spinal cord towards the cauda equina, group B animals suffered significantly more severe damage than group A animals (at L4: $p = 0.049$; at L5: $p = 0.041$; at S1: $p = 0.001$; see Fig. 4).

3.6. Neurologic outcome (Tarlov score)

Neurologic recovery differs significantly when comparing the survivors of the two groups. Three of the five group A pigs recovered normal function, but one suffered paraplegia and one paraparesis. In group B, survivors had a worse neurologic outcome ($p = 0.001$): all suffered paraplegia (one immediate, and two on day 2, after initial recovery). During the first 24 h postoperatively, the modified Tarlov score was not significantly different between the two groups ($p = 0.75$). Thereafter, individual group A survivors showed progress in function ($p = 0.0005$), whereas spinal cord function in group

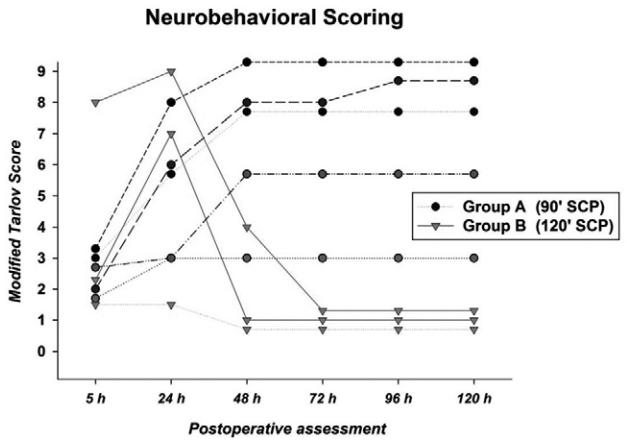

Fig. 5. Postoperative neurobehavioral recovery after 90 min ($N = 5$) and 120 min ($N = 3$) of SCP at 28C using a modified Tarlov score, as detailed in the text. Recovery was defined as a score of >6, which requires the pig to get up without assistance and walk for <1 min. Group A: circles; group B: triangles. There is a significant ($p = 0.0005$) increase in function among group A animals from 5 h postoperatively to the later time points (24 h, 48 h, 72 h, 96 h), whereas among group B animals, the spinal cord function declines significantly ($p = 0.0117$) after the 5-h time point. During the first 24 h postoperatively, the modified Tarlov score is not significantly different between the two groups ($p = 0.75$).

B pigs declined significantly ($p = 0.012$), resulting in significantly different neurologic recovery in group A compared to group B animals at 48 h ($p = 0.004$), 72 h, 96 h and 120 h ($p = 0.001$; Fig. 5; see also Table 2).

4. Discussion

The adoption by various clinical groups of SCP at 28 °C for cerebral protection during aortic surgery without explicit discussion of the possible risk of spinal cord injury prompted us to undertake this experimental study. The specific details of the experimental protocol were determined in the context of results from previous studies of cerebral and spinal cord protection in the same experimental model.

In 2003, experimental data from our laboratory clearly demonstrated that SCP for 90 min is safe at a body temperature of 20 °C, with no impairment of spinal cord function [18]. The duration of spinal cord ischaemia, which is safe at normothermia and during mild hypothermia, has principally been studied because of its relevance to repair of the descending aorta, especially using the so-called clamp-and-sew technique. Studies from our laboratory in pigs have demonstrated that after only 25 min of normothermic (36.5 °C) aortic cross-clamping, two of three animals suffer postoperative paraplegia, but 20 min of cross-clamping at 36.5 °C does not result in either paraparesis or paraplegia [26]. With mild hypothermia — at 32 °C — the spinal cord's ischaemic tolerance allows 50 min of aortic cross-clamping with normal neurological recovery, whereas a 60-min interval of aortic cross-clamping results in delayed paraplegia in all animals [26].

From these cross-clamp experiments, we derived the graph of time and temperature in relation to severe spinal cord injury shown in Fig. 6A, and determined the time points

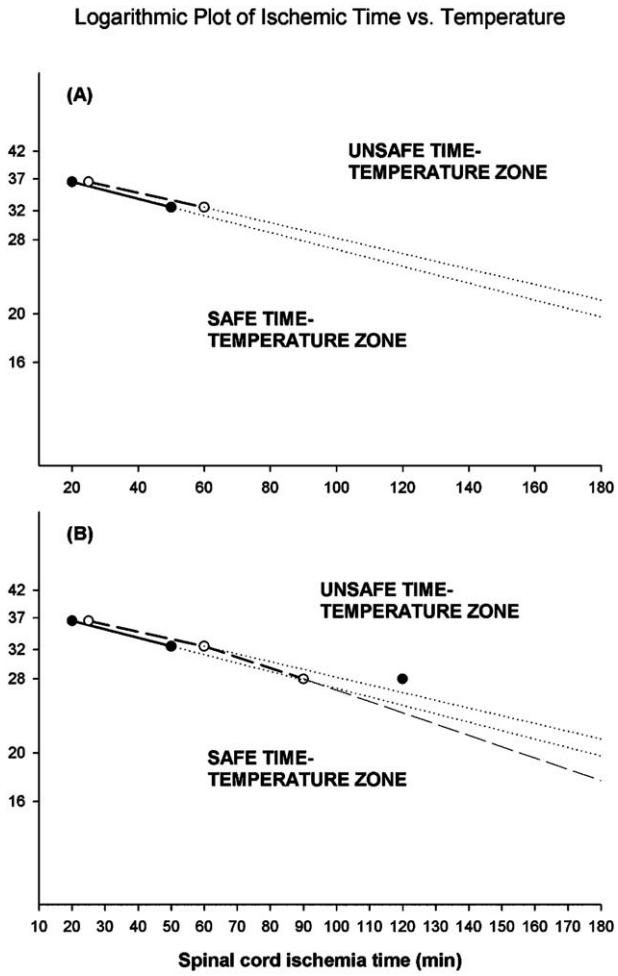

Fig. 6. (A) Plot indicating safe (solid line) and unsafe (bold dashed line) time–temperature points following aortic cross-clamping with a straight line extrapolation from the data of Strauch et al. [26]: Aortic cross-clamping was safe for 20 min at 36.5 °C and for 50 min at 32.5 °C (black circles); unsafe for 25 min at 36.5 °C and for 60 min at 32.5 °C (open circles). The *y* axis is a logarithmic scale for temperature. (B) The 90- and 120-min points for SCP at 28 °C from the current experiment are added to define the unsafe zone. Obviously the 120 min at 28 °C point falls within the unsafe time–temperature zone. The *y* axis is a logarithmic scale for temperature. The dashed line represents the revised extrapolated border between safe and unsafe time–temperature combinations using the data from the current experiment and that of Strauch et al. [26].

for the present study. In accord with basic biological phenomena, it is reasonable to anticipate a straight line relationship between the logarithm of temperature versus time. Fig. 6A — from the data of Strauch et al. [26] — is a logarithmic plot (see *y* axis for temperature) indicating safe (solid line) and unsafe (bold dashed line) time/temperature points following aortic cross-clamping, with a straight line extrapolation to predict other time–temperature combinations. Cross-clamping was safe for 20 min at 36.5 °C and for 50 min at 32 °C (black circles); it was unsafe for 25 min at 36.5 °C and for 60 min at 32 °C (open circles). From these studies, we anticipated that both 60 and 90 min of SCP at 28 °C would likely prove safe, and that these pigs would not demonstrate any functional or histological impairment which could be correlated with microsphere determinations of spinal cord blood flow to provide new insights. So we elected

to compare moderate hypothermia at 28 °C for 90 min – which we expected to be safe in terms of spinal cord ischaemic tolerance – with 120 min of LBCA at 28 °C, which we thought would result in paraplegia. But with the data from the current study, we can now modify the unsafe line by adding an additional point: 90 min at 28 °C (Fig. 6B).

The intent of this study was to confirm the hypothesis that SCP/upper body perfusion with only mild hypothermia can lead to spinal cord injury if the duration is – usually inadvertently – sufficiently prolonged. We are not suggesting that spinal cord injury is likely at the usual durations and temperatures at which SCP is carried out, but that the margin of safety is not as great as has widely been assumed. Although the technique is probably quite safe under ideal conditions – in the hands of experienced surgeons in specialised centres – SCP at 28 °C is also likely to be used by surgeons who deal with aortic cases infrequently, who may be hesitant to use deep hypothermia. The evidence from this study – that there is essentially no perfusion of the spinal cord during SCP – suggests that carrying out SCP under mild hypothermia by relatively inexperienced surgeons, in whose hands its duration may be prolonged, can be dangerous. We believe that the times we chose allowed us clearly to demonstrate this risk.

The results of this experiment document a more severe insult following prolonged SCP at 28 °C than we had predicted. These poorer results are in line with the clinical findings of Kamiya et al., who found a significantly higher rate of paraplegia in patients with prolonged (>60 min) SCP at 28 °C than with prolonged SCP at deep hypothermia: 18% versus 0% [14]. Kamiya et al. also documented a mortality of 27% with prolonged moderately hypothermic SCP, which is reflected by our experimental finding that nearly 60% of our experimental animals did not survive even 90 min of moderately hypothermic SCP, whereas the mortality in pigs subject to prolonged SCP at deep hypothermia in previous experiments was much lower.

The high paraplegia rate in our experiments seems quite plausible in light of our finding that virtually no flow to the lumbar spinal cord occurs during SCP at 28 °C, resulting in severe damage to the lower lumbar spinal cord, which becomes steadily worse with longer intervals of ischaemia. Ischaemia to the lower body and abdominal viscera without the protection afforded by deep hypothermia likely results in acidosis and vascular instability that impairs blood flow to the spinal cord during rewarming and recovery from SCP: in the current study, an immediate increase in flow relative to baseline is seen after SCP in the cervical and thoracic cord, but not in the lumbar portion of the spinal cord, where the most severe histological damage occurs. This portion of the cord may be too damaged or too oedematous to mount an immediate hyperaemic response, although flow to it is later restored.

Respiratory failure was the principal cause of death in the nearly 60% of pigs that died during the first 48 h, post-operatively. Although pulmonary ischaemia may contribute to the respiratory failure, the late effects of prolonged warm visceral ischaemia are probably principally responsible for the pulmonary damage. Post-ischaemic pulmonary and haemodynamic problems following SCP at moderate hypothermia may well be more successfully overcome in many patients in an intensive care unit setting than in our pigs, but the clinical report from Hannover suggests that there is still a significantly higher incidence of paraplegia and of mortality with moderate rather than deep hypothermia during prolonged SCP.

The proponents of SCP with only moderate hypothermia argue that the avoidance of deep hypothermia averts serious coagulopathy. Bleeding has not, in our experience, been more severe following SCP at 15 °C than what is reported following SCP at more moderate temperatures, but it is hard to find clinical evidence that the rates of re-operation for haemorrhage, for example, are higher following deep rather than moderate hypothermia. In a study of HCA at different temperatures, Harrington et al. [27] did not find an increase in postoperative haemorrhage with profound as compared with deep hypothermia. And in a recent retrospective study, Kamiya et al. did not find a significant difference in bleeding complications between deeply hypothermic LBCA versus moderately hypothermic LBCA, either when analysing the entire population, or when using 92 propensity-matched pairs. The only suggestive evidence linking temperature with bleeding was found when looking at temperature as a continuous variable in the propensity-matched cohort of this study: the mean temperatures at the initiation of LBCA revealed a difference of 0.8 °C between patients who underwent re-exploration for bleeding and those who did not: 24.1 °C versus 24.9 °C [14].

Among the organs not perfused during SCP, the spinal cord is unquestionably the one most sensitive to ischaemia. The spinal cord likely suffers not only immediate ischaemic injury during LBCA, but is further damaged by the late consequences of visceral ischaemia, which impair reperfusion of the cord by contributing to haemodynamic instability and by disrupting vascular integrity. The pattern of spinal cord injury observed in the group B pigs, initial recovery and later deterioration, supports the idea that the neurological insult in this experiment may have both an intra-operative and a postoperative component.

We would expect that any animal with multi-organ failure would have severe spinal cord injury occurring concurrently, and do not doubt that multi-organ failure worsens any neurological damage which has occurred intra-operatively. The repercussions of reperfusion injury to multiple organs are likely to contribute to the ultimate severity of intra-operative spinal cord damage in non-fatal cases of multi-organ failure. We think it is almost certain that any pig with ischaemia severe enough to suffer fatal multi-organ failure would have emerged paraplegic even with optimal postoperative care, given the vulnerability of nerve tissue to irreversible ischaemia. It is arguable that with care equivalent to that in a clinical intensive care unit, some of the pigs with lesser intra-operative ischaemia might have recovered somewhat better. In practice, however, it is not feasible to duplicate clinical conditions perfectly in the laboratory. Furthermore, the greater incidence of paraplegia after longer SCP duration in this experiment argues for a dominant intra-operative insult, which makes the quality of postoperative care somewhat less relevant.

The requirement for prolonged SCP certainly depends upon the technique used for arch reconstruction and the

experience of the surgical team. Although the percentage of patients requiring prolonged SCP may be low for hemiarch replacements in high-volume aortic centres, it may be much higher in centres with less extensive experience with arch replacement. In a recent series of 150 trifurcated arch operations in our centre, mortality was 4.6%, but SCP lasted 67 ± 21 min (albeit at a mean temperature of 16 °C) [28]. Mild or moderately hypothermic SCP would most likely have put a number of these patients at significant risk of spinal cord injury. Using more deeply hypothermic temperatures with a combination of HCA and SCP, only 2.8% of patients in this series had to return to the operating room for control of postoperative haemorrhage, and no patient had spinal cord injury.

It is important to realise that once SCP has been initiated at 28 °C, there is virtually no way to change the surgical strategy if technical complications occur unexpectedly and the duration of SCP threatens to become more prolonged than anticipated. We are therefore hesitant to endorse moderately hypothermic SCP for routine use.

5. Conclusion

This study emphasises that the duration of upper body perfusion at moderate hypothermia clearly has safety limits with regard to the spinal cord and the viscera. After 90 min of upper body perfusion at 28 °C, irreversible spinal cord damage often occurs; after 120 min, the rate of paraplegia is expected to approach 100%. These observations augment those made in earlier aortic cross-clamping experiments, refining time and temperature guidelines for avoiding spinal cord injury. Moderate or mild hypothermic upper body perfusion should not be generally advocated for aortic arch surgery, and particular caution should be exercised when more complex surgical interventions may require prolonged SCP.

References

[1] Bachet J, Guilmet D, Goudot B, Dreyfus GD, Delentdecker P, Brodaty D, Dubois C. Antegrade cerebral perfusion with cold blood: a 13-year experience. Ann Thorac Surg 1999;67:1874—8 [Discussion 1891—1874].
[2] Bachet J, Guilmet D, Goudot B, Termignon JL, Teodori G, Dreyfus G, Brodaty D, Dubois C, Delentdecker P. Cold cerebroplegia. A new technique of cerebral protection during operations on the transverse aortic arch. J Thorac Cardiovasc Surg 1991;102:85—93 [Discussion 93—84].
[3] Kazui T, Washiyama N, Muhammad BA, Terada H, Yamashita K, Takinami M, Tamiya Y. Total arch replacement using aortic arch branched grafts with the aid of antegrade selective cerebral perfusion. Ann Thorac Surg 2000;70:3—8 [Discussion 8—9].
[4] Jacobs MJ, de Mol BA, Veldman DJ. Aortic arch and proximal supraaortic arterial repair under continuous antegrade cerebral perfusion and moderate hypothermia. Cardiovasc Surg 2001;9:396—402.
[5] Di Eusanio M, Wesselink RM, Morshuis WJ, Dossche KM, Schepens MA. Deep hypothermic circulatory arrest and antegrade selective cerebral perfusion during ascending aorta-hemiarch replacement: a retrospective comparative study. J Thorac Cardiovasc Surg 2003;125:849—54.
[6] Hagl C, Khaladj N, Peterss S, Hoeffler K, Winterhalter M, Karck M, Haverich A. Hypothermic circulatory arrest with and without cold selective antegrade cerebral perfusion: impact on neurological recovery and tissue metabolism in an acute porcine model. Eur J Cardiothorac Surg 2004;26:73—80.
[7] Ergin MA, Griepp EB, Lansman SL, Galla JD, Levy M, Griepp RB. Hypothermic circulatory arrest and other methods of cerebral protection during operations on the thoracic aorta. J Card Surg 1994;9:525—37.
[8] Spielvogel D, Strauch JT, Minanov OP, Lansman SL, Griepp RB. Aortic arch replacement using a trifurcated graft and selective cerebral antegrade perfusion. Ann Thorac Surg 2002;74:S1810—4 [Discussion S1825—S1832].
[9] Strauch JT, Spielvogel D, Lauten A, Zhang N, Rinke S, Weisz D, Bodian CA, Griepp RB. Optimal temperature for selective cerebral perfusion. J Thorac Cardiovasc Surg 2005;130:74—82.
[10] Halstead JC, Meier M, Wurm M, Zhang N, Spielvogel D, Weisz D, Bodian C, Griepp RB. Optimizing selective cerebral perfusion: deleterious effects of high perfusion pressures. J Thorac Cardiovasc Surg 2008;135:784—91.
[11] Kamiya H, Hagl C, Kropivnitskaya I, Weidemann J, Kallenbach K, Khaladj N, Haverich A, Karck M. Quick proximal arch replacement with moderate hypothermic circulatory arrest. Ann Thorac Surg 2007;83:1055—8.
[12] Kamiya H, Klima U, Hagl C, Kallenbach K, Shrestha ML, Khaladj N, Bog A, Haverich A, Karck M. Short moderate hypothermic circulatory arrest without any adjunctive cerebral protection for surgical repair of the ascending aorta extending into the proximal aortic arch: is it safe? Heart Surg Forum 2006;9:E759—61.
[13] Zierer A, Aybek T, Risteski P, Dogan S, Wimmer-Greinecker G, Moritz A. Moderate hypothermia (30 degrees C) for surgery of acute type A aortic dissection. Thorac Cardiovasc Surg 2005;53:74—9.
[14] Kamiya H, Hagl C, Kropivnitskaya I, Bothig D, Kallenbach K, Khaladj N, Martens A, Haverich A, Karck M. The safety of moderate hypothermic lower body circulatory arrest with selective cerebral perfusion: a propensity score analysis. J Thorac Cardiovasc Surg 2007;133:501—9.
[15] Halstead C, Wurm M, Etz C, Zhang N, Bodian C, Weisz D, Griepp RB. Preservation of spinal cord function after extensive segmental artery sacrifice: regional variations in perfusion. Ann Thorac Surg 2007;84:789—94.
[16] Halstead JC, Etz C, Meier DM, Zhang N, Spielvogel D, Weisz D, Bodian C, Griepp RB. Perfusing the cold brain: optimal neuroprotection for aortic surgery. Ann Thorac Surg 2007;84:768—74 [Discussion 774].
[17] Strauch JT, Spielvogel D, Haldenwang PL, Shiang H, Zhang N, Weisz D, Bodian CA, Griepp RB. Changes in regional cerebral blood flow under hypothermic selective cerebral perfusion. Thorac Cardiovasc Surg 2004;52:82—9.
[18] Strauch JT, Spielvogel D, Haldenwang PL, Zhang N, Weisz D, Bodian CA, Griepp RB. Impact of hypothermic selective cerebral perfusion compared with hypothermic cardiopulmonary bypass on cerebral hemodynamics and metabolism. Eur J Cardiothorac Surg 2003;24:807—16.
[19] Strauch JT, Spielvogel D, Haldenwang PL, Lauten A, Zhang N, Weisz D, Bodian CA, Griepp RB. Cerebral physiology and outcome after hypothermic circulatory arrest followed by selective cerebral perfusion. Ann Thorac Surg 2003;76:1972—81.
[20] Strauch JT, Lauten A, Zhang N, Wahlers T, Griepp RB. Anatomy of spinal cord blood supply in the pig. Ann Thorac Surg 2007;83:2130—4.
[21] Lazorthes G, Gouaze A, Zadeh JO, Santini JJ, Lazorthes Y, Burdin P. Arterial vascularization of the spinal cord. J Neurosurg 1971;35:253—62.
[22] Etz CD, Homann TM, Luehr M, Kari FA, Weisz DJ, Kleinman G, Plestis KA, Griepp RB. Spinal cord blood flow and ischemic injury after experimental sacrifice of thoracic and abdominal segmental arteries. Eur J Cardiothorac Surg 2008;33:1030—80.
[23] Etz CD, Homann TM, Plestis KA, Zhang N, Luehr M, Weisz DJ, Kleinman G, Griepp RB. Spinal cord perfusion after extensive segmental artery sacrifice: can paraplegia be prevented? Eur J Cardiothorac Surg 2007;31:643—8.
[24] Etz CD, Di Luozzo G, Zoli S, Lazala R, Plestis KA, Bodian CA, Griepp RB. Direct spinal cord perfusion pressure monitoring in extensive distal aortic aneurysm repair. Ann Thorac Surg 2009;87:1764—73 (Discussion 1773—4).
[25] Etz CD, Di Luozzo G, Bello R, Luehr M, Khan MZ, Bodian CA, Griepp RB, Plestis KA. Pulmonary complications after descending thoracic and thoracoabdominal aortic aneurysm repair: predictors, prevention, and treatment. Ann Thorac Surg 2007;83:S870—876 [Discussion S890—S872].
[26] Strauch JT, Lauten A, Spielvogel D, Rinke S, Zhang N, Weisz D, Bodian CA, Griepp RB. Mild hypothermia protects the spinal cord from ischemic injury in a chronic porcine model. Eur J Cardiothorac Surg 2004;25:708—15.
[27] Harrington DK, Lilley JP, Rooney SJ, Bonser RS. Nonneurologic morbidity and profound hypothermia in aortic surgery. Ann Thorac Surg 2004;78:596—601.

[28] Spielvogel D, Etz CD, Silovitz D, Lansman SL, Griepp RB. Aortic arch replacement with a trifurcated graft. Ann Thorac Surg 2007;83:S791—795 [Discussion S824—S731].

Appendix A. Conference discussion

Dr R. Di Bartolomeo (*Bologna, Italy*): Antegrade selective cerebral perfusion, as demonstrated by various authors, represents the most effective method of cerebral protection during thoracic aorta surgery.

However, the appropriate degree of hypothermia, which guarantees an optimal protection of the spinal cord and the visceral organs, has not been well established. The pros and cons have to be balanced to choose the level of systemic hypothermia.

We totally agree with the authors that moderate hypothermia at 28 °C is not an effective method of protection against the ischaemic injuries of the spinal cord and the visceral organs.

This level of hypothermia has successfully been utilized in clinical practice associated with perfusion of the thoracoabdominal aorta in order to avoid any distal ischaemia. However, it is more technically demanding mainly in patients with acute and chronic aortic dissections. We use antegrade selective cerebral perfusion associated with a nasopharyngeal hypothermia of 26 °C.

In our experience involving more than 400 patients, we have not observed any ischaemic spinal injuries for periods of less than 60 min of circulatory arrest. However, for periods of circulatory longer than 70 min, this hypothermia may not be sufficient to allow effective protection of the distal organs.

And my question is, it's better for us to use this technique or the retrograde perfusion of thoracoabdominal aorta?

Dr Etz: In comparing retrograde with antegrade cerebral perfusion, the evidence for retrograde cerebral perfusion that seemed to be promising a decade ago was basically based on the effect of retrograde flushing of debris. But we have studies from our laboratory done about ten years ago that show that there is not sufficient flow to the brain to prevent ischaemia. I think we have clinical and experimental evidence that retrograde cerebral perfusion cannot compete with antegrade cerebral perfusion. Although the maintenance of adequate hypothermia is good using retrograde perfusion, there is really not sufficient flow. We therefore don't use retrograde cerebral perfusion, and we don't recommend it.

With regard to retrograde distal arterial perfusion, we are reluctant to use it in patients with atherosclerotic aneurysms because of the potential of dislodging atheromata from the distal aorta during retrograde flow.

Dr C. Hagl (*Hannover, Germany*): I would like to have your opinion on a fictive third group with perioperative CSF drainage. Do you think this adjunct would reduce the incidence of neurological complications?

Dr Etz: This is indeed a very important question, and I absolutely agree: I think we would see an improvement with CSF drainage. We have seen a trend toward better neurological outcome with lower sagittal sinus pressures. Although this trend did not reach statistical significance, this is a small group.

We have not done CSF drainage routinely, although we have done a couple of pilot studies. The problem is that it is difficult to maintain CSF drainage in the awake pig, which would be necessary in order to keep the animals alive for at least five days to study long-term recovery. I absolutely agree that we would likely see an improvement, but we would probably see it in both groups. There is no question that it would be very interesting to see the impact of CSF drainage.

Dr J. Bavaria (*Philadelphia, Pennsylvania*): I would like for you to comment more on the visceral ischaemic issues. The Duke group in North Carolina has shown, in an animal model, that there are histological problems with the kidneys and liver with a similar type of protocol at 28 °C and 60 min of cerebral perfusion.

So could you comment on the hepatic and renal function parameters that you noted in your study?

Dr Etz: Yes. Unfortunately in this study, we had no enzymatic liver or kidney parameters, so I cannot really give you an objective answer to that question. We do have some samples of liver and kidney, and hope that we are going to get these analysed in the future, since the impact of relatively mild ischaemia on the viscera is certainly a very important consideration. But I cannot give you a precise answer as to the histological problems or the enzymatic changes at this point.

Dr Jean E. Bachet (*Abu Dhabi, UAE*): May I ask you a question or make a comment? As you know, we started selective cerebral perfusion more than 20 years ago in my group, and in about 250 patients — we used to perfuse the patients at 25 °C — we had only 3 cases of paraplegia.

What surprises me is that in your study the chosen durations of circulatory arrest are extremely long. Why didn't you imitate what happens in clinical settings? Our mean time of circulatory arrest was 32 min, that is the time necessary to perform the distal anastomosis. That's all. We never exceeded one hour of distal circulatory arrest.

And the 3 paraplegia that were observed were in acute dissection, so it's very difficult to tell what their exact cause was.

Why did you choose so long durations, which we never see in clinical practice?

Dr Etz: The rationale for choosing these points was the logarithmic plot that I showed you based on earlier experiments which predicted what we would expect to be safe and unsafe durations at various temperatures. But I think that the durations for SCP differ very much in different series. You cite your SCP duration of 30 min on average, but if you look at this table, it shows that different groups use SCP at various temperatures for different durations. In discussing the question of the adequacy of distal perfusion during aneurysm repair, we must be sure that we are talking about total lower body ischaemic time. Sometimes the lower body ischaemic time is equivalent to the SCP time, but sometimes lower body visceral ischaemic time properly includes HCA and SCP times combined.

In the paper that we published in 2007 in the Annals, we can see that we have a longer average SCP duration than many groups, but many of our cases have difficult distal reconstructions with anastomoses deep in the left chest and often necessitate removal of clot or loose atheroma. We chose 90 min because we thought that if anything goes wrong, we will probably exceed our average durations and end up with SCP times of 90 min or even longer. I absolutely agree that the durations we studied are very long, but we wanted to show that temperature makes a difference. We were hoping that 90 min at 28 °C would prove safe.

Dr Bachet: And a last small criticism. So, your conclusion is: 'you have to be cautious in using selective cerebral perfusion because of the spinal cord'.

I think that you may say 'be careful in not arresting the circulation too long', but selective cerebral perfusion is definitely an undisputable progress.

Dr Etz: That's certainly true.