Optimal pH strategy for selective cerebral perfusion

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Abstract

Objective: Selective cerebral perfusion (SCP) affords brain protection superior to hypothermic circulatory arrest (HCA) for prolonged aortic arch procedures. Optimal pH strategy for HCA is controversial; for SCP it is unknown. We compared pH strategies during SCP in a survival pig model. Methods: Twenty juvenile pigs (26 ± 2.4 kg), randomized to alpha-stat (n = 10) or pH-stat (n = 10) management, underwent cooling to 20 °C on cardiopulmonary bypass (CPB) followed by 90 min of SCP at 20 °C. SCP was conducted with a mean pressure of 50 mmHg and hematocrit of 22.5%. Using fluorescent microspheres and sagittal sinus blood sampling, cerebral blood flow (CBF) and oxygen metabolism (CMRO₂) were assessed at the following time points: baseline, after 30 min cooling (20 °C), 30 min of SCP, 90 min of SCP, 15 min post-CPB and 2 h post-CPB. Visual evoked potentials (VEP) were assessed at baseline and monitored for 2 h during recovery. Neurobehavioral recovery (10 items) was assessed in a blinded fashion for 7 postoperative days. Results: There were no significant differences between the groups at baseline. CBF was significantly higher at the end of cooling, and after 30 and 90 min of SCP in the pH-stat group (P = 0.02, 0.007, 0.03). CMRO₂ was also higher with pH-stat (P = 0.06, 0.04, 0.10). Both groups showed prompt return to values close to baseline after rewarming (P = ns). VEP suggested a trend towards improved recovery in the alpha-stat group at 2 h post-CPB, P = 0.15. However, there were no significant differences in neurobehavioral score: (alpha-stat versus pH-stat) median values 7 and 7.5 on day 1; 9 and 9 on day 4, and 10 and 10 on day 7. Conclusions: These data suggest that alpha-stat management for SCP provides more effective metabolic suppression than pH-stat, with lower CBF. Clinically, the better preservation of cerebral autoregulation during alpha-stat perfusion should reduce the risk of embolization.

Keywords: pH management; Selective cerebral perfusion; Experimental

1. Introduction

The optimal pH management strategy for cardiovascular procedures utilizing cardiopulmonary bypass and hypothermia is unknown. The two main strategies utilized clinically, alpha-stat and pH-stat, differ in their approach to the acid-base alterations that occur with hypothermia. As the blood cools, gas solubility rises, and the partial pressure of carbon dioxide falls. With alpha stat management, the resulting alkalosis remains untouched during cooling; with pH-stat management, carbon dioxide is added to the gaseous inflow of the cardiopulmonary bypass circuit so that the pH is corrected to the levels usual during normothermia. The advocates of alpha-stat point to potential enzymatic benefits [1] and the advantage of preserving cerebral autoregulation. Proponents of pH-stat, which results in cerebral vasodilation, cite as advantages higher levels of oxygen delivery to the brain [2] and more homogeneous cooling, but the higher flows associated with pH-stat also have the potential to carry more particulate emboli.

In both clinical and experimental arenas no clear consensus exists. Clinical trials have focused on the influence of pH management strategy on outcome after deep hypothermic circulatory arrest (DHCA) in pediatric populations, and moderate hypothermic cardiopulmonary bypass in adult patients. Experimental work has principally addressed pH management in DHCA models. There has been very little assessment of the impact of pH management in clinical aortic surgery.

Selective cerebral perfusion (SCP) is gaining widespread popularity as a neuroprotective technique in aortic arch surgery [3,4]. There is clinical and experimental evidence of improved neurological outcome using SCP rather than HCA alone when prolonged cerebral protection is required. However, there have been no clinical or experimental studies assessing optimal pH strategy during SCP. In the current study, we sought to compare the outcomes of different pH management techniques in a porcine survival model.


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model, which has been used in previous studies to explore other aspects of cerebral physiology during SCP [5].

2. Materials and methods

2.1. Study design

Twenty juvenile female Yorkshire pigs (approximately 3 months of age) with a mean weight of 26 ± 2.4 kg were studied (Animal Biotech Industries, Inc., Danboro, PA). The animals were all subjected to 90 min of SCP at 20 °C using either alpha-stat (Group α, n = 10) or pH-stat management (Group pH, n = 10) during cooling, SCP and rewarming. Computer-generated randomization was carried out (CB), with individual group allocation revealed at the onset of cardiopulmonary bypass.

All animals received humane care in accordance with the guidelines from 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 Institutes of Health. The Mount Sinai Institutional Animal Care and Use Committee approved the protocol for this experiment.

2.2. Perioperative management and anesthesia

The animals were premedicated with intramuscular ketamine (15 mg/kg) and atropine (0.03 mg/kg) to induce deep sedation and facilitate endotracheal intubation. The pigs were mechanically ventilated with an inspired oxygen fraction of 0.7. During normothermia, the minute volume was adjusted to produce an arterial carbon dioxide tension of 35–45 mmHg. Anesthesia was maintained with isoflurane at 1.5% and paralysis was achieved with intravenous pancuronium (0.1 mg/kg). Arterial oxygen tension was maintained above 100 mmHg at all times.

An 8F Foley bladder catheter was placed for continuous assessment of urine output. Rectal and esophageal temperatures probes were inserted and electrocardiographic monitoring instituted. A 14G arterial line was placed in the right axillary artery for pressure monitoring, arterial blood gas sampling (Ciba Corning 865, Chiron Diagnostics, Norwood, MA), and the withdrawal of reference samples for regional blood flow determinations.

2.3. Intracranial monitoring

Before heparinization, a midline scalp incision was made and carried down to the peristome to reveal the intersection of the sagittal and coronal sutures. A 2 mm cutting tool was used to create a 1 cm diameter burr hole through which the superior sagittal sinus was visualized. The sinus was cannulated with a 24 G catheter and used for blood gas analyses and sinus pressure monitoring. An intracranial pressure (ICP) monitoring probe was passed extradurally through this burr hole to allow continuous assessment (Codman ICP Express, Johnson and Johnson Prof., Inc., Raynham, MA), and a temperature probe was inserted into the cerebral parenchyma.

2.4. Operative technique

The chest was opened via a small left thoracotomy in the fourth intercostal space. The pericardium was opened and the heart and great vessels were identified. After heparinization (300 IU/kg), the right atrium was cannulated with a 26F single-stage cannula and the aortic arch with a 16F arterial cannula. Cardiopulmonary bypass (CPB) was initiated at a flow rate of 80–100 ml/kg per min 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 and injecting fluorescent microspheres.

The CPB circuit consisted of non-pulsatile roller heads: a membrane oxygenator (VPCLM Plus, Cobe Cardiovascular, Inc., Arvada, CO) and heat exchanger (Hemotherm Cooler/Heater, Cincinnati Sub-Zero, Cincinnati, OH); cardiotomy suction was used. The circuit was primed with 1000 ml 0.9% saline and 4000 IU heparin. Once stable CPB was established, cooling to 20 °C was undertaken. In those animals randomized to alpha-stat management, no carbon dioxide was added to the oxygenator’s gaseous inflow, and arterial pH, measured at 37 °C, was maintained at 7.40 irrespective of the animal’s temperature. For the animals assigned to pH-stat management, 3–5% carbon dioxide was added to the inflow to give a temperature-corrected pH of 7.40. CPB was continued for a minimum of 30 min after initiation to ensure thorough cooling, and the operating room was kept between 18 and 20 °C to prevent an upward temperature drift.

Just prior to the commencement of SCP, diastolic cardiac arrest was achieved by adding 1 mEq/kg potassium chloride to the venous reservoir. Clamps were placed across the ascending aorta and the proximal descending aorta to isolate the arch, and SCP was initiated and maintained at a pressure of 50 mmHg. Myocardial protection was supplemented by the irrigation of the pericardium with iced saline (~4 °C).

Following the 90-min SCP interval, the clamps were removed and CPB with whole-body perfusion reinstituted. Rewarming was undertaken and carried through to a brain temperature of 36.5 °C. Care was taken to avoid a temperature difference of more than 10 °C between the perfusate and brain/rectal measurements. Cardiac defibrillation was achieved electrically without the need for pharmacological adjuncts.

2.5. Cerebral blood flow and metabolism determination

Fluorescent microspheres were used to determine cerebral blood flow (CBF), as detailed in previous studies [5]. This study utilized six colors, with each one injected at a specific time point: at baseline; after 30 min of cooling (20 °C); at 30 min of SCP; at 90 min of SCP; 15 min post-CPB, and 2 h post-CPB. For each injection, 2.5 million microspheres (15 μm diameter, Interactive Medical Technologies Ltd, Irvine, CA) were administered into the left atrial catheter at baseline, after cooling and post-CPB; the microspheres were delivered directly into the arterial catheter for the measurements during SCP. To allow calculation of regional blood flow rates, a reference sample was withdrawn from the axillary catheter at a rate of
2.91 ml/min with a Harvard pump (Harvard Bioscience, Inc., Holliston, MA).

After the 1-week period of neurobehavioral assessment, the animals were sacrificed by exsanguination under anesthesia and their brains were removed. The two hemispheres were divided and the samples (1-3 g in weight) were taken from the right hemisphere at four locations: hippocampus, neocortex, cerebellum and brainstem. Microspheres were recovered from the samples by sedimentation and counted using a fluorescent spectrophotometer. CBF was then determined from the fluorescent intensities of the tissue and blood reference samples using the formula:

\[
\text{CBF}(\text{ml/100 g per min}) = 100 \times \left( \frac{(R \times I_t)}{(I_{br} \times Wt)} \right)
\]

where \( R \) = blood reference withdrawal rate (2.91 ml/min), \( I_t \) and \( I_{br} \) are the tissue and blood reference samples’ fluorescent intensities, and \( Wt \) is the weight of the tissue sample (g). From this the cerebral metabolic rate for oxygen (\( \text{CMRO}_2 \)) can be derived:

\[
\text{CMRO}_2(\text{ml/100 g per min}) = 100 \times \left( \text{CBF} \times \text{arterial O}_2 \text{ content} - \text{sagittal sinus O}_2 \text{ content} \right)
\]

2.6. Hemodynamic and blood sample analyses

In addition to the injection of microspheres detailed above, various hemodynamic and arterial and sagittal sinus blood gas data were collected. These were taken for the following time points: baseline, after 15 min of cooling, after 30 min of cooling, 30 min SCP, 60 min SCP, 90 min SCP, after 15 min of rewarming, 30 min of rewarming, 15 min post-CPB, and 2 h post-CPB. The following data were recorded: brain temperature, mean arterial pressure (MAP), ICP, sagittal sinus pressure (SSP), cardiopulmonary bypass flow (where appropriate), pH, \( pO_2 \), \( pCO_2 \), \( O_2 \) content, hemoglobin, hematocrit, and lactate concentrations.

2.7. Visual evoked potential (VEP) recording

Through the midline scalp incision, two sterile stainless steel screw electrodes were attached to the skull. They were placed bilaterally 10 mm lateral and 10 mm posterior to the intersection of the sutures, and secured to the skull close to the underlying occipital cortex. The pig’s left eyelid was closed and secured with transparent tape. Supramaximal visual stimuli were delivered to the retina from a photo stimulator (Grass, model PS 22A). Each VEP consisted of the averaged response from 150 flashes. These responses were amplified, bandpass filtered, digitized, and stored on an optical disk for subsequent analysis (Spectrum 32 neurophysiological recording system, Cadwell Laboratories, Inc., Kennewick, WA, USA). At each time point, three averaged VEPs were recorded. The waves analyzed were the first retinal potential, which has a peak latency of approximately 9-10 ms, and the first cortical wave, which has a peak latency of approximately 60 ms. VEPs were assessed at baseline, 15 min post-CPB and 2 h post-CPB.

2.8. Behavior and postoperative neurological outcome

In the early recovery phase (defined as the first 3 h after extubation), the animals were blindly scored according to a six-point scale reflecting both early mental alertness and activity, as published previously [6].

Pigs were scored on a 12-point behavioral scale for 7 days postoperatively at the same time each day [7]. The scale allows a maximum of 12 points for a healthy pig, and is composed of measures of mental alertness (0-4), motor function (0-4), and appetite (0-4).

Furthermore, on a daily basis the animals were also taken from their holding areas and allowed to explore a larger environment in a specially designed room. Animals were videotaped and scored in a blinded manner (10=normal score, 0=dead) by a neuroscientist.

2.9. Statistical methods

The animals were randomized to alpha-stat or pH-stat management by a member of the Biomathematics Department. The group assignment was revealed just prior to the institution of CPB.

Hemodynamic and intraoperative variables were compared at baseline using t-tests between groups. Later comparisons were based on absolute values or on changes from baseline if deemed more relevant. For data that were consistent with the requisite assumptions, groups were compared by ANOVA separately for periods of cooling, SCP, rewarming and recovery post-CPB. Tests at individual time points were conducted if the corresponding average difference or time by group interaction was statistically significant. Other variables were compared by Wilcoxon tests at each time point (SAS Institute, Cary, NC).

3. Results

3.1. Comparability of experimental groups

The preoperative animal weights in the two groups were comparable (Group \( \alpha \) 26.0±1.6 kg and Group pH 27.2±3.0 kg). Baseline values of all variables subsequently presented were tested between groups and found to be comparable. All animals were examined daily by a veterinary team and found to be in normal health prior to surgery.

3.2. Hemodynamic and CPB-related data

Brain temperature at baseline was in close agreement between the two groups. However, both during cooling and rewarming (\( P=0.02 \)), more rapid temperature change was observed in the pH-stat animals, possibly because of the vasodilatation associated with this technique (see Table 1). Mean arterial pressure (MAP) was almost identical between the groups, although during cardiopulmonary bypass and SCP higher flow rates were necessary to achieve these target pressures in the pH-stat group (Table 1).

The intended pH targets were achieved. All blood gases were measured at 37 °C. In those animals randomized to alpha-stat, the pH was kept at 7.40. In those randomized to
### Table 1

Hemodynamic and CPB-related data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>After 15 min cooling</th>
<th>After 30 min cooling</th>
<th>After 30 min SCP</th>
<th>60 min SCP</th>
<th>90 min SCP</th>
<th>15 min rewarm</th>
<th>30 min rewarm</th>
<th>15 min post-CPB</th>
<th>2 h post-CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-stat</td>
<td>35.8 ± 0.2</td>
<td>24.7 ± 0.5</td>
<td>20.0 ± 0.0</td>
<td>19.8 ± 0.1</td>
<td>19.8 ± 0.0</td>
<td>19.8 ± 0.0</td>
<td>24.1 ± 0.4</td>
<td>30.6 ± 0.8</td>
<td>35.2 ± 0.2</td>
<td>36.0 ± 0.4</td>
</tr>
<tr>
<td>pH-stat</td>
<td>36.2 ± 0.3</td>
<td>23.8 ± 0.6</td>
<td>20.0 ± 0.0</td>
<td>19.8 ± 0.0</td>
<td>19.8 ± 0.0</td>
<td>19.8 ± 0.0</td>
<td>26.2 ± 0.6</td>
<td>32.8 ± 0.8</td>
<td>35.5 ± 0.1</td>
<td>36.1 ± 0.3</td>
</tr>
<tr>
<td>MAP (mmHg ± SE)</td>
<td></td>
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<tr>
<td>Alpha-stat</td>
<td>62 ± 6</td>
<td>46 ± 0</td>
<td>46 ± 1</td>
<td>50 ± 0</td>
<td>50 ± 0</td>
<td>50 ± 0</td>
<td>46 ± 1</td>
<td>49 ± 2</td>
<td>55 ± 2</td>
<td>51 ± 2</td>
</tr>
<tr>
<td>pH-stat</td>
<td>62 ± 6</td>
<td>46 ± 0</td>
<td>46 ± 1</td>
<td>50 ± 0</td>
<td>50 ± 0</td>
<td>50 ± 0</td>
<td>45 ± 1</td>
<td>49 ± 2</td>
<td>53 ± 1</td>
<td>52 ± 1</td>
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<tr>
<td>pH (at 37°C ± SE)</td>
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</tr>
<tr>
<td>Alpha-stat</td>
<td>7.45 ± 0.01</td>
<td>7.41 ± 0.01</td>
<td>7.42 ± 0.01</td>
<td>7.41 ± 0.01</td>
<td>7.40 ± 0.00</td>
<td>7.40 ± 0.00</td>
<td>7.39 ± 0.01</td>
<td>7.42 ± 0.01</td>
<td>7.39 ± 0.00</td>
<td>7.42 ± 0.02</td>
</tr>
<tr>
<td>pH-stat</td>
<td>7.45 ± 0.01</td>
<td>7.23 ± 0.01</td>
<td>7.16 ± 0.00</td>
<td>7.15 ± 0.00</td>
<td>7.15 ± 0.00</td>
<td>7.15 ± 0.00</td>
<td>7.19 ± 0.01</td>
<td>7.32 ± 0.02</td>
<td>7.35 ± 0.02</td>
<td>7.39 ± 0.02</td>
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<tr>
<td>pCO2 (at 37°C ± SE)</td>
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<tr>
<td>Alpha-stat</td>
<td>41.5 ± 0.7</td>
<td>47.1 ± 2.0</td>
<td>46.8 ± 1.7</td>
<td>42.5 ± 1.2</td>
<td>39.2 ± 1.1</td>
<td>38.1 ± 1.4</td>
<td>36.6 ± 0.7</td>
<td>38.4 ± 0.5</td>
<td>41.6 ± 1.3</td>
<td>39.9 ± 1.2</td>
</tr>
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<td>pH-stat</td>
<td>42.3 ± 1.5</td>
<td>76.5 ± 2.9</td>
<td>89.9 ± 2.4</td>
<td>88.2 ± 1.9</td>
<td>83.5 ± 2.0</td>
<td>78.6 ± 1.7</td>
<td>72.9 ± 3.0</td>
<td>42.5 ± 1.8</td>
<td>43.6 ± 1.8</td>
<td>42.4 ± 2.3</td>
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<tr>
<td>Art. O2 sat. (% ± SE)</td>
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<tr>
<td>Alpha-stat</td>
<td>99.8 ± 0.0</td>
<td>99.8 ± 0.0</td>
<td>99.8 ± 0.0</td>
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<td>99.8 ± 0.0</td>
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<td>99.7 ± 0.0</td>
<td>99.7 ± 0.0</td>
<td>99.7 ± 0.0</td>
<td>99.7 ± 0.0</td>
</tr>
<tr>
<td>pH-stat</td>
<td>99.8 ± 0.0</td>
<td>99.7 ± 0.0</td>
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<td>99.7 ± 0.0</td>
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<td>99.7 ± 0.0</td>
<td>99.5 ± 0.0</td>
<td>99.5 ± 0.0</td>
<td>99.7 ± 0.0</td>
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<tr>
<td>Hematocrit (% ± SE)</td>
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<tr>
<td>Alpha-stat</td>
<td>29 ± 1</td>
<td>23 ± 0</td>
<td>24 ± 1</td>
<td>24 ± 1</td>
<td>24 ± 1</td>
<td>23 ± 1</td>
<td>23 ± 1</td>
<td>27 ± 1</td>
<td>29 ± 1</td>
<td>35 ± 1</td>
</tr>
<tr>
<td>pH-stat</td>
<td>29 ± 1</td>
<td>23 ± 0</td>
<td>24 ± 1</td>
<td>24 ± 1</td>
<td>24 ± 1</td>
<td>22 ± 1</td>
<td>22 ± 1</td>
<td>25 ± 1</td>
<td>26 ± 1</td>
<td>30 ± 1</td>
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<tr>
<td>CPB flow (ml/min ± SE)</td>
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<td></td>
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</tr>
<tr>
<td>Alpha-stat</td>
<td>No flow</td>
<td>1878 ± 118</td>
<td>1770 ± 136</td>
<td>391 ± 70</td>
<td>391 ± 62</td>
<td>416 ± 74</td>
<td>1758 ± 169</td>
<td>1939 ± 122</td>
<td>No flow</td>
<td>No flow</td>
</tr>
<tr>
<td>pH-stat</td>
<td>No flow</td>
<td>2044 ± 65</td>
<td>2013 ± 217</td>
<td>970 ± 263</td>
<td>834 ± 253</td>
<td>802 ± 228</td>
<td>2127 ± 132</td>
<td>2221 ± 107</td>
<td>No flow</td>
<td>No flow</td>
</tr>
</tbody>
</table>

All values are shown as mean ± SE. Temperature values shown are those recorded from the brain parenchyma. MAP denotes mean arterial pressure. pH and pCO2 values are for arterial blood, likewise Art. O2 sat. is the arterial oxygen saturation.

pH-stat, the gases were temperature-corrected; hence, a target of 7.15 was adopted for gases taken whilst the in vivo temperature was 20°C. The mean pCO2 values reflected the group allocation.

Hematocrit values were in close agreement at baseline. Thereafter, the values were marginally higher in the alpha-stat group during SCP (P = 0.35), and significantly higher during rewarming (P = 0.03) and after the end of CPB (0.0015). This probably reflects the addition of slightly higher volumes of saline to the venous reservoir to sustain the high flow rates required with the pH-stat strategy (Table 1).

#### 3.3. Intracranial and superior sagittal sinus (SSSP) pressures

Close attention was paid to the assessment of ICP, which has previously been shown to correlate with postoperative behavioral outcome [8]. There were no important differences in ICP between the groups, as values remained within a safe range throughout. However, during cooling the ICP was significantly higher in the pH-stat group (P = 0.04), and there was a trend towards higher values in the α-stat group immediately after discontinuation of CPB (Fig. 1). The SSSP closely correlated with ICP (typically SSSP was 1-2 mmHg higher).

#### 3.4. Cerebral blood flow

The mean values for CBF at the different time points for the two groups are shown in Fig. 2. With alpha-stat management, there was a fall in CBF during cooling, with a further fall during SCP, consistent with data from earlier experiments utilizing alpha-stat cooling and SCP [9]. During rewarming, the CBF increased to just above baseline and remained fairly stable. In sharp contrast, there was no fall in CBF with cooling undertaken using pH-stat principles. Furthermore, once SCP was initiated, the CBF increased...
However, CMRO\(_2\) was lower during cooling and SCP with the in comparison with baseline values in both groups (Fig. 3).

During cooling and SCP, CMRO\(_2\) was significantly reduced in comparison with baseline values in both groups (Fig. 3). However, CMRO\(_2\) was lower during cooling and SCP with the alpha-stat strategy than with pH-stat, significantly so after 30 min of SCP (Wilcoxon test, \(P = 0.04\)). At the end of cooling, and after 90 min of SCP, the differences were close to significance (\(P = 0.06\) and 0.10, respectively). In the recovery phase, the CMRO\(_2\) values returned to marginally above baseline in both groups, with no significant between-group differences.

### 3.5. Cerebral oxygen extraction and metabolic rate for oxygen

Cerebral oxygen extraction was calculated from the difference between the oxygen content of the arterial and superior sagittal sinus blood. The mean values at the different time points for the two groups are shown in Table 2. The results show lower oxygen extractions at the end of cooling and during SCP than at baseline. This is presumably due to a variable degree of loss of autoregulation with increasing hypothermia. The drop in oxygen extraction in the pH-stat group is greater than in the alpha-stat group, reflecting the more complete disruption of autoregulation in this group, resulting in greater levels of luxury perfusion.

During cooling and SCP, CMRO\(_2\) was significantly reduced in comparison with baseline values in both groups (Fig. 3). However, CMRO\(_2\) was lower during cooling and SCP with the alpha-stat strategy than with pH-stat, significantly so after 30 min of SCP (Wilcoxon test, \(P = 0.04\)). At the end of cooling, and after 90 min of SCP, the differences were close to significance (\(P = 0.06\) and 0.10, respectively). In the recovery phase, the CMRO\(_2\) values returned to marginally above baseline in both groups, with no significant between-group differences.

### 3.6. Visual evoked potentials

The early recovery scores for each group are shown in Fig. 4. The results show somewhat superior scores in the alpha-stat group, coming close to statistical significance at the 3-h time point (\(P = 0.08\)).

### 3.7. Early recovery scores and neurobehavioral assessment

The early recovery scores for each group are shown in Fig. 4. The results show somewhat superior scores in the alpha-stat group, coming close to statistical significance at the 3-h time point (\(P = 0.08\)).

During the 7-day observation period, the results of both neurobehavioral assessments, namely the 12-point score and the videotaped analysis, showed similar patterns of recovery in both groups (Fig. 5a and b). There were no significant differences between the groups in the results of either method of assessment.

### 4. Discussion

In nature, both alpha-stat and pH-stat responses to hypothermia are seen. Poikilotherms allow their blood pH...
to rise as they cool, establishing a state of respiratory alkalosis that approximates alpha-stat management. Conversely, hibernators increase the total carbon dioxide content of the blood so that their pH remains at 7.40 when corrected to their body temperature, thus following pH-stat principles. For humans, hypothermia is not a natural state, and so it is unclear which of these approaches is superior, as neither can be viewed as physiological.

Alpha-stat management is based on the notion that the pK of the histidine imidazole group changes with temperature in a manner nearly identical to physiologic blood buffers. Hence, the ionization state $\alpha$ of this group stays the same, irrespective of temperature. Given that this group’s ionization state is a key determinant of intracellular protein function, advocates of alpha-stat management contend that this strategy promotes normal protein charge states and function, even at low temperatures.

The pH-stat approach increases the total carbon dioxide content of the blood as the temperature falls in order to maintain fixed temperature-corrected pH values. The optimal pH of most enzymatic reactions does vary with hypothermia, mostly in accordance with alpha-stat predictions. Hence, the relative acidemia of pH-stat would be expected to lower those enzymatic reaction rates. Whether this is beneficial in reducing energy consumption, or harmful, by impairing key cellular homeostatic mechanisms, is unclear. Furthermore, when conditions of circulatory arrest (DHCA) or abnormal perfusion states (e.g., CPB or SCP) are added to the scenario, it becomes even more unclear which is theoretically superior in terms of preserving cellular function, and whether a higher or lower metabolic rate, or cerebral blood flow, best achieves the goal of optimal cerebral protection.

Experimental work has largely focused on the influence of pH management strategies on the conduct of DHCA. They have shown better tissue oxygenation with pH-stat strategy, both before and after a period of DHCA [2,10,11], probably due to higher levels of CBF and superior cooling [11]. Moreover, pH-stat strategy has shown superior functional and histological outcomes following DHCA in piglets [10,12]. Circulatory arrest is a potent cause of neurological injury in both experimental and clinical studies [13], and therefore any strategy producing improved cooling should result in better cerebral protection.

In the absence of a period of circulatory arrest, there may be more important considerations than the rapidity of cooling and rewarming. These may favor the use of alpha-stat management, which most clinicians prefer when employing mildly hypothermic cardiopulmonary bypass. Provided that sufficient flow is being maintained to sustain an adequate level of cerebral metabolism, it can be argued that the loss of cerebral autoregulation, which occurs with pH-stat management, exposes the brain to an unnecessarily large potential embolic load. The increased flow may result in elevation of ICP—seen transiently during cooling in this study—which tends to correlate with less favorable cerebral outcome.

Most clinical studies have also focused on pH management for deep hypothermic circulatory arrest (DHCA) although some have concerned moderate hypothermic cardiopulmonary bypass. In pediatric populations undergoing DHCA, it appears that a pH-stat approach may be beneficial, resulting in lower morbidity and less systemic-pulmonary collateral flow [14]. However, whilst pH-stat facilitates earlier perioperative return of electroencephalographic activity [15], developmental and neurological outcomes revealed no significant differences attributable to pH management strategy [16]. In adults, most work has focused on hypothermic cardiopulmonary bypass and has shown either no impact [17] or improved cerebral autoregulation and neurological outcome with alpha-stat management [18,19].

There has been less focus on pH management for DHCA in adults, and very little on its impact on SCP. Clearly, in
adults, the mechanisms of intraoperative cerebral injury are different from those in children, with a much greater potential for embolic damage. In the absence of differences in outcome, it is not clear whether a higher metabolic rate during SCP is beneficial, especially if it is associated with luxury perfusion. The results of the present study show that both CMRO₂ and CBF are lower with alpha-stat than with pH-stat management. This implies better preservation of cerebral autoregulation with alpha-stat management, and should result in the delivery of fewer emboli to the brain. This may be especially relevant to aneurysm surgery, because patients often have extensive atherosclerosis. There is no evidence from this study that alpha-stat results in cerebral hyperperfusion during SCP, in that the cerebral oxygen extraction remains far below baseline in both groups during the SCP period, and there is prompt recovery to baseline metabolism after rewarming. The lower CMRO₂ associated with alpha-stat management is conserved from the end of cooling throughout the SCP period; it is possible that this more profound metabolic suppression leads to enhanced cerebral protection. However, since our assessments of clinical cerebral outcomes are similar in both groups, we cannot convincingly assert that either strategy is superior. It could be argued that the higher metabolic rate seen in the pH-stat animals during SCP is beneficial, and that the slight increase in post-bypass CMRO₂ in the alpha-stat group represents payback of an oxygen debt to cerebral tissues inadequately perfused during SCP. However, such borderline statistical findings should be interpreted with caution, because, on the one hand, larger sample sizes might have produced statistically significant differences, and on the other hand, they do not reflect any corrections for multiple testing.

Previous clinical [20] and experimental [21] studies of hypothermic cardiopulmonary bypass have reported similar CMRO₂ suppression with alpha-stat and pH-stat techniques. Earlier observations in our pig model using alpha-stat management have shown that there is a higher rate of cerebral metabolism at the same temperature during SCP as compared with CPB. Thus, there may be some property unique to SCP that leads to enhanced metabolic suppression with alpha-stat as compared with pH-stat management. Perhaps, communication between the brachiocephalic vessels and the systemic circulation is enhanced under hypercarbic circumstances, and metabolites from the ischemic lower body drive the cerebral metabolic rate higher during SCP with pH-stat management than during SCP with alpha-stat management. The only experimental SCP study looking at pH management was undertaken in dogs [22]. It was shown that pH-stat reduces biochemical markers of ischemic injury if an old cerebral infarct is present; in normal animals these markers were similar between alpha and pH-stat strategies. Furthermore, this study did not include functional neurobehavioral assessment and so the impact of these biochemical differences is hard to evaluate.

It is clear from the results of the tests of neurobehavioral outcome that neither group sustained a lasting cerebral insult, since they recovered promptly in a comparable fashion. Given the equivalency of neurobehavioral outcome and the possible disadvantage of luxury perfusion in patients at risk of cerebral embolization, the present study supports the ongoing use of alpha-stat acid-base management in clinical aortic surgery involving SCP. Further studies will be necessary to characterize the differences in cerebral metabolism which occur with the two hypothemic strategies, and to examine their possible impact on long-term subtle changes in post-hypothermic cerebral function.

References

Appendix A. Conference discussion

**Dr C. Hagl (Hannover, Germany):** I wonder if you have any data on the intracranial pressure? I am sure you know that we have shown in the past that the ICP was a very good marker to detect cerebral injury. In my opinion it would be interesting,—especially in your setup—since overperfusion may be an issue in your experimental groups.

**Dr Halstead:** Your work previously has shown the importance of intracranial pressure in determining the outcome of this very model here that we have at Mount Sinai.

I think there are two points to mention, really. Firstly, there was a drop in intracranial pressure during cooling with alpha-stat management and an increase with pH-stat management. That’s probably as a result of the higher flow rates and relatively greater levels of volume addition to achieve those higher flow rates associated with that, i.e. pH-stat technique. So we did see this statistically significant change at baseline.

But I think the second point to make is that clearly the ICP remained within very reasonable ranges throughout the whole of the time course of the experiment in the vast majority of our animals, so I don’t think we actually encroached upon an area where we would actually be concerned at the level of the ICP per se.

**Dr A. Wechsler (Philadelphia, Pennsylvania, USA):** I’m sort of impressed that perhaps there was statistical significance in the differences in cerebral oxygen consumption during the hypothermic interval, but it doesn’t seem like there’s much of a biologic effect in terms of—there’s pretty close.

**Dr Halstead:** Yes, that’s absolutely right. I think that there are two potential explanations. One is that this difference in CMRO$_2$ just isn’t important. I would argue that so much of the basis of aortic surgery is the use of hypothermia, and the very central tenet of the use of hypothermia is metabolic suppression, so I wouldn’t run against this being at least an interesting finding.

So I would, therefore, favor the second explanation, which is that our neurobehavioural outcomes just aren’t detecting what difference there is that’s there. Clearly, it would be great if we could subject these animals to the kind of battery of neuropsychologic assessments that one can humans, but, you know, they just don’t talk too much on day one.