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Brain preservation with selective cerebral perfusion for operations requiring circulatory arrest: protection at 25 °C is similar to 18 °C with shorter operating times

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Abstract

Background: Hypothermic circulatory arrest (HCA) is employed for aortic arch and other complex operations, often with selective cerebral perfusion (SCP). Our previous work has demonstrated real-time evidence of improved brain protection using SCP at 18 °C. The purpose of this study was to evaluate the utility of SCP at warmer temperatures (25 °C) and its impact on operating times. Methods: Piglets undergoing cardiopulmonary bypass (CPB) and 60 min of HCA were assigned to three groups: 18 °C without SCP, 18 °C with SCP and 25 °C with SCP (n = 8 animals per group). CPB flows were 100 ml kg⁻¹ min⁻¹ using pH-stat management. SCP flows were 10 ml kg⁻¹ min⁻¹ via the innominate artery. Cerebral oxygenation was monitored using NIRS (near-infrared spectroscopy). A microdialysis probe placed into the cerebral cortex had samples for determination of substrates glucose (p < 0.05), lactate (p < 0.001) and pyruvate (p < 0.001) which to operate and presumed adequate neurological protection. Though most children appear to do well after these operations from a gross neurological perspective, with long-term follow-up, a significant incidence of cognitive, motor and behavioural deficits has become evident [1–3]. CPB and HCA are well-known contributors to post-operative morbidity and mortality. CPB has been shown to induce a significant inflammatory response, coagulopathies and a multitude of other systemic sequelae that contribute to end-organ dysfunction [4,5]. HCA has been shown to have deleterious effects on both the central nervous system and other end-organ systems through inducing endothelial dysfunction, apoptosis and necrosis [6,7]. In particular, HCA has been demonstrated to cause injury in selective regions of the brain, with neurons in the sensory and motor neocortex as well as the hippocampus displaying evidence of acute injury [7]. In order to mitigate the impact surgical intervention has on the central nervous system, a number of different
strategies to improve neuroprotection are now being put forward. The use of selective cerebral perfusion (SCP) during HCA has become one of the more commonly employed strategies to try to minimise neurological injury [8]. The specific strategies used for SCP vary significantly between institutions, with strategies supported by anecdotal or relatively insensitive outcome measures rather than real-time data at a cellular level.

Moderate hypothermia for circulatory arrest in combination with SCP is a technique our group and others have studied in order to reduce postoperative neurological and end-organ sequelae [9,10]. By using more tepid temperatures, we hypothesise there will be shortened operating times, resulting in less inflammation from exposure to CPB and less ischaemia/reperfusion injury secondary to HCA, while still providing adequate neurological and end-organ protection. A precedent for this approach stems from the extended end-to-end repair of coarctations in neonates and other children. These repairs are performed routinely via thoracotomy at near-normothermia without the use of CPB [11], perfusing the brain through the innominate artery only for periods of up to 20 min. This approach is well tolerated and without clinically significant neurological or end-organ injury [11].

The aim of this study is to evaluate the neurological and systemic end-organ protection afforded when performing HCA at 25 °C with SCP, as compared to the more traditional approaches of HCA at 18 °C ± SCP, using real-time data obtained at a cellular level. Employing both traditional near-infrared spectroscopy (NIRS) monitoring and a novel application of cerebral microdialysis, we are able to more accurately define the efficacy of these surgical approaches. Our previous work has demonstrated that HCA at 18 °C with SCP provides superior neuroprotection to traditional HCA without SCP [12]. Our hypothesis was that HCA at 25 °C with SCP would provide equal neurological and end-organ protection to that of HCA at 18 °C with SCP, while significantly decreasing total operating times.

2. Materials and methods

All procedures were carried out according to a protocol approved by the Wilford Hall Medical Center Institutional Animal Care and Use Committee. Animals were maintained in an American Association for Accreditation Laboratory Animal-accredited facility and received care in compliance with the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences and published by the National Institutes of Health.

2.1. Experimental design

Twenty-seven 4–5-week-old, 8–10-kg, male Yorkshire piglets were anaesthetised, intubated, placed on mechanical ventilation and randomised to: (1) HCA at 18 °C without SCP, (2) HCA at 18 °C with SCP or (3) HCA at 25 °C with SCP (n = 9 per study group). After a 60-min circulatory arrest period, animals were warmed, weaned from CPB and recovered for 4 h. Each animal received standard pre-, intra- and postoperative haemodynamic monitoring, as well as multimodal neurological monitoring, from the time of intubation until sacrifice.

2.2. Intracerebral monitoring and microdialysis

Following initial central-line placement and prior to median sternotomy, animals were temporarily placed prone for placement of intracerebral catheters. One Burr hole, 0.7 mm in diameter, was drilled in the skull just off midline to access the right posterior frontal lobe. In this Burr hole, a microdialysis catheter (CMA-70, CMA Microdialysis, Stockholm, Sweden) was inserted into the superficial cerebral cortex following puncture of the dura. A physiological sodium solution was perfused continuously through the catheter at 1.0 μl min⁻¹. After a 60-min equilibration period following insertion, samples were collected every 15 min for subsequent analysis of metabolites (CMA-600, CMA Microdialysis). NIRS was used to measure regional oxygen saturation (rSO₂ index) by placing a probe midline over the piglet’s frontal cortex (Somanetics®, Troy, MI, USA).

2.3. Surgical and CPB protocol

Anaesthesia and paralysis were provided through inhaled isoflurane (0.5–1.5%), continuous intravenous fentanyl (25 μg kg⁻¹ h⁻¹) and continuous pancuronium (0.2 mg kg⁻¹ h⁻¹). Both the femoral artery and vein were cannulated for measurement of blood and central venous pressures as well as infusion of medications and fluids. The right axillary artery was cannulated for continuous blood pressure monitoring. Noninvasive continuous monitoring included rectal and nasopharyngeal temperature probes, electrocardiogram and pulse oximetry. All animals were ventilated with a standard protocol using 0.50 FiO₂ and tidal volumes adjusted to maintain pCO₂ values between 35 mmHg and 45 mmHg.

The protocols and surgical techniques used mimic those commonly employed in the clinical operating room. After systemic heparinisation (400 IU kg⁻¹), the ascending aorta was cannulated with a 12F, wire-reinforced, flexible paediatric cannula (Medtronic Bio-Medicus®, Minneapolis, MN, USA) and the right atrium was cannulated with an 18F malleable venous cannula (Medtronic, Minneapolis, MN, USA). Non-pulsatile CPB was then instituted at a flow rate of 100 ml kg⁻¹ min⁻¹. The CPB circuit consisted of a roller pump, membrane oxygenator (SX-10 with X-Coating, Terumo, Ann Arbor, MI, USA) and sterile Terumo X-Coated 1/4-inch tubing with Capiox AF02 Arterial Filter and HC05 Hemoconcentrator. The circuit was primed with blood previously harvested from a donor pig and ultrafiltrated with a crystalloid prime solution (0.9% normal saline) to maintain the CPB blood prime haematocrit value greater than 25%. Electrolytes in the prime were analysed and normalised as indicated, and all in-line monitoring was calibrated.

Once on CPB, animals were randomised and cooled, using an 8 °C temperature gradient, to a target nasopharyngeal temperature of either 18 °C or 25 °C. Prior to the induction of circulatory arrest, the ascending aorta was clamped, followed by instillation of cold blood cardioplegic solution into the aortic root to induce electromechanical myocardial arrest. A 10F flexible cannula was passed via the left atrial appendage into the left atrium to maintain adequate ventricular decompression. Animals assigned to receive SCP then received perfusion at a flow rate of 10 ml kg⁻¹ h⁻¹ by advancing the aortic cannula into the innominate artery and snaring it. The
other arch vessel was snared to minimise steal, as in the clinical operating room.

Cerebral perfusion pressure was monitored via the axillary artery and targeted to 35—40 mmHg. Following completion of the 60-min circulatory arrest period, the snares on the arch vessels were released and the aortic cross-clamp was removed. The aortic cannula was then redirected from the innominate artery to the ascending aorta and full CPB was re-established. Warming was undertaken using a temperature gradient of no more than 10°C until a nasopharyngeal temperature of 36°C was reached. While weaning from CPB, low-dose norepinephrine (0.01—0.03 mcg kg⁻¹ min⁻¹) and volume administration were routinely employed to ensure haemodynamic stability. Once the piglet was weaned from CPB, modified ultrafiltration was employed to a filtrate volume of 500 ml and a target haematocrit of 35%. Protamine was given, and the CPB cannulae were removed. A right atrial line was placed to provide further central access.

A pH-stat acid–base management strategy was used throughout the procedure. Perfusion parameters continuously monitored during CPB included pump flow rate, mean arterial pressure, temperature, sweep gas flow and FiO₂, and arterial pH, PaO₂, PaCO₂, SVO₂ and haematocrit (via CDI 500™, Terumo). Activated clotting times were assessed at a minimum of every 30 min using the I-STAT® (Abbott Laboratories Abbott Park, IL, USA).

2.4. Statistical analysis

One animal in each study group died prior to completion of the study protocol and therefore were not included in the analysis, leaving a total of n = 8 per group. All data are presented as mean ± SD. Two-way analysis of variance (ANOVA) with correction for repeated measures was used to compare serial data using SPSS® Software (Version 12.0, Chicago, IL, USA). Reported p values include p group, assessing level of difference between groups; p time × group, assessing group–time interaction; and p time, assessing change over time of measured variables. Data between study groups were analysed using unpaired Student’s t-test or Mann–Whitney rank-sum test as appropriate using Sigma Stat® Software (Version 3.5, Richmond, CA, USA). For all data, p ≤ 0.05 was considered significant.

3. Results

3.1. Cerebral oxygenation

As demonstrated by NIRS, cerebral oxygenation was maintained at baseline levels throughout the procedure, including circulatory arrest, when SCP was employed at either 18°C or 25°C (Fig. 1). By comparison, significant desaturation was seen during circulatory arrest in animals undergoing HCA at 18°C without SCP (p < 0.01). This cerebral desaturation persisted into recovery.

3.2. Cerebral microdialysis data

Markers of cerebral ischaemia and injury were significantly elevated when HCA at 18°C without SCP was employed (Table 1). Lactate (p < 0.01) and glycerol (p < 0.01) concentrations were significantly elevated without SCP, and the lactate/pyruvate ratio (p < 0.001) was particularly increased. Cerebral energy substrates glucose (p < 0.001) and pyruvate (p < 0.001) were profoundly depleted without SCP (Table 1). Most of these derangements persisted into recovery. For the 18°C and 25°C groups receiving SCP, cerebral metabolites were preserved relative to baseline (Table 1). Figs. 2—4 further demonstrate the impact on cerebral metabolism of HCA at 18°C in the absence of SCP. Brain glucose values were markedly diminished following circulatory arrest, taking over 2 h to return to baseline (Fig. 2). Both cerebral glycerol and the lactate/pyruvate ratio, acute markers of ongoing cellular injury, were markedly increased following arrest and did not return to baseline 4 h following separation from CPB (Figs. 3 and 4).

![Graph of NIRS oxygenation data](image1)

**Fig. 1.** NIRS oxygenation data (rSO₂ index) in each group over course of experimental protocol, c p < 0.05 versus preCPB; preCPB = baseline pre-surgery, End CA = end of 60 min circulatory arrest period, post 2 Hr = 2 h after separation from CPB, post 4 Hr = 4 h after separation from CPB.

![Graph of cerebral microdialysis glucose](image2)

**Fig. 2.** Cerebral microdialysis glucose (mmol l⁻¹) measured at selected study time points, d p < 0.001 and b p < 0.05 versus 18°C and 25°C with SCP; preCPB = baseline pre-surgery, End CA = end of 60 min circulatory arrest period, post 2 Hr = 2 h after separation from CPB, post 4 Hr = 4 h after separation from CPB.
3.3. Operating times

Mean total operating time, defined as the time beginning with initiation of CPB and ending with separation from CPB, was 114.0 min for animals in the group undergoing HCA at 25 °C with SCP (Fig. 5). This is compared to operating times of 162.5 min and 155.7 min for animals undergoing HCA at 18 °C with and without SCP, respectively (p < 0.02).

When analysing cooling times to circulatory arrest and warming times to normothermia, times were significantly shorter with a target temperature of 25 °C versus 18 °C (Fig. 6).

3.4. Serum lactate

No statistically significant differences in serum lactate concentrations were noted between the study groups (Fig. 7). All groups demonstrated mild increases in serum lactate after circulatory arrest, with near normalisation of values by the end of the study. Serum lactates for the 25 °C with SCP and 18 °C without SCP groups were slightly higher compared to baseline (Fig. 7, p < 0.05).

Table 1
Cerebral microdialysis data.

<table>
<thead>
<tr>
<th></th>
<th>PreCPB</th>
<th>End CA</th>
<th>Recovery 2 h</th>
<th>Recovery 4 h</th>
<th>p group</th>
<th>p time × gp</th>
<th>p time</th>
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<tbody>
<tr>
<td>Lactate (mmol L⁻¹)</td>
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<tr>
<td>18C no SCP</td>
<td>1.19 (1.04—1.33)</td>
<td>3.61 (3.07—4.16)</td>
<td>2.33 (1.93—2.72)</td>
<td>2.67 (1.55—3.79)</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>18C SCP</td>
<td>1.24 (1.15—1.37)</td>
<td>0.97 (0.79—1.14)</td>
<td>1.45 (1.11—1.81)</td>
<td>1.36 (0.65—2.08)</td>
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<tr>
<td>25C SCP</td>
<td>1.23 (1.08—1.39)</td>
<td>1.26 (1.11—1.40)</td>
<td>1.30 (1.01—1.59)</td>
<td>1.76 (1.28—2.24)</td>
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<tr>
<td>Glycerol (mmol L⁻¹)</td>
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<tr>
<td>18C no SCP</td>
<td>12.9 (10.3—15.5)</td>
<td>40.4 (26.9—53.9)</td>
<td>30.3 (26.9—33.8)</td>
<td>24.7 (18.8—30.6)</td>
<td>0.000</td>
<td>0.000</td>
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<tr>
<td>18C SCP</td>
<td>11.6 (9.8—13.4)</td>
<td>10.4 (9.4—11.4)</td>
<td>14.2 (12.6—15.7)</td>
<td>13.3 (10.0—16.7)</td>
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<tr>
<td>25C SCP</td>
<td>12.4 (11.2—13.6)</td>
<td>13.4 (11.7—15.2)</td>
<td>14.6 (13.6—15.5)</td>
<td>13.3 (11.9—14.7)</td>
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<td>Glucose (mmol L⁻¹)</td>
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<tr>
<td>18C no SCP</td>
<td>1.16 (0.97—1.35)</td>
<td>0.11 (0.05—0.18)</td>
<td>0.75 (0.61—0.89)</td>
<td>1.27 (1.13—1.42)</td>
<td>0.000</td>
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<tr>
<td>18C SCP</td>
<td>1.29 (1.11—1.47)</td>
<td>1.24 (1.12—1.37)</td>
<td>1.55 (1.36—1.76)</td>
<td>1.32 (1.20—1.45)</td>
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<tr>
<td>25C SCP</td>
<td>1.22 (1.30—1.44)</td>
<td>1.27 (1.10—1.42)</td>
<td>1.53 (1.45—1.62)</td>
<td>1.25 (1.13—1.37)</td>
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<td>Pyruvate (µmol L⁻¹)</td>
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<tr>
<td>18C no SCP</td>
<td>124 (88.3—116)</td>
<td>17.6 (13.0—22.3)</td>
<td>122 (98.1—146)</td>
<td>141 (113—168)</td>
<td>0.000</td>
<td>0.015</td>
<td>0.000</td>
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<tr>
<td>18C SCP</td>
<td>114 (76.4—151)</td>
<td>74.4 (64.3—84.4)</td>
<td>119 (101—138)</td>
<td>118 (102—134)</td>
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<tr>
<td>25C SCP</td>
<td>102 (86.4—116)</td>
<td>65.6 (51.0—80.3)</td>
<td>105 (92.1—117)</td>
<td>107 (92.9—121)</td>
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<td>L/P ratio</td>
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<tr>
<td>18C no SCP</td>
<td>10.3 (7.86—12.8)</td>
<td>205 (168—242)</td>
<td>20.4 (12.3—28.5)</td>
<td>19.7 (14.0—25.4)</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>18C SCP</td>
<td>11.4 (9.11—13.7)</td>
<td>20.3 (15.8—24.7)</td>
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<td>12.4 (7.86—12.8)</td>
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</table>

Temperatures reflect systemic cooling and the temperature of the selective cerebral perfusate. 18C no SCP = hypothermic circulatory arrest at 18 °C with no selective cerebral perfusion, 18C SCP = selective cerebral perfusion at 18 °C, 25C SCP = selective cerebral perfusion at 25 °C. p group = level of difference between groups, p time × gp = difference between groups as a function of time, p time = change over time.

a Analysis includes data from entire study period (only selected time points shown in table), values represent mean and 95% confidence intervals.

b p < 0.01.
c p < 0.05.
d p < 0.001.
In this study, NIRS and cerebral microdialysis demonstrated that SCP provides similar neuroprotection during HCA at 18°C and 25°C. Traditional HCA at 18°C without SCP is associated with marked cerebral hypoxia and ischaemia. Real-time, multimodal neuromonitoring demonstrated that HCA at 25°C with SCP did not exacerbate cerebral nor systemic ischaemia, and resulted in a more favourable cerebral metabolic profile when compared to HCA at 18°C without SCP. Additionally, cooling to only 25°C significantly shortened operating times.

When HCA without SCP is used, cerebral desaturation on NIRS monitoring was observed during the circulatory arrest period, as has been described by others [13,14]. The relationships among hypoxia, HCA and neuronal necrosis/apoptosis have been well documented [15,16]. Prior work has shown that neuronal apoptosis and histological ischaemic injury are lessened when HCA at 18°C with SCP is used, in part due to maintenance of cortical oxygen content [17,18]. Hagl and co-workers nicely demonstrated that when HCA at 18°C with SCP is used, better neurophysiological recovery was achieved when compared to HCA without SCP. In their study, animals receiving SCP showed quicker electroencephalogram and cortical somatosensory evoked potential recovery and lower intracranial pressures. This finding was believed to be related in part to prevention of hypoxia [19].

Our observation that HCA at 25°C with SCP prevents cerebral desaturation as effectively as HCA at 18°C with SCP suggests that more tepid hypothermia is successful at reducing neuronal hypoxic—ischaemic injury and improving neurological results.

Cerebral microdialysis metabolite concentrations have been shown to have a strong correlation with both short-term and long-term neurological outcomes, making this a powerful tool to assess the impact that various surgical and cerebral perfusion strategies have on neuroprotection [20–22]. In our study, animals undergoing HCA at 18°C without SCP had significant elevations in lactate and glycerol, as well as the lactate/pyruvate ratio. Lactate is a well-recognised marker of tissue ischaemia. Elevated glycerol, a marker of cellular injury following ischaemia due to phospholipase-activated degradation of cell membranes, has been demonstrated to correlate with poor neurological outcomes [22]. The lactate/pyruvate ratio, in particular, has been shown to have a strong association with neurological outcomes [20,21]. Specifically, a ratio greater than 20—25 has been shown to have a high level of correlation with extremely poor outcomes due to rises in intracranial pressure as well as neuronal apoptosis and necrosis related to mitochondrial dysfunction [22]. This raises significant concern considering the markedly elevated ratio found when HCA without SCP is used as a neuroprotective strategy. It is also important to note that these markers of ischaemia and injury failed to normalise by the end of the 4-h recovery period. Our data demonstrate that elevations in both lactate and glycerol, as well as the lactate/pyruvate ratio, do not occur in animals receiving SCP during HCA at either 18°C or 25°C. This suggests that tepid hypothermia with selective cerebral perfusion may be equally neuroprotective when compared to more traditional deep hypothermia with SCP.

The cerebral microdialysate results were also remarkable for the depletion of energy substrates, glucose and pyruvate, when HCA without SCP was employed. Glucose is the primary fuel source for metabolically active neurons and allows for the maintenance of cell membrane integrity [20]. Particu-
larly concerning are the low glucose levels observed in animals not receiving SCP, as diminished glucose concentrations have been associated with periods of hypoxia and poor cerebral perfusion. This in turn has been associated with poor neurological outcomes in the adult neurocritical care setting [21,22]. SCP at either 18 °C or 25 °C prevents this exhaustion of energy substrates. This again suggests that tepid HCA with SCP is a superior neuroprotective strategy to deep HCA without SCP.

A prevalent concern with cooling to more tepid temperatures for HCA is that end-organ protection will not be as effective as with deep hypothermia. In order to address this concern, serum lactate levels were followed throughout the study protocol. No clinically or statistically significant differences were noted among groups undergoing circulatory arrest at either 18 °C or 25 °C. Though there was a trend towards slightly higher serum lactate levels in the animals cooled only to 25 °C, these values quickly normalised upon the re-institution of and recovery from CPB. Clinically, a number of trials looking at more moderate degrees of hypothermia have failed to demonstrate any clinically significant increased end-organ morbidity when compared to traditional deep hypothermia at 18 °C [10,23]. This finding could be in part due to the limited amount of somatic perfusion that occurs with the use of SCP that has been documented, but this is not fully understood [4,23].

A number of studies have demonstrated the considerable contribution time on CPB makes to surgical morbidity. CPB has been shown to induce significant impairment in vascular endothelial function in multiple organ systems, including the renal, pulmonary and cerebral vasculature [6]. CPB has also been shown to precipitate significant coagulopathies and major inflammatory responses [5]. The addition of deep HCA during CPB further exposes the brain to ischaemia/reperfusion injury as well as substantially lengthening the time required on CPB. These effects are exacerbated by the loss of cerebral autoregulation and the ability of the cerebral vasculature to respond to carbon dioxide during the immediate recovery period [24]. Cooling and warming times, as well as the overall operating time, were significantly shortened when using a target temperature of 25 °C for circulatory arrest. This approach has the potential advantage of decreasing the aforementioned side effects associated with CPB and HCA, but this needs to be studied further.

A substantial number of variables contribute to the long-term outcome of children with complex congenital heart defects who require surgical intervention. When trying to optimise these patients’ care, it is imperative that these variables be controlled for in such a way as to isolate each one so that its role in long-term outcome can be understood. This animal model affords this opportunity by analysing real-time data that has been shown to be extremely sensitive to neuronal stress and injury. Intra-operative management, operative techniques and CPB circuit management were uniform among the groups, allowing the data collected to reflect changes only in perfusion strategy and cooling temperature and their effects on neurometabolic activity. Future work by our group is aimed at optimising other currently debated variables such as blood gas management (alpha vs pH-stat), pO2 management, SCP flow rates, haemoglobin concentrations and pharmaceutical interventions. Survival studies to correlate real-time data acquired during circulatory arrest with neurobehavioural outcomes also are warranted.

This study is subject to some limitations. Though the piglet has been commonly accepted for use as a model for neonatal CPB as well as neonatal cerebral injury, there are some anatomical differences that are important to note that apply specifically when studying SCP. Because piglets have a common carotid trunk, when providing SCP via the innominate artery, flow is directed up the common trunk to both the left- and right-sided cerebral circulations. Having said this, the positive effect of SCP is clear. Further study in piglets with one carotid snared and bilateral cerebral microdialysis is indicated. It is also important to note that although our data suggest a real-time neurometabolic protective effect of SCP during the circulatory arrest period, this model is not a survival model, allowing us to correlate our data with neurobehavioural assessments. We are, however, presently analysing cerebral tissue from our animals to define any pathological correlates to our findings. Other areas of focus for the future include evaluating the need for increased SCP flows at warmer temperatures while minimising oxidative stress and inflammation. Furthermore, investigation of the neurological impact of shorter periods of HCA, at different temperatures, is indicated.

In summary, our study supports the conclusion that systemic circulatory arrest with selective cerebral perfusion at 25 °C can be safely performed while providing comparable cerebral and end-organ protection to that of 18 °C with SCP. In addition, the employment of a more tepid temperature allows for significantly shorter operative times, which may clinically translate into improved outcomes for children undergoing surgical repair of complex congenital heart defects.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not reflect the official policy or position of the Air Force Medical Department, Department of the Air Force, the Department of Defense, or the United States Government.

References

Appendix A. Conference discussion

Dr. R. Di Donato (Rome, Italy): The issue of the best neuroprotective strategy during aortic arch or other complex arch surgery in children is still highly contentious, as we could gather also at this meeting, and far from being conclusively settled as yet.

With this elegant study, Salazar and co-workers provide additional experimental evidence that selective cerebral perfusion lessens the cerebral insult typically associated with deep hypothermic circulatory arrest. Furthermore, they show that selective cerebral perfusion at moderate hypothermia, such as a temperature of 25 degrees centigrade, while equally effective in terms of cerebral protection, allows for significantly shorter operating times than selective cerebral perfusion at deep hypothermia, that is, I think, at 18 degrees. In so doing, it theoretically decreases the classical side effects of cardiopulmonary bypass, such as impairment of vascular endothelial function in multiple organ systems, activation of systemic inflammatory response, and induction of coagulopathy.

Skepticism about adequate perfusion of the lower part of the body, when the thoracic descending aorta is cross-clamped at moderate hypothermia, is counter-argued by the observation that relatively long ischemic periods of the descending aorta territory are well tolerated during routine extended end-to-end anastomosis through a left thoracotomy at normothermia.

I personally share your preference for selective cerebral perfusion as opposed to deep hypothermic circulatory arrest for arch reconstruction in infants and children, but I honestly recognise that this perfusion strategy still requires improvement and fine-tuning. By and large, however, I believe that the best perfusion strategy for this type of surgery is the one that best fits both the patient’s and the surgeon’s characteristics on a pure individual basis. I have one comment and a few questions for you.

Comment: Your argument that reduction of operating times by 25% to 30% using moderately hypothermic selective cerebral perfusion is truly relevant is probably an overstatement considering the technical advances and the refinements in the conduction of cardiopulmonary bypass such as miniaturisation of the circuits, ultrafiltration, and so forth, capable of minimising the side effects of extracorporeal circulation.

And then I have a few questions. One, the first issue I would ask you to expand on is the flow rate. Did you modulate selective cerebral perfusion flow, and how? In your experiments you started at 10 mm kg^-1 min^-1, which seems a relatively low flow rate. Were you afraid of a hyperperfusion cerebral injury? Did you further adjust this flow rate? And according to which parameters, pressure or near infrared spectroscopy? And what about transcranial Doppler or BIS-EEG monitoring?

The other issue concerns the lower body perfusion. The slight and temporary lactate elevation in the group receiving selective cerebral perfusion at 25 degrees centigrade rings a bell concerning the adequacy of lower body perfusion. What is your position with respect to adding concomitant descending aorta perfusion? Would it be redundant? Or would it be essential in the case you decided to perform this type of surgery at higher temperatures?

This question is safe perfusion? When you transfer this experience to the clinical setting, how long do you think the safe selective cerebral perfusion period could be?

And finally, during the 4 hours preceding the sacrifice of the animals, did you notice any anomalous neurologic or temperature behaviour with any of the perfusion strategies, possibly suggesting the presence of a cerebral ischemia-reperfusion mechanism?

Dr Salazar: With regard to the impact on operating times, I agree that oftentimes the warming period is utilised for subsequent steps of the procedure. For example, in the Norwood operation, the Sano can be performed after the Damus connection and arch reconstruction are completed. The time savings in cooling to 25 degrees centigrade may be less in this case, but the patient is still spared the repercussions of deep hypothermia. Having said this, I certainly have seen that my operating times are shorter for isolated arch reconstructions performed at 25 degrees. Time saving is important, but I believe that the avoidance of deep hypothermia is the more important point.

With regard to flow rates, we’re looking at this very carefully in the laboratory so that we can isolate the influence of the different variables influencing cerebral protection. For instance, ideal flow rates need to be determined, whether they are 10 ml kg^-1 min^-1, 40 ml kg^-1 min^-2, or some other amount, taking into account other important variables such as the use of an alpha stat versus a pH-stat strategy. How to best judge moment to moment brain perfusion — whether we make adjustments based on cerebral oximetry, mean arterial pressures in the right axillary artery, EEG, or other variables — also needs to be determined in the laboratory in a carefully controlled manner afforded by this model.

With regard to lower body perfusion, many surgeons including myself are now performing Norwood palliations and arch reconstructions at 25 degrees, or warmer. I have not seen any clinical evidence of end organ ischaemia with
circulatory arrest periods of less than 1 hour. As you mentioned, this is further supported by the experience with performing extended end-to-end arch reconstructions at near normothermia without distal perfusion. In the very rare case that a very long period of circulatory arrest is required, some distal perfusion strategy might be considered.

Lastly, during the 4-hour period of recovery, we did see in the animals not receiving brain perfusion a trend toward elevated intracranial pressures. The EEGs that we performed, which are pending publication, were relatively similar between the groups. We also performed multiple evaluations of the brain tissue, including looking at evidence of oxidative stress and inflammation, which are in progress and will be reported soon. I do believe that both the 25 degree and 18 degree patients do better, as evidenced by all these different factors, with selective cerebral perfusion.

Dr A. Corno (Liverpool, United Kingdom): Before you do any inference valid for the patients, I have major reservation on the model you have used. First of all, you have used piglets 8 to 10 kg, and this means they are far beyond the equivalent age of neonates of human beings, being the age/ratio pigs/humans = 1 to 7.

Second, the piglet is a wonderful model to study the myocardial metabolism because in piglets and in humans the heart is almost the same, but the brain is totally different. The metabolism in the brain in the piglets is totally different than in human beings, particularly regarding the ratio between aerobic and anaerobic metabolism. For instance, we measured in our experimental laboratory the saturation in the superior vena cava. In human beings it is, of course, much lower than in the inferior vena cava because the brain is the organ with the highest oxygen consumption, at least in almost all the human beings. In piglets the saturation in the superior vena cava is much higher than in the inferior vena cava because the cerebral oxygen consumption in piglets is very limited.

Did you consider this difference in metabolism between piglets and human beings?

Dr Salazar: The points made are appreciated, and we are familiar with your excellent work. Certainly there are drawbacks to any animal model trying to approximate the human situation, and I think this just further points out why we need better noninvasive diagnostic modalities to be able to test these hypotheses in the children. No animal model or specific age of animal will completely represent a newborn’s cerebral metabolism or response to perfusion strategies. If anything, the piglet would be less sensitive to ischaemia and hypoperfusion, making the findings of this study even more dramatic. Circulatory arrest without regional brain perfusion clearly results in injury. The fact that previous clinical studies have failed to demonstrate a difference in neurological outcomes (with selective cerebral perfusion) only points out the lack of real time, sensitive measures that are not confounded by multiple other variables. This leads to type 2 errors in statistics.

I will say that at 25 degrees we’re having very good results clinically, and I am strongly in favour of it. I do advocate bilateral NIRS monitoring in all babies undergoing these operations at 25 degrees, and further study is necessary to determine the ideal perfusion strategy to maximise neurological protection.
Brain preservation with selective cerebral perfusion for operations requiring circulatory arrest: protection at 25 °C is similar to 18 °C with shorter operating times

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