Selective Cerebral Perfusion: Real-Time Evidence of Brain Oxygen and Energy Metabolism Preservation

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Background. **Deep hypothermic circulatory arrest (DHCA) is commonly used for complex cardiac operations in children, often with selective cerebral perfusion (SCP). Little data exist concerning the real-time effects of DHCA with or without SCP on cerebral metabolism. Our objective was to better define these effects, focusing on brain oxygenation and energy metabolism.**

Methods. **Piglets undergoing cardiopulmonary bypass were assigned to either 60 minutes of DHCA at 18°C (n = 9) or DHCA with SCP at 18°C (n = 8), using pH-stat management. SCP was administered at 10 mL/kg/min. A cerebral microdialysis catheter was implanted into the cortex for monitoring of cellular ischemia and energy stores. Cerebral oxygen tension and intracranial pressure also were monitored. After DHCA with or without SCP, animals were recovered for 4 hours off cardiopulmonary bypass.**

Results. **With SCP, brain oxygen tension was preserved in contrast to DHCA alone ($p < 0.01$). Deep hypothermic circulatory arrest was associated with marked elevations of lactate ($p < 0.01$), glycerol ($p < 0.01$), and the lactate to pyruvate ratio ($p < 0.001$), as well as profound depletion of the energy substrates glucose ($p < 0.001$) and pyruvate ($p < 0.001$). These changes persisted well into recovery. With SCP, no significant cerebral microdialysis changes were observed. A strong correlation was demonstrated between cerebral oxygen levels and cerebral microdialysis markers ($p < 0.001$).**

Conclusions. **Selective cerebral perfusion preserves cerebral oxygenation and attenuates derangements in cerebral metabolism associated with DHCA. Cerebral microdialysis provides real-time metabolic feedback that correlates with changes in brain tissue oxygenation. This model enables further study and refinement of strategies aiming to limit brain injury in children requiring complex cardiac operations.**

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Since being popularized in the 1970s, deep hypothermic circulatory arrest (DHCA) has been used as an adjunctive therapy with cardiopulmonary bypass (CPB) to facilitate repair of complex congenital heart defects [1]. This technique provides surgeons a bloodless, uncluttered field and presumed adequate neurologic protection. With increased survival rates after these complex operations, significant neurodevelopmental sequelae are now observed on long-term follow-up [2–6]. As surgical outcomes and postoperative management have improved, focus is shifting to minimize neurologic sequelae. Although neurologic injury in children with congenital heart disease is recognized as having a multifactorial origin, considerable effort is being made to limit any aggravating factors occurring at the time of repair.

Selective antegrade cerebral perfusion (SCP) during operations requiring circulatory arrest has been adopted by a number of centers during the past decade to minimize cerebral injury (Fig 1) [7–9]. The assertion that SCP lessens cerebral injury by mitigating hypoxia and ischemia associated with DHCA is supported largely with indirect and anecdotal evidence. Differences in methodology and clinical application for SCP make it difficult to sort out its true utility for improving outcomes. Factors likely to impact outcomes include SCP flow rates, the duration of DHCA, degree of systemic cooling, blood gas strategy (alpha versus pH stat), hemodilution, oxygen management, and cerebral monitoring [9–16]. Clinical studies published to date have detected no difference in neurodevelopmental outcome between children undergoing DHCA for their repair versus those not undergoing DHCA. Other studies have not detected a difference in neurologic outcome between those receiving or not receiving SCP with operations requiring DHCA. The failure to detect substantial differences may be related to the significant number of confounding variables involved and the relative insensitivity and lack of specificity of the tools used to measure these outcomes [17, 18].

Although a number of studies recommend targeting SCP flow to either cerebral saturations or perfusion pressure, it

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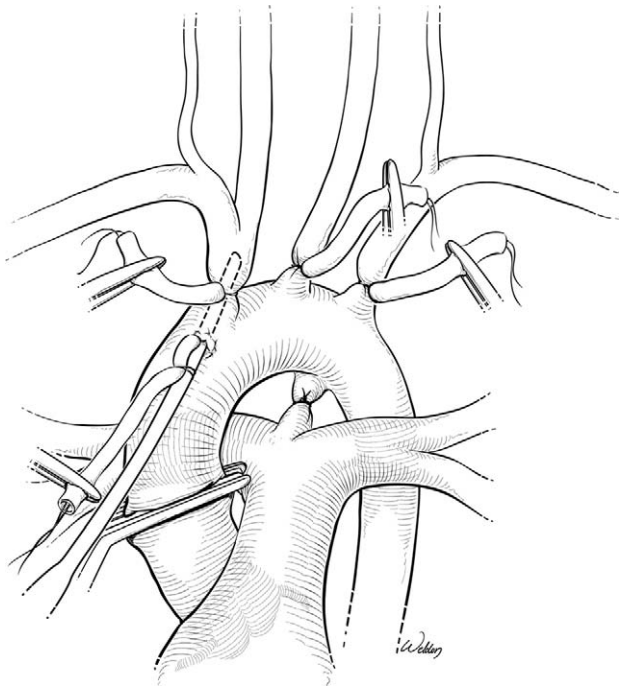

Fig 1. Example of operative technique used for selective cerebral perfusion.

remains unclear as to what actually constitutes optimal or even adequate cerebral oxygenation during hypothermia. Recent advances in neuromonitoring, however, have provided improved technologies for measuring real-time changes in brain metabolism, and their use may assist in gaining a better understanding of the pathophysiology of cerebral injury associated with CPB and circulatory arrest [19–21]. In the neurosurgical critical care setting, clinicians directly measure brain oxygen tension ($Pbto_2$) and perform continuous cerebral microdialysis (CMD) using surgically implanted catheters placed into the superficial cerebral cortex of patients [22, 23]. A number of studies in the neurosurgical literature using multimodal neuromonitoring have shown strong correlations between threshold changes in cerebral $Pbto_2$, CMD, and neurologic outcomes, with clinical interventions being made based on this technology [19, 21, 24–27].

Few data exist examining the real-time effects of DHCA with or without SCP on cellular neurometabolic activity. The aim of this study is to use multimodal neuromonitoring to assess the efficacy of SCP in acutely preserving brain tissue metabolism. Our hypothesis was that SCP would significantly improve cerebral oxygenation and attenuate CMD changes reflective of cellular injury that occur with DHCA. Additionally, we sought to demonstrate that changes in CMD correlate well with changes in brain tissue oxygenation. In accomplishing these goals, we believe our experimental model will facilitate future investigation aimed at refining surgical management of children with complex congenital heart disease.

Material 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 Association for Assessment and Accreditation of Laboratory Animal Care–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.

Experimental Design

Twenty male Yorkshire piglets, between 4 and 5 weeks of age and weighing 8 to 10 kg, were randomized to 60

Table 1. Cardiopulmonary Bypass and Hemodynamic Variables[a]

Variable	Before CPB	Cooling	End CA	End CPB	2 Hours	4 Hours	*p group*	*p time*gp*	*p time*
Brain Temp (°C)									
DHCA	34.7 ± 0.8	24.7 ± 2.5	18.5 ± 0.8	35.6 ± 0.9	35.8 ± 0.9	36.3 ± 2.1	0.590	0.835	0.000
SCP	35.2 ± 1.1	24.9 ± 0.2	18.3 ± 0.9	35.6 ± 1.3	35.6 ± 1.5	35.9 ± 1.4			
MAP (mm Hg)									
DHCA	53.5 ± 11	48.3 ± 5.4	. . .	55.5 ± 11	59.8 ± 9.1	61.3 ± 19	0.685	0.140	0.000
SCP	50.4 ± 10	48.2 ± 9.0	. . .	63.2 ± 13	62.1 ± 9.6	55.0 ± 9.1			
ICP (mm Hg)									
DHCA	12.6 ± 3.1	10.8 ± 3.5	9.9 ± 4.1	14.5 ± 4.3	15.0 ± 6.4	16.2 ± 7.4	0.471	0.340	0.000
SCP	10.5 ± 2.1	9.2 ± 2.2	10.5 ± 2.1	13.1 ± 3.7	14.6 ± 6.3	15.0 ± 3.1			
Hct (%)									
DHCA	28.3 ± 3.4	28.2 ± 0.8	28.7 ± 3.8	31.0 ± 4.5	34.1 ± 3.8	31.5 ± 3.6	0.007	0.134	0.000
SCP	26.8 ± 2.0	29.8 ± 4.4	26.8 ± 2.0	27.3 ± 3.1	33.7 ± 5.1	29.9 ± 4.1			

[a] Analysis includes data from entire study period (only selected time points shown); values represent mean ± standard deviation.

Brain Temp = superficial cortical temperature measured invasively; CA = circulatory arrest; CPB = cardiopulmonary bypass; DHCA = standard deep hypothermic circulatory arrest; Hct = hematocrit; ICP = intracranial pressure; MAP = mean arterial pressure; *p group* = level of difference between groups; *p time*gp* = difference between groups as a function of time; *p time* = change as a function of time; SCP = DHCA with selective cerebral perfusion.

Table 2. Blood Gas Data[a]

Variable	Before CPB	Cooling	End CA	End CPB	2 Hours	4 Hours	*p group*	*p time*gp*	*p time*
pH[c]									
DHCA	7.45 ± 0.08	7.26 ± 0.06	7.18 ± 0.09	7.31 ± 0.10	7.35 ± 0.13	7.31 ± 0.04	0.599	0.355	0.000
SCP	7.44 ± 0.09	7.28 ± 0.07	7.15 ± 0.10	7.29 ± 0.06	7.31 ± 0.04	7.29 ± 0.11			
Pao_2 (mm Hg)									
DHCA	239 ± 80	229 ± 23	211 ± 80	162 ± 60	213 ± 29	189 ± 27	0.500	0.463	0.000
SCP	200 ± 53	210 ± 29	230 ± 77	180 ± 58	187 ± 35	201 ± 38			
Pco_2 (mm Hg)[c]									
DHCA	38.4 ± 4.2	68.7 ± 6.3	75.3 ± 6.5	47.2 ± 9.6	46.2 ± 3.1	49.6 ± 4.1	0.815	0.000	0.000
SCP	40.0 ± 5.6	62.8 ± 3.9	81.0 ± 7.1	46.0 ± 4.4	42.3 ± 2.7	41.3 ± 1.9			
Lactate (mmol/L)									
DHCA	1.1 ± 0.5	1.7 ± 0.5	4.3 ± 1.9	4.0 ± 1.3[b]	3.5 ± 2.6	4.1 ± 2.7	0.010	0.381	0.000
SCP	0.8 ± 0.2	1.7 ± 0.7	3.4 ± 2.1	2.9 ± 0.9	2.1 ± 0.6	2.8 ± 1.5			

[a] Analysis includes data from entire study period (only selected time points shown); values represent mean ± standard deviation. [b] $p < 0.05$. [c] pH and Pco_2 data measured at 37°C.

CA = circulatory arrest; CPB = cardiopulmonary bypass; DHCA = standard deep hypothermic circulatory arrest; Pao_2 = arterial oxygen partial pressure; Pco_2 = carbon dioxide partial pressure; *p group* = level of difference between groups; *p time*gp* = difference between groups as a function of time; *p time* = change as a function of time; SCP = DHCA with selective cerebral perfusion.

minutes of DHCA at 18°C with or without SCP. After DHCA, animals were warmed, weaned from CPB, and recovered for 4 hours. Each animal received standard hemodynamic monitoring and multimodal neurologic monitoring from the time of intubation until sacrifice.

Intracerebral Monitoring and Microdialysis

After intubation and the establishment of vascular access, animals were placed prone for placement of intracerebral catheters. Two small burr holes (0.7 mm diameter) were drilled in the skull just off midline, allowing access to the right posterior frontal lobe. In the initial burr hole, an intraparenchymal pressure catheter (Codman ICP Express, Raynham, MA) and temperature and oxygenation probe (Licox Integra, Plainsboro, NJ) were placed into the superficial cerebral cortex after puncture of the dura. The Licox probe, a Clark-type electrode, allowed for continuous monitoring of cortical temperature and tissue oxygen tension ($Pbto_2$) [22]. In the second burr hole, a microdialysis catheter (CMA-70, CMA Microdialysis, Stockholm, Sweden) was inserted into the superficial cerebral cortex after puncture of the dura. A physiologic saline solution was continuously perfused through the catheter at 1.0 μL/min with samples collected every 15 minutes for subsequent analysis of metabolites after an initial equilibration period of 60 minutes (CMA-600, CMA Microdialysis).

Surgical and Cardiopulmonary Bypass Protocol

Anesthesia and paralysis were provided throughout the study period with inhaled isoflurane (0.5% to 1.5%) and continuous intravenous fentanyl (25 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and pancuronium (0.2 $mg \cdot kg^{-1} \cdot h^{-1}$). The right axillary artery was cannulated for continuous blood pressure monitoring. All animals were ventilated with a standard protocol using 0.50 inspired oxygen fraction and tidal volumes (10 mL/kg) adjusted to maintain carbon dioxide partial pressure values between 35 and 45 mm Hg.

The protocols and surgical techniques used mimic those commonly used in the clinical operating room. After achieving cardiac exposure through a median sternotomy, the ascending aorta was cannulated with a 12F, wire-reinforced, flexible pediatric cannula (Medtronic Bio-Medicus, Minneapolis, MN), and the right atrium was cannulated with an 18F malleable venous cannula (Medtronic Bio-Medicus). After systemic heparinization (400 IU/kg), nonpulsatile CPB was instituted at a flow rate of 100 $mL \cdot kg^{-1} \cdot min^{-1}$. The CPB circuit consisted of a roller pump, membrane oxygenator (SX-10 with X-Coating, Terumo, Ann Arbor, MI), and sterile Terumo X-Coated 0.25-inch tubing with Capiox AFO2 Arterial Filter

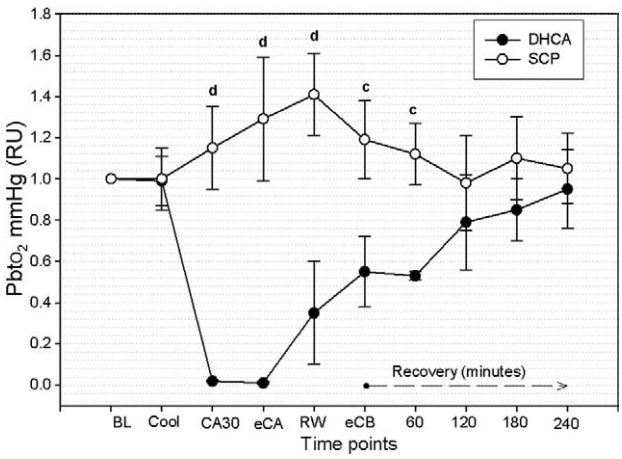

Fig 2. Cerebral tissue oxygenation is shown in piglets undergoing deep hypothermic circulatory arrest (DHCA) with or without selective cerebral perfusion (SCP). Cerebral tissue oxygenation ($Pbto_2$) is shown as relative units (RU), normalized to before cardiopulmonary bypass baseline (BL; mm Hg). Measurements are shown at the following times: BL, before cardiopulmonary bypass baseline; Cool, cooling; CA30, 30 minutes of DHCA; eCA, end DHCA; RW, rewarming; eCB, end CPB. [d]$p < 0.001$, [c]$p < 0.01$.

Table 3. Microdialysis Data[a]

Variable	Baseline	30 min CA	End CA	End CPB	2 Hours	4 Hours	*p group*	*p time*gp*	*p time*
Glucose (mmol/L)									
DHCA	1.16 ± 0.56	0.34 ± 0.09[d]	0.11 ± 0.13[d]	0.15 ± 0.03[d]	0.75 ± 0.39[b]	1.28 ± 0.19	0.000	0.000	0.000
SCP	1.29 ± 0.45	1.27 ± 0.19	1.24 ± 0.11	1.31 ± 0.18	1.56 ± 0.49	1.32 ± 0.12			
Lactate (mmol/L)									
DHCA	1.19 ± 0.17	2.02 ± 0.58[c]	3.61 ± 0.87[d]	4.69 ± 1.2[d]	2.33 ± 0.49[c]	2.67 ± 1.3[b]	0.000	0.003	0.002
SCP	1.24 ± 0.23	1.23 ± 0.22	0.97 ± 0.21	1.36 ± 0.25	1.46 ± 0.52	1.36 ± 1.1			
Pyruvate (μmol/L)									
DHCA	123 ± 45	78.1 ± 21	17.6 ± 5.5[d]	112 ± 17	122 ± 28	141 ± 33	0.181	0.001	0.000
SCP	114 ± 56	94.9 ± 26	74.4 ± 12	101 ± 69	119 ± 22	118 ± 19			
Glycerol (μmol/L)									
DHCA	12.9 ± 3.1	22.9 ± 7.3[c]	40.0 ± 16[c]	49.6 ± 8.9[d]	30.3 ± 4.1[c]	24.7 ± 7.9	0.000	0.003	0.002
SCP	11.6 ± 2.2	12.1 ± 1.9	10.4 ± 1.2	13.9 ± 2.8	14.2 ± 1.8	13.1 ± 4.1			
L/P ratio									
DHCA	10.3 ± 3.2	26.8 ± 11[c]	205 ± 45[d]	42.6 ± 13[c]	20.4 ± 9.8[b]	19.7 ± 6.7	0.000	0.000	0.000
SCP	11.4 ± 2.9	14.1 ± 1.6	20.3 ± 5.2	15.9 ± 9.1	14.1 ± 3.4	11.9 ± 6.1			

[a] Analysis includes data from entire study period (only selected time points shown); values represent mean ±standar deviation. [b] $p < 0.05$. [c] $p < 0.01$. [d] $p < 0.001$.

CA = circulatory arrest; CPB = cardiopulmonary bypass; DHCA = standard deep hypothermic circulatory arrest; L/P ratio = lactate to pyruvate ratio; *p group* = level of difference between groups; *p time*gp* = difference between groups as a function of time; *p time* = change as a function of time; SCP = DHCA with selective cerebral perfusion.

and HCO5 Hemoconcentrator (Terumo, Ann Arbor, MI). The circuit was primed with blood previously harvested from a donor pig and ultrafiltrated with a crystalloid prime solution (0.9% normal saline solution) to maintain the CPB blood prime hematocrit value at greater than or equal to 28%. Electrolytes in the prime solution were analyzed and normalized as indicated, and all in-line monitoring was calibrated.

Once on CPB, animals were cooled to a target nasopharyngeal temperature of 18°C using an 8°C gradient. Before 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 placed in the left atrial appendage to ensure adequate decompression. Animals assigned to the DHCA with SCP group then received SCP at a flow rate of 10 mL · kg^{-1} · min^{-1} at 18°C by advancing the aortic cannula into the innominate artery and snaring it. The distal arch vessel was snared to minimize steal [28]. Cerebral perfusion pressure was then monitored by

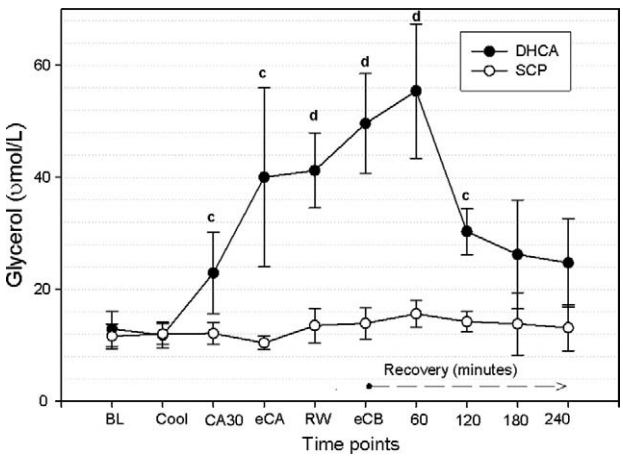

Fig 3. Cerebral microdialysis glycerol is shown in piglets undergoing deep hypothermic circulatory arrest (DHCA) with or without selective cerebral perfusion (SCP). Measurements are shown at the following times: BL, before cardiopulmonary bypass baseline; Cool, cooling; CA30, 30 minutes of DHCA; eCA, end DHCA; RW, rewarming; eCB, end CPB. [d]$p < 0.001$; [c]$p < 0.01$.

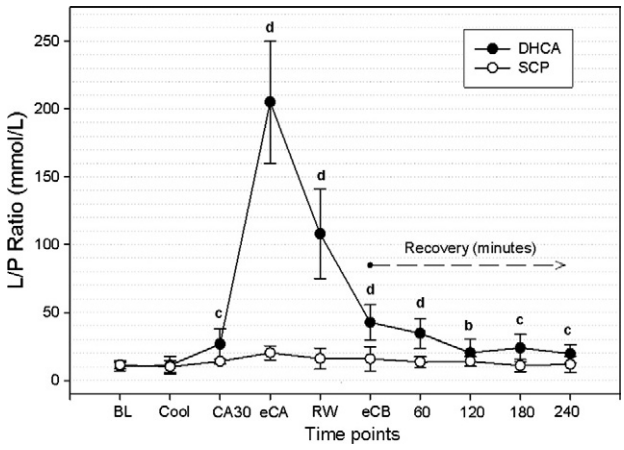

Fig 4. Cerebral microdialysis lactate to pyruvate (L/P) ratio is shown in piglets undergoing deep hypothermic circulatory arrest (DHCA) with or without selective cerebral perfusion (SCP). Measurements are shown at the following times: BL, before cardiopulmonary bypass baseline; Cool, cooling; CA30, 30 minutes of DHCA; eCA, end DHCA; RW, rewarming; eCB, end CPB. [d]$p < 0.001$, [c]$p < 0.01$, [b]$p < 0.05$.

means of the axillary artery and targeted to 35 to 40 mm Hg. After completion of the 60-minute circulatory arrest period, the snares on the arch vessels were released. The aortic cannula was then redirected from the innominate artery back to the ascending aorta and full CPB was reestablished. 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, norepinephrine and volume administration were used as necessary to ensure hemodynamic stability. Modified ultrafiltration was used to achieve a filtrate volume of 500 mL and a target hematocrit of 35%. A pH-stat acid-base management strategy was used throughout the procedure.

Statistical Analysis

One DHCA animal and 2 SCP animals died during protocol development and therefore were excluded from analysis. All data are presented as mean ± standard deviation unless otherwise noted. Two-way analysis of variance with correction for repeated measures was used to compare serial data using SPSS software (Version 12.0, Chicago, IL). Reported probability values include *p group,* assessing level of difference between groups; *p time*group,* assessing group-time interaction; and *p time,* assessing change as a function of time of measured variables. Data between study groups were analyzed

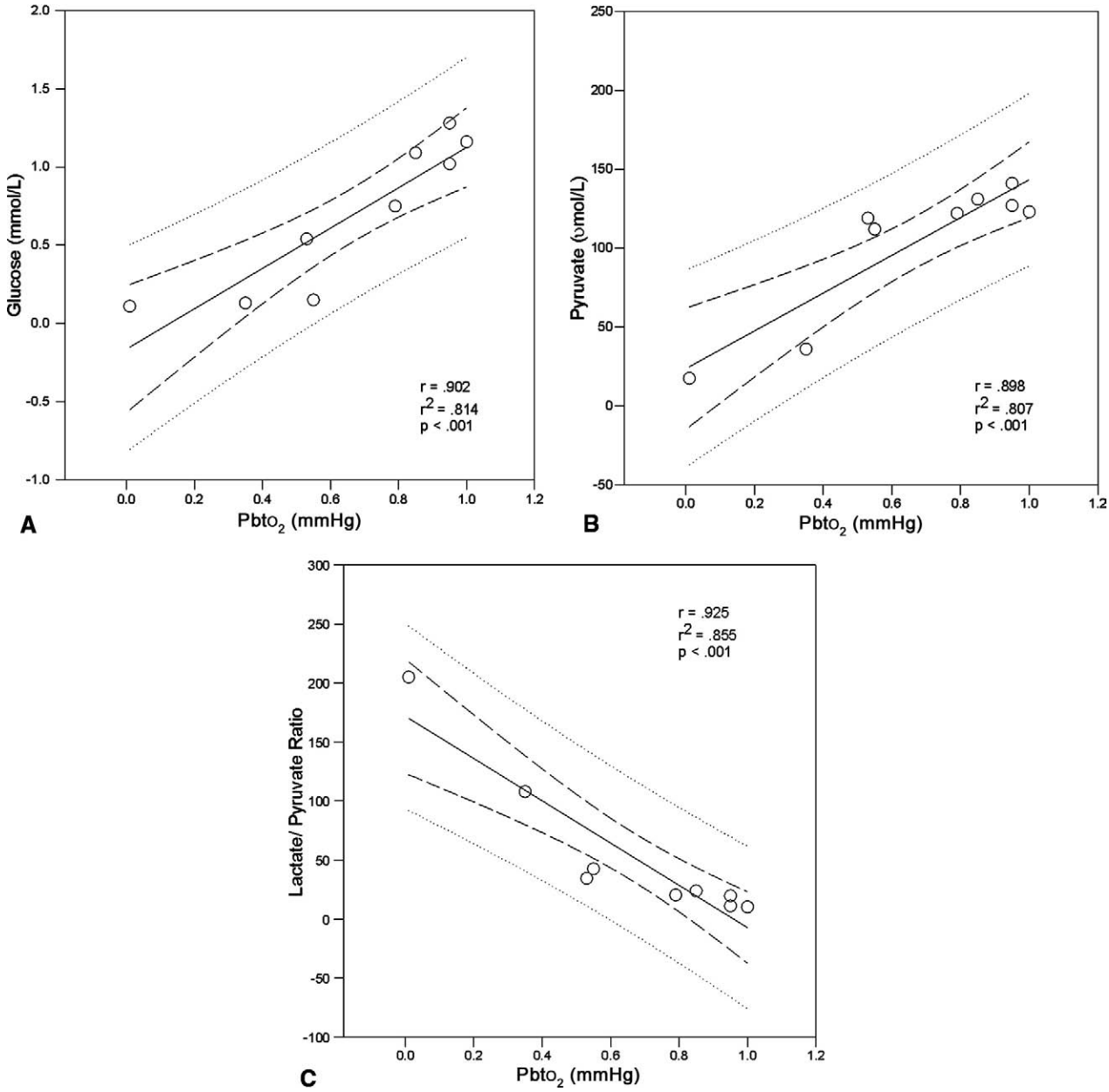

Fig 5. Linear regressions are shown for measurements of glucose (A), pyruvate (B), and lactate to pyruvate (L/P) ratio (C) versus cerebral tissue oxygenation ($Pbto_2$). Regressions are shown with 95% confidence and prediction limits for data points, shown as inner and outer lines, respectively.

using Student's *t* test or Mann-Whitney rank-sum test as appropriate using Sigma Stat Software (Version 3.1, Richmond CA). Simple linear regression was used to determine correlation (Sigma Stat Software). For all data, a probability value of 0.05 or less was considered significant.

Results

Hemodynamic and Physiologic Data

The mean weights between the two study groups were similar, 9.2 ± 1.4 kg for DHCA and 9.5 ± 2.1 kg for SCP animals. Table 1 shows CPB and hemodynamic data of interest recorded throughout the study period. The central nervous system temperature generally correlated well with simultaneously recorded rectal and nasopharyngeal temperatures (data not shown). Intracranial pressure decreased mildly with cooling in both groups and then trended higher during rewarming and recovery from CPB. No significant differences were noted between groups in intracranial pressure or other hemodynamic variables at any time (Table 1).

Table 2 reviews the blood gas variables from the experiments. Of note, serum lactate levels in DHCA animals trended slightly higher after circulatory arrest and were significantly higher by the end of CPB ($p < 0.05$).

Brain Tissue Oxygenation Data

Figure 2 shows selected times for cerebral oxygenation values as assessed by the Licox probe. Pre-bypass $Pbto_2$ values were similar between groups, but cerebral oxygenation fell dramatically with the institution of DHCA ($p < 0.001$) and did not recover to baseline levels until well after separation from CPB ($p < 0.01$). Cerebral oxygenation was preserved with SCP.

Cerebral Microdialysis Data

Real-time measurement (CMD) of cellular energy substrates (glucose and pyruvate) and markers of injury (lactate and glycerol) is presented in Table 3. There were no differences noted at baseline between study groups. Deep hypothermic circulatory arrest animals had critical reductions in glucose and pyruvate versus baseline ($p < 0.001$). Although pyruvate recovered, glucose levels remained significantly below baseline more than 2 hours into recovery ($p < 0.05$). At 30 minutes, depletion of energy substrates was more moderate than at 60 minutes. Selective cerebral perfusion prevented cerebral energy substrate depletion.

Table 3 additionally shows significant elevations in the injury metabolite markers lactate and glycerol at the end of DHCA ($p < 0.001$). Both markers remained elevated well into the recovery period, with cerebral lactate levels failing to normalize by study's end ($p < 0.05$). Elevation of injury metabolites at 30 minutes of DHCA was more moderate than at 60 minutes. With SCP, no significant alterations in either lactate or glycerol were noted. Glycerol values from DHCA compared with SCP animals are shown in Figure 3.

Also of note, the lactate to pyruvate (L/P) ratio was dramatically elevated after DHCA and remained elevated throughout the recovery period ($p < 0.01$). The L/P ratio was moderately elevated at 30 minutes of DHCA. Changes in the L/P ratio for DHCA compared with SCP animals are shown in graphic form in Figure 4. The ratio was mildly elevated after circulatory arrest in SCP animals ($p < 0.05$), but rapidly returned to baseline with rewarming.

Correlation of $PbtO_2$ and CMD Data

The relationship of CMD metabolites to cerebral tissue hypoxia and ischemia in DHCA animals was described by linear regression. All of the CMD markers measured correlated relatively well to changes in tissue $Pbto_2$: glucose, $r^2 = 0.814$; pyruvate, $r^2 = 0.807$; lactate, $r^2 = 0.620$; glycerol, $r^2 = 0.504$; and L/P ratio, $r^2 = 0.855$ (all $p < 0.001$). In particular, the energy substrates glucose and pyruvate, as well as the L/P ratio, demonstrated high correlation to tissue $Pbto_2$ (Fig 5).

Comment

In the present study, we used multimodal neuromonitoring in a piglet DHCA model to characterize with CMD and cerebral oxygenation the real-time effects of SCP on cerebral metabolism. We found that SCP preserved cerebral oxygenation during and after recovery from DHCA, while at the same time attenuating evidence of cellular energy depletion and ischemia. We also demonstrated excellent correlation between CMD and $Pbto_2$ values, suggesting that CMD can serve as a reliable and sensitive indicator of inadequate cerebral oxygenation. From these findings, we believe that animal studies with this model will enable further assessment of optimal neuroprotective strategies during complex cardiac operations in children.

For this study, a SCP flow rate of 10 mL · kg^{-1} · min^{-1} was used. Recommended flow rates for SCP in the literature vary from less than 10 to up to 100 mL · kg^{-1} · min^{-1}. We chose to use relatively low flow based on previous studies and to establish a baseline for future investigation [15, 28]. Myung and colleagues [15] found that piglets receiving SCP at 10 mL kg^{-1} min^{-1} for 90 minutes compared with DHCA alone had less histopathologic brain injury and better neurobehavioral scores after short-term survival. DeCampli and associates [29] in follow-up work with this same model found that SCP flow rates of 20 mL · kg^{-1} · min^{-1} resulted in better clinical recovery, despite lower cerebral oxygenation values, than rates of 40 mL · kg^{-1} · min^{-1}. Concerns relating to inadequate perfusion with SCP at lower flows have led a number of authors to recommend using higher SCP flows (up to 40 to 80 mL · kg^{-1} · min^{-1}) in an effort to target baseline cerebral oxygenation [9, 13, 30]. Whether a strategy of attempting to match pre-CPB oxygenation with SCP is beneficial while the brain is in a suppressed metabolic state remains unclear. The poten-

tial for increased oxidative stress, inflammation, and excess cerebral perfusion pressure exacerbating rather than attenuating neurologic injury needs to be carefully considered and investigated in the future.

Different from the studies of Myung and colleagues [15] and DeCampli and associates [29], we used pH-stat blood gas management and limited DHCA to 60 minutes. Briefly, when alpha-stat is used, blood carbon dioxide content is allowed to follow its temperature-mediated dissociation changes, resulting in an alkaline shift in blood pH. In comparison, pH-stat management introduces carbon dioxide to correct blood carbon dioxide partial pressure, maintaining a more acidotic state. This is of particular importance when looking at cerebral protection strategies, as carbon dioxide is a well-known cerebral vasodilator. Several recent animal studies have demonstrated that pH-stat provides better cerebral oxygenation and results in less neurologic injury, especially when used with SCP. Dahlbacka and coworkers [31] directly compared pH-stat to alpha-stat during SCP and with microdialysis showed lower brain lactate production in pH-stat animals [31]. Duebener and colleagues [32] also compared alpha-stat to pH-stat, finding increased cerebrocortical vessel diameter, increased tissue oxygenation, and decreased serum lactate levels associated with using a pH-stat strategy. Clinical experience with neonates and other congenital heart patients supports the relationship between carbon dioxide partial pressure and cerebral perfusion.

Results from our paper further add to the literature in supporting the beneficial effects of SCP. Although Schears and associates [33] previously used microdialysis to measure extracellular dopamine as a marker of acute brain injury, our study directly measured multiple CMD markers to assess the effect of SCP on energy metabolism. Specifically, we were able to demonstrate that SCP attenuates the production of both glycerol and lactate, as well as dramatically limit the increase in the L/P ratio as compared with DHCA. Glycerol is known to be a sensitive and reliable CMD marker of cellular injury after ischemia, with elevated concentrations resulting from the phospholipase-activated degradation of cell membranes [25, 34]. Additionally, lactate is a universally recognized marker of tissue ischemia, and the L/P ratio has been shown to be an extremely sensitive indicator of tissue ischemia, hypoxia, and cellular mitochondrial failure [21, 25, 34]. Our CMD data also showed maintenance of glucose and pyruvate levels with SCP, both important energy substrates known to be essential for the maintenance of cellular function and integrity [25, 34]. The CMD markers, particularly glucose, the L/P ratio, and glycerol, have been shown in the neurocritical care setting to highly correlate with patient morbidity and mortality, and continue to be investigated and used as bedside tools for clinical decision making [20, 35].

In addition to CMD, we continuously measured cerebral $Pbto_2$ in our protocol. As previously noted, SCP maintained $Pbto_2$ during and after DHCA. Tissue $Pbto_2$ represents a balance between cerebral oxygen delivery and cellular oxygen consumption. Similar to CMD, it has been used to titrate clinical care and predict outcomes, mainly in traumatic brain injury patients [20, 27]. Threshold $Pbto_2$values have been suggested in several studies involving neurosurgery patients. What absolute level or percentage change from baseline actually results in ischemia or injury, especially during hypothermic circulatory arrest, remains to be determined [36, 37]. We were able to show in this study, however, that CMD markers indicative of tissue ischemia and substrate depletion strongly correlate with changes in $Pbto_2$. This suggests that the hypoxia and ischemia associated with DHCA results in significant cellular injury that likely contributes to neurologic injury. The fact that low-flow SCP nearly eradicated these negative changes significantly supports its potential clinical utility. Further investigation using multimodal neuromonitoring is indicated to better define threshold changes in $Pbto_2$ and CMD that result in neurologic injury.

The findings of this study are based on a period of DHCA lasting 60 minutes. Although the most complex repairs (eg, Norwood palliation) require 30 to 50 minutes of DHCA, other repairs are performed with shorter times and may not result in the same degree of neurologic injury at 18°C. The data from this study at 30 minutes of DHCA support this conclusion, and further study is warranted. For operations requiring shorter or longer periods of circulatory arrest, SCP may enable less cooling and therefore avoidance of the cerebral and systemic repercussions of deep hypothermia.

Limitations of our present study include the nonsurvival experimental design and the use of an animal model. Although the impact of SCP on preventing the acute findings of cerebral ischemia and energy substrate depletion are striking, it remains to be demonstrated clinically that SCP translates into improved neurologic outcomes. We do believe, however, that this model provides a solid foundation for future experiments aimed at optimizing cerebral protection during complex cardiac operations in children.

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