The impact of temperature and pump flow rate during selective cerebral perfusion on regional blood flow in piglets

Jian Wang, MD, PhD,[a] Richard M. Ginther, CCP,[a] Matthew Riegel, DVM,[b] Rong Huang, MS,[c] Mahesh S. Sharma, MD,[a] Kristine J. Guleserian, MD,[a] and Joseph M. Forbess, MD[a]

Objective: Ideal temperature and flow rate for selective cerebral perfusion (SCP) are not known. We examined regional organ perfusion in a piglet SCP model.

Methods: Three groups underwent SCP at 30 mL/kg/min at different temperatures (15°C, 25°C, and 32°C) and 4 groups remained at 25°C for SCP at different flow rates (10, 30, 50 and 75 mL/kg/min). Fluorescent microspheres were injected at 5 minutes of normothermic cardiopulmonary bypass (CPB), immediately before SCP, SCP 45 minutes, SCP 90 minutes, and 2 hours after CPB. Brain and lower body organs were collected to examine regional blood flow (RBF, mL/min/g).

Results: At 2 hours after CPB, RBF of the 32°C group was higher than that of the 15°C group ($P < .05$) at the caudate nucleus and hippocampus; RBF of the 32°C group was higher than that of the 25°C and 15°C groups ($P < .05$) at the neocortex. No significant difference in RBF was observed among any of the 25°C groups at different flow rates. Also, there was no significant difference between the RBF to the left and right sides of brain in either the temperature or flow rate groups. RBF did significantly increase with temperature in the liver and quadriceps during SCP ($P < .05$). At the kidney, RBF at SCP 90 minutes was significantly higher than that at SCP 45 minutes when all temperature groups were combined ($P < .05$).

Conclusions: SCP at 32°C provides higher brain RBF 2 hours after CPB. Increasing SCP flow rate does not increase RBF significantly at 25°C. Higher temperature during SCP results in improved RBF to the liver and quadriceps. (J Thorac Cardiovasc Surg 2013;145:188-95)

CHD

Cerebral protection during aortic arch reconstruction remains a major challenge in pediatric cardiac surgery. Although hypothermic circulatory arrest (HCA) is known to be neuroprotective, the safe duration of HCA alone is limited and a significant number of children undergoing such operations may have neurologic complications.[1] Antegrade selective cerebral perfusion (SCP) is a cardiopulmonary bypass (CPB) technique in heavy clinical use. SCP provides a potentially more physiologic method of perfusion and may extend the safe time limits for aortic arch repair. HCA and SCP are sometimes used in combination for neuroprotection in infants and children. There is some clinical evidence that HCA supplemented by SCP improved neurologic outcomes when prolonged periods of HCA were required.[2]

Although SCP is widely used for cerebral protection, technical issues relating to the use of hypothermic SCP, such as ideal temperature and flow rate, are still unresolved. There is also no information about the changes in regional blood flow (RBF) for different regions of the brain during SCP. Blood does return into the descending aorta to visceral organs through collaterals during SCP. However, limited information about the degree of blood flow in lower body organs during SCP is limited.

In this study, we used a piglet model of CPB and SCP to examine cerebral RBF changes, measured using fluorescent microspheres, at variable temperatures and pump rates. The technique of fluorescent microspheres has been used previously in the brain and other organs.[3,4] We also sought to examine blood flow to various lower body organs during SCP in this model.

MATERIALS

Experiment Design

All animals received humane care in compliance with the ''Guide for the Care and Use of Laboratory Animals'' published by the National Institutes of Health (NIH publication no. 85-23, revised 1985), and all animal procedures were approved by the Institutional Animal Care and Use Committee at the University of Texas Southwestern Medical Center at Dallas.

Thirty Yorkshire piglets (4 weeks of age; weight, 4-11 kg) were used. Animals were assigned to 7 groups (n = 5 per group) Three groups underwent SCP for 90 minutes at 30 mL/kg/min at different temperatures (15°C, 25°C, and 32°C) and 4 groups remained at 25°C for 90 minutes of SCP at

From the Division of Pediatric Cardiothoracic Surgery,[a] University of Texas Southwestern Medical Center and Children's Medical Center, the Animal Resources Center,[b] University of Texas Southwestern Medical Center, and the Clinical Research Department,[c] Children's Medical Center, Dallas, Tex.

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Address for reprints: Joseph M. Forbess, MD, Division of Pediatric Cardiothoracic Surgery, University of Texas Southwestern Medical Center, Children's Medical Center, 1935 Medical District Dr, Suite C3211, Dallas, TX 75235 (E-mail: Joseph.Forbess@UTSouthwestern.edu).

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Abbreviations and Acronyms
CPB = cardiopulmonary bypass
HCA = hypothermic circulatory arrest
RBF = regional blood flow
SCP = selective cerebral perfusion

different pump flow rates (10, 30, 50, and 75 mL/kg/min). After SCP, animals were rewarmed, weaned from CPB, and allowed to recover for 2 hours. Fluorescent microspheres were injected at the following time points: 5 minutes of normothermic CPB, immediately before SCP, 45 minutes of SCP, 90 minutes of SCP, just after CPB, and 2 hours after CPB. Brain tissues (bilateral neocortex, hippocampus, cerebellum, caudate nucleus, and brain stem) and lower body organs (quadriceps, stomach, duodenum, liver, and kidney) were collected to examine RBF.

Surgical and CPB Protocol

The piglets were administrated intramuscular ketamine (20 mg/kg) and xylazine (4 mg/kg). After endotracheal intubation, the piglets were ventilated mechanically with a fraction of inspired oxygen of 0.21. The ventilation rate and tidal volume were adjusted to maintain normal arterial pH and carbon dioxide pressure. Anesthesia was maintained with fentanyl (25 μg/kg/h), midazolam (0.2 mg/kg/h), and pancuronium (0.2 mg/kg/h) using infusion pumps. The animals were initially placed supine on a water-circulating heating blanket to prevent hypothermia. Temperature probes were placed in the nasopharynx and rectum. The right axillary artery was cannulated for reference blood sampling and the right femoral artery was cannulated for measurement of artery blood pressure. A median sternotomy was performed. After administration of heparin (400 IU/kg), the ascending aorta was cannulated with a single 10F arterial cannula, and the right atrium was cannulated with a single 18F cannula. As a port for fluorescent microsphere injection, a 3-way stopcock was attached to the arterial cannula. Tourniquets were placed around the proximal innominate and left carotid arteries.

The CPB circuit consisted of a roller pump (Cardiovascular Instrument Corp, Wakefield, Mass), a Baby RX05 hollow membrane oxygenator, Capiox AF02 arterial line filter, CDI 500 blood gas monitor, HPH400 hemoconcentrator (Terumo Cardiovascular Systems, Ann Arbor, Mich), and sterile ¼-inch polyvinyl chloride tubing. The circuit was primed with Plasma-Lyte-A electrolyte solution (Abbott Laboratories, North Chicago, Ill), heparin (3000 IU), sodium bicarbonate (15 mEq), methylprednisolone (30 mg/kg), mannitol (0.5 mg/kg), furosemide (0.25 mg/kg), and fresh whole blood previously harvested from a donor pig. Hemoconcentration was used to maintain a hematocrit value of greater than 30% during CPB. At 5 minutes of full-flow (100 mL/kg/min) normthermic CPB, a 0.2 mg/kg dose of phentolamine was administered and the animal was cooled to desired temperature. The pH-stat management strategy was used. Low flow of carbon dioxide was added to the oxygenator to maintain a temperature-corrected pH of 7.4. All animals were cooled for a minimum of 25 minutes to reach the target nasopharyngeal and rectal temperatures. When the desired core temperature was reached, the arterial cannula was advanced into the innominate artery and the proximal innominate was snugged to the cannula using a vascular tourniquet kit. At the same time, the left carotid artery was occluded. The ascending aorta was not crossclamped and myocardial protection was afforded by applying topical iced saline slush in the pericardium during the 90-minute interval of SCP.

After 90 minutes of SCP, full-flow (100 mL/kg/min) CPB was reinstituted by pulling the arterial cannula back into aorta. The animals were warmed for a minimum of 25 minutes until the core temperature reached approximately 37°C. The heart was defibrillated as necessary at a nasopharyngeal temperature of 30°C. The animals were weaned from CPB, and the arterial and venous cannulas were removed. Protamine (5 mg/kg) was administered intravenously.

Microsphere Injections and Tissues Processing

Six fluorescent microsphere injections were performed in each animal, using 6 different colors of 15-μm–diameter microspheres: Coral-High, Purple-High, Pink-High, Yellow-High, Coral-Medium, and Purple-Medium. At each time point, approximately 2 million microspheres were injected and flushed with 5-mL saline solution. To allow calculation of absolute blood flow rates, we withdrew a reference blood sample from the right axillary artery into syringes at 5 mL/min with a Harvard withdrawal pump (Harvard Bioscience, Inc, Holliston, Mass) beginning at 10 seconds and continuing until 2 minutes after injection.

After the animals had been humanely killed and the skull removed, the left and right cerebral hemispheres were divided. Tissue samples were taken for microsphere counts at Interactive Medical Technologies Ltd, Irvine, California. The microspheres were recovered from the tissues by sedimentation and from the blood by using a commercial protocol. RBF was then calculated from the intensity of fluorescence microspheres in blood and tissue samples using this formula: RBF (mL/min/g) = $(R \times I_T)/(I_R \times Wt)$, where R is the rate at which the reference blood samples was withdrawn, I_T is the fluorescence intensity of the tissue samples, I_R is the fluorescence intensity of the blood samples, and Wt is the weight of the tissue sample.

Statistics

Results are expressed as mean ± standard deviation. All statistical analyses were performed with SAS software (SAS Institute, Inc, Cary, NC). Analysis of variance was used to compare baseline physiologic parameters among temperature and flow rate groups. Mixed model was used to analyze blood flow change from baseline among temperature and flow rate groups. A paired *t* test was used to compare the blood flow change between SCP at 45 minutes and 90 minutes.

RESULTS

No significant differences were seen in the physiologic parameters of either the temperature or flow rate groups at baseline (Tables 1 and 2).

During the SCP phase, all regions of brain showed slightly higher brain blood flow in the 32°C group compared with the 15°C and 25°C groups; however, there was no significant difference. At 2 hours after CPB (Figure 1), the RBF of the 32°C group was higher than that of the 15°C group ($P < .05$) in the caudate nucleus and hippocampus; RBF of the 32°C group was higher than that of the 25°C and the 15°C groups ($P < .05$) at the neocortex. In the cerebellum and brain stem, RBFs were higher in the 32°C group compared with the 25°C and the 15°C groups at 2 hours after CPB; however, there was no significant difference ($P = .31$ vs 25°C and $P = .07$ vs 15°C groups at the cerebellum; $P = .46$ vs 25°C and $P = .27$ vs 15°C groups at the brain stem).

No significant association was observed between SCP flow rate and RBF at a fixed temperature of 25°C in all investigated regions of the brain (Figure 2). No significant difference in RBF to the left or right sides of brain tissues was observed in either temperature or flow rate groups.