A Comparison of Complete Blood Replacement With Varying Hematocrit Levels on Neurological Recovery in a Porcine Model of Profound Hypothermic (<5°C) Circulatory Arrest

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Profound hypothermia (<5°C) may afford better neurological protection after circulatory arrest; however, there are theoretical concerns related to microcirculatory sludging of blood components at these ultra-low temperatures. We hypothesized that at temperatures <5°C, complete blood replacement results in superior neurological outcome. Twelve Yorkshire pigs (30 kg) underwent thoracotomy, cardiopulmonary bypass (CPB), and were randomly assigned to one of three target hematocrits during circulatory arrest: 0%, 5%, 15%. Hextend® (6% hetastarch in a balanced electrolyte vehicle) was used for the CPB prime and as an exchange fluid. Animals were cooled to a temperature <5°C, underwent 1-h circulatory arrest, and were warmed to 35°C with administration of blood to increase the hematocrit to >25% before separation from CPB. The primary outcome, peak postoperative neurobehavioral score, was compared between groups. The 0% group (mean ± SD) had significantly ($P <$ 0.02) better neurobehavioral scores than the 5% and 15% groups (6.0 ± 2.9 vs 1.3 ± 1.0 and 1.5 ± 0.6) respectively. Other variables (e.g., intracranial pressure) were similar between groups. In a porcine model of profound hypothermia (<5°C) and circulatory arrest, complete blood replacement resulted in superior neurological outcome. This finding suggests that at ultralow temperatures, the presence of some blood component (e.g., erythrocytes, leukocytes) may be deleterious.

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Since its introduction in 1975, deep hypothermic circulatory arrest (DHCA) has become a routinely practiced technique during cardiac and neurosurgical procedures (1–4). The optimal temperature at which DHCA is safe in regard to cerebral protection and neurological recovery remains unknown. Initially, Griepp et al. (2) suggested that a temperature of 12–18°C provides adequate cerebral protection provided that the duration of DHCA does not exceed 45 min. More recently, this same group has recommended that patients be cooled to 10–11°C if DHCA is expected to exceed 30 min (5).

DHCA longer than 45 min has been associated with an increased incidence of neurological events postoperatively (2). Injury in this setting may be a result of the fact that significant cerebral metabolism ($CMRO_2$) exists at a temperature of 18°C (2,5,6). McCullough et al. (5) determined that the cerebral metabolic rate for oxygen ($CMRO_2$) is still 17% of the normothermic baseline at a temperature of 18°C. One can speculate that a greater degree of hypothermia should further decrease $CMRO_2$ and may provide for superior cerebral protection. This theory is supported by studies in animal models (7–9). There is a concern, however, that profound hypothermia (<5°C) may be deleterious (10). At these extremely low temperatures, blood may change rheologically (i.e., there may be "sludge" in the microcirculation), causing organ dysfunction and increased morbidity. Observations in patients (11) and data from animal studies suggest that hemodilution is an important component of conducting DHCA safely (1).

Ultraprofound hypothermia (mean temperature 1.7°C) with complete blood replacement was achieved in a series of eight dogs without evidence of postoperative neurological dysfunction (12). That study, however, did not randomize animals to different hematocrit levels nor address the impact of hematocrit on outcome. In addition, that study used continuous whole body perfusion rather than circulatory arrest.

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Our study was designed to evaluate the impact of hematocrit on neurological outcome after 60 min of circulatory arrest under profound hypothermia (<5°C) using an established porcine model (13–16).

Methods

All study animals received humane care in compliance with the "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 National Institutes of Health (NIH-Publications No 88–23, revised 1985). The protocol for these experiments was approved by the Mount Sinai Institutional Animal Care and Use Committee.

Animals were transferred to the animal facility at the Mount Sinai School of Medicine 4 days before initiation of the experiment to allow for recovery from the stress of transportation.

Twelve female Yorkshire pigs aged 2–3 mo, weighing 27–31 kg, were randomly assigned to one of the following three target hematocrit groups using a sealed envelope technique: Group 1, Hematocrit 0%; Group 2, Hematocrit 5%; Group 3, Hematocrit 15% (Table 1).

On the morning before surgery animals were examined preoperatively for behavioral and neurological deficits. All animals were assigned a neurobehavioral score (NBS) by a veterinarian blinded as to the experimental protocol using a grading scale that evaluated mental status, appetite and gait as has been described previously (13–16). NBS consists of a nine-point scale as follows: Mental Status: 0 = comatose, 1 = stuporous, 2 = depressed, 3 = normal; Appetite: 0 = refuses liquids, 1 = refuses solids, 2 = decreased, 3 = normal; Motor Function: 0 = unable to stand, 1 = unable to walk, 2 = unsteady gait, 3 = normal. Therefore, NBS can range from 0 (profound neurological injury) to 9 (normal).

On the morning of surgery animals were anesthetized with ketamine 20 mg/kg IM. After placing an 18-gauge IV catheter, pentobarbital 12 mg/kg IV was given followed by tracheal intubation orally with a single lumen cuffed endotracheal tube. Cefazolin (1 gm), methyl prednisolone (250 mg), chlorpheniramine maleate (50 mg), and ranitidine (50 mg) were given IV. General anesthesia was maintained with isoflurane (1–2%) by inhalation. The animals were paralyzed with pancuronium (0.1 mg/kg) in intermittent doses as needed. They were maintained on positive pressure ventilation (F_{IO_2} 1.0) and the minute ventilation was titrated to maintain an arterial P_{CO_2} of approximately 30 mm Hg. All surgical procedures were performed in a sterile operating room including the use of aseptic technique, gowns, gloves and masks. A urinary catheter was inserted and urine output was measured at regular intervals. A femoral arterial catheter was inserted and a pulmonary arterial catheter (93A831H 7.5F, Baxter Healthcare Corp., Irvine, CA) was inserted into the pulmonary artery via the femoral vein. A catheter for intracranial pressure monitoring and temperature probes to measure esophageal, epidural, deep brain and rectal temperatures were inserted as described previously (16). End-tidal P_{CO_2} and inspiratory and expiratory isoflurane concentrations were monitored continuously and arterial blood gas analyses obtained at regular intervals.

Measurements

Arterial blood gas, hematocrit, and glucose analyses as well as esophageal, epidural, deep brain and rectal temperatures were measured at various time points during the experiment.

Arterial blood pH, P_{O_2}, P_{CO_2}, hematocrit, and blood glucose levels were measured using a model 288 Ciba-Corning analyzer (Ciba-Corning Diagnostics Corp., Medfield, MA). Hematocrits below 11% were measured directly after centrifugation.

A right thoracotomy was performed in the fourth intercostal space to expose the heart and great vessels. In all groups, after administration of heparin (300 U/kg), the ascending aorta was cannulated with a 16F arterial cannula and the right atrium was cannulated with a single 24F atrial cannula via the right atrial appendage. Nonpulsatile cardiopulmonary bypass (CPB) was instituted and a heat exchanger was used for core cooling. Surface cooling was achieved with the use of a cooling blanket as well as ice packs placed along the dorsum of the animal. Isoflurane was administered via the oxygenator and 60 mEq of potassium chloride was injected into the venous reservoir to render the heart isoelectric. A membrane oxygenator (VPCML plus; Cobe Laboratories Inc., Lakewood, CO) primed with a bloodless solution consisting of Hextend® (Abbott Laboratories, Chicago, IL), furosemide (1 mg/kg), and heparin (5000 U) was used.

CPB was established at a rate of 100 mL/kg per minute. The arterial pH was maintained, using α-stat principles, at 7.45 ± 0.05 with a targeted arterial P_{CO_2} of 30–35 mm Hg, uncorrected for temperature. CPB was continued until the esophageal temperature equaled 10–12°C, at which point the animals were hemodiluted as close to their target hematocrit as possible (e.g., 0%, 5%, or 15%) by removing blood via the venous cannula and replacing it with ice-cold Hextend®. Although the target hematocrit for the 0% group was 0, we recognized that it was not practical to remove every last red blood cell, hence we terminated hemodilution when the hematocrit decreased below 1%. Each of the four animals in the 0% group required exchanges with 12 L of Hextend® to achieve a hematocrit of <1%. Blood that had been withdrawn was

Table 1. Study Variables

Group	Target Hct (%)	Weight (kg)	Exchange volume (L)	Cooling time (min)	Warming time (min)
1	0	28 ± 1	12.0 ± 0.0*	93 ± 10	94 ± 11
2	5	29 ± 3	3.7 ± 0.3*	88 ± 23	76 ± 10
3	15	30 ± 1	1.5 ± 0.0*	98 ± 25	85 ± 15

Exchange volume = volume of Hextend® administered to achieve target hematocrit (Hct) and includes 1.5 liters of Hextend® added to cardiopulmonary bypass prime; Cooling time = duration from initiation of cardiopulmonary bypass to initiation of circulatory arrest; Warming time = duration from termination of circulatory arrest to esophageal temperature of 35°C.

Except for differences between exchange volume values (* $P < 0.05$ for all intergroup comparisons), there were no significant intergroup differences for other variables.

stored at 4°C. During the fluid exchange, the central venous pressure was maintained at 7–10 mm Hg by adjusting the relative rates of inflow and outflow. Animals were cooled to an esophageal temperature of 3.5°C (deep brain temperature of 2.6–5.5°C). The animals' heads were packed in ice and all animals were subjected to a 60-min period of circulatory arrest. Myocardial protection was afforded by applying iced saline topically during the circulatory arrest period.

After circulatory arrest, CPB (100 mL/kg per minute) was reinstituted, and core and surface rewarming were begun. Once the esophageal temperature reached approximately 11°C, re-exchange with the most dilute autologous blood began, followed by more concentrated autologous blood, and if necessary heterologous blood, during rewarming to maintain a hematocrit of at least 10%. Rewarming and re-exchange of fluid was continued until the esophageal temperature reached 35°C and the hematocrit was more than 20%. No animal's deep brain temperature was allowed to exceed 37°C. Animals were weaned from CPB with the administration of epinephrine, phenylephrine, lidocaine, sodium bicarbonate and electrical defibrillation as needed. Animals were administered cefazolin (1 gm), methyl prednisolone (250 mg), chlorpheniramine maleate (50 mg), and ranitidine (50 mg) IV after CPB was discontinued. Animals were extubated when they exhibited good respiratory mechanics and good oxygenation. Postoperative analgesia consisted of butorphanol (0.05 to 0.1 mg/kg administered subcutaneously twice a day) for 2 days. Animals were monitored for 7 days and then euthanized with a pentobarbital overdose on postoperative day 7.

Each postoperative day for 7 days, animals underwent examination and evaluation of behavioral outcome in the manner described for preoperative behavioral evaluation.

All results are expressed as mean ± SD. Significance was set at 0.05. The primary outcome of this study was the peak postoperative NBS. The Kruskal-Wallis Test (nonparametric analysis of variance) initially tested for potential differences among any of the three study groups with regard to the primary outcome. Dunn's multiple comparison tests were then used to compare differences between individual groups. Parametric analysis of variance and two-tailed *t*-tests with Tukey-Kramer multiple comparison tests were used to test for differences among groups with respect to continuous data (e.g., cooling time).

Results

All 12 animals underwent the surgical procedure without incident. All three study groups were similar with respect to study variables at baseline (Tables 1 and 2). Intraoperative changes for study variables are presented in Tables 1 and 2 and in Figure 1. With the exception of arterial P_{CO_2} at one time point and glucose levels at one time point, there were no significant differences among groups in any of these variables (e.g., intracranial pressure) at baseline or at other time points. Of note, there were no significant differences in cooling or warming times.

With respect to the primary outcome of the study, i.e., peak postoperative NBS, results for the three groups are depicted in Figure 1. Animals from the 0% hematocrit group had significantly ($P < 0.05$) better postoperative NBS (mean ± SD) compared with the 5% and 15% groups. (6.0 ± 2.9 vs 1.3 ± 1.0 and 1.5 ± 0.6) respectively. There was no significant difference between the 5 and 15% groups. Three of the four animals in the 0% hematocrit group were awake and had baseline mental status at the end of surgery (each of them scored a 3 for mental status). Two of these animals went on to achieve peak scores of 8 and 9. The third animal with excellent mental status (3 points) was able to drink liquids (1 point), and was already attempting to stand (0 points because not actually able to stand) within hours of surgery (total score at this point of 4). Unfortunately, this animal, which probably would have ultimately achieved complete recovery, died within 24 h after surgery, possibly as a result of a butorphanol overdose, and thus its peak score remained a 4. The fourth animal in this group lived for the entire 7-day postoperative observation period but exhibited poor mental status and was not able to stand (peak total score of 3).

Most of the animals in the 5% and 15% hematocrit groups had poor mental status and poor neurological

Table 2. Intraoperative Changes

Group	Time point	Hct	DBT	MAP	ICP	Arterial pH	Pao_2	$Paco_2$	Glucose
0%	Base	29 ± 3	32 ± 1	70 ± 11	11 ± 3	7.6 ± 0.0	305 ± 60	35 ± 4.6	126 ± 12
	Prearrest	0 ± 0	5 ± 0	34 ± 8	13 ± 3	7.5 ± 0.1	511 ± 48	20 ± 8*	95 ± 4
	Close	29 ± 4	35 ± 1	74 ± 7	11 ± 4	7.5 ± 0.1	476 ± 119	35 ± 2.5	194 ± 56
5%	Base	31 ± 3	34 ± 1	71 ± 9	9 ± 3	7.5 ± 0.1	277 ± 42	39 ± 3	108 ± 16
	Prearrest	5 ± 1	4 ± 1	39 ± 4	8 ± 4	7.5 ± 0.1	553 ± 47	34 ± 3.5	102 ± 8
	Close	27 ± 1	34 ± 1	73 ± 21	7 ± 3	7.4 ± 0.1	518 ± 133	43 ± 4.6	176 ± 51
15%	Base	30 ± 3	34 ± 2	71 ± 13	8 ± 4	7.5 ± 0.1	345 ± 172	40 ± 3	122 ± 19
	Prearrest	14 ± 2	3 ± 1	40 ± 12	8 ± 3	7.5 ± 0.0	537 ± 27	39 ± 3	119 ± 9*
	Close	24 ± 1	35 ± 2	71 ± 14	12 ± 6	7.4 ± 0.1	618 ± 63	45 ± 8	218 ± 59

Data are reported as mean ± SD.

Base = immediately prior to initiation of cardiopulmonary bypass (CPB); Pre-Arrest = immediately prior to initiation of circulatory arrest; Close = at the time of skin closure; Hct = hematocrit; DBT = deep brain temperature (°C); MAP = mean arterial pressure (mm Hg); ICP = intracranial pressure (mm Hg); Glucose = blood glucose (mg/dL).

* Significantly different ($P < 0.05$) from the other two groups at the same time point; all other intergroup comparisons for other variables were not significant.

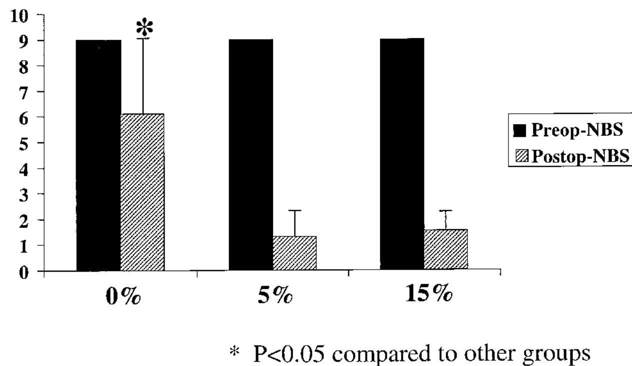

Figure 1. This figure depicts the neurobehavioral score (NBS) values (mean ± SD) in the three study groups at the following study time points: Preop (before surgery) and Postop (peak value in the postoperative period). Of note, SD for Preop is 0.0 for all groups because all animals had a NBS of 9.

recovery. Despite adequate oxygenation and ventilation, these animals had very poor mental status that did not improve significantly over time. Although animals improved somewhat over several days, it generally becomes apparent within 24–48 h whether the animal had done well after surgery. Many of animals with poor mental status also exhibited shallow breathing and tachypnea of unclear etiology. No differences were observed in coagulation or degree of bleeding among the three experimental groups.

Discussion

Since the widespread adoption of the use of hypothermic circulatory arrest for cerebral protection clinicians have searched for methods of extending the safe duration of hypothermic circulatory arrest. McCullough et al. (5) determined that the $CMRO_2$ is still 17% of the normothermic baseline at a temperature of 18°C and it has been proposed that lower temperatures (<5°C) may provide for superior neurological protection during periods of circulatory arrest (2,5).

There are concerns, however, that the presence of blood at these ultralow temperatures may be deleterious. For example, sludging of erythrocytes and leukocytes at these temperatures may result in occlusion of the microvasculature (10). In 1962 Björk and Hultquist (11) described a frequent incidence of brain damage in patients subjected to deep hypothermic CPB (5.8–13.8°C) compared with mild/moderate CPB at 30–37°C. They speculated that this injury might be because of an increased viscosity of the blood and "sequestration of thrombocytes and white blood corpuscles forming thrombi in the brain capillaries" during profound hypothermia. This and other reports led to the routine use of moderate hemodilution (hematocrit ≈ 15–25%) during periods of hypothermic (≈ 15–32°C) CPB. It is unknown, however, if moderate hemodilution is sufficient to prevent neurologic injury at ultralow temperatures (<5°C).

Our study was designed to test the hypothesis that at temperatures <5°C, complete blood replacement results in superior neurological outcome. Using an established porcine model (13–16), we randomized animals to three different target hematocrits during circulatory arrest. In this model, complete blood replacement resulted in superior postoperative neurological outcome compared with lesser degrees of hemodilution. This result does not appear to be attributable to differences in temperature, blood pressure, or other hemodynamic variables, as most of these variables were similar among groups. We cannot eliminate the remote possibility that anesthetic drug levels were different among groups (because of the exchange of fluids) or that the addition of more "fresh" Hextend® (12 L) in the 0% group during the exchanges resulted in differences in outcome. There was a small difference in blood glucose concentrations among some of the groups at one time point only. At

this time point (prearrest), the 15% group's glucose level (119 ± 9) was statistically larger than the 5% (102 ± 8) and 0% (95 ± 4) group's glucose levels. Of note, at this time point there was no statistically significant difference between the 0 and 5% groups' glucose levels. The differences between the 15% and 0%, and 15% and 5% groups, despite being statistically significant, are quite small (≈25 mg/dL). It is unlikely that these differences accounted for the study's outcome findings because the 5% group, which had a glucose level (102 ± 8) comparable to that of the 0% group (95 ± 4, no significant difference between glucose levels), did as poorly as the 15% group.

The following theoretical arguments, in our opinion, are potential mechanisms for the worse outcome observed in pigs undergoing circulatory arrest with residual blood. The different potential mechanisms described below could either act alone or work together to cause injury.

One possibility is that at these very low temperatures the rheology of erythrocytes and leukocytes changes making them more likely to occlude the microvasculature (11). This mechanism of injury would be consistent with the global nature of the injury we observed in all animals with brain injury. A second possibility is that at these low temperatures leukocytes become activated. The presence of activated leukocytes in the microvasculature, in close proximity to the endothelium, may lead to endothelial injury. This type of injury would also be consistent with evidence of global injury as observed in our study. This mechanism was suggested by a study of 16 piglets undergoing 60 minutes of hypothermic circulatory arrest at 18°C in which animals randomized to use of a leukocyte filter had a trend toward better recovery of cerebral blood flow (17). In another example, Cooper et al. (18) described multisystem vascular endothelial dysfunction and apoptosis in pigs randomized to hypothermic circulatory arrest.

A third possibility is that one or more noncellular components of the blood become "activated" at these low temperatures resulting in systemic and/or regional inflammation and injury. For example, platelet-activating factor is a blood-borne substance that can have numerous pathologic functions. In a study of 14 piglets undergoing 60 minutes of circulatory arrest at 18°C, animals randomized to receive ginkgolide B (a potent antagonist of platelet activating factor) demonstrated improved recovery of cerebral blood flow and oxygen metabolism (19). Hence, it is not unreasonable to speculate that elimination of platelet activating factor and other blood-borne compounds by total body washout might result in improved neurological outcome during circulatory arrest and profound hypothermia.

A fourth possibility relates to the lower prearrest $Paco_2$ of the animals in the 0% group. We found it difficult to achieve the target $Paco_2$ in the 0% group animals perhaps related to the lack of blood constituents in these animals. The animals in this group were the same temperature as in the other groups so that this difference in $Paco_2$ was unlikely to be related to differences in carbon dioxide production. It is possible that the more pronounced hypocarbia at the prearrest time point may have contributed to or accounted for the differences in postoperative neurological outcome.

Our results in mature pigs undergoing circulatory arrest at profound hypothermia (<5°C) are different from those described in piglets undergoing circulatory arrest at 15°C (20,21). In these studies, piglets exposed to higher hematocrits had the best outcome. It is possible that the deleterious effects of hypothermia on blood cells or other blood components become apparent only at the profound levels of hypothermia used in our study. It is also possible that immature pigs respond differently to this type of insult compared with the mature pigs used in our study. Our study was not designed to explore these interesting issues.

Hemodilution in our study was achieved using Hextend®. Hextend® is a colloid solution composed of 6% hetastarch in a balanced electrolyte vehicle that contains lactate and physiologic levels of glucose (22). It contains sodium (143 mEq/L), potassium (3 mEq/L), chloride (124 mEq/L), calcium (5 mEq/L), magnesium (0.9 mEq/L), glucose (0.99 mg/dL), and lactate (28 mEq/L). We deemed use of a colloid solution essential for this study given the plan for total replacement of the blood and plasma with this fluid. Use of a crystalloid fluid may have resulted in dangerous or lethal levels of tissue edema. With the exception of Hextend®, all available colloid plasma volume expanders are formulated in normal saline-based vehicles. Use of a normal saline-based vehicle (e.g., Hespan®; DuPont Pharma, Wilmington, DE) to completely replace the blood and plasma of animals in our study may have resulted in lethally small levels of potassium, calcium, and glucose as well as very large levels of chloride. In addition, lactate, found in Hextend®, is important in providing substrate for the liver to synthesize new stores of bicarbonate.

In conclusion, in an established porcine model, complete blood replacement resulted in superior neurological outcome in animals exposed to profound hypothermia (<5°C) and circulatory arrest. This finding suggests that at ultralow temperatures the presence of some blood component (e.g., erythrocytes, leukocytes, serum protein) may be deleterious.

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