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Brain Blood Flow and Metabolism Do Not Decrease at Stable Brain Temperature during Cardiopulmonary Bypass in Rabbits

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Cerebral blood flow (CBF) during human hypothermic cardiopulmonary bypass has been reported to decrease with time, suggesting that progressive cerebral vasoconstriction or embolic obstruction may occur. We tested the hypotheses: 1) that observed CBF reductions were due to continued undetected brain cooling and 2) that CBF during cardiopulmonary bypass would be stable after achievement of constant brain temperature. Anesthetized New Zealand White rabbits underwent cardiopulmonary bypass (membrane oxygenator, centrifugal pump, bifemoral arterial perfusion) and were assigned to one of three bypass management groups based on perfusate temperature and Pa_{CO_2} management: group 1 (37° C, n = 8); group 2 (27° C, *p*H-stat, n = 9); and group 3 (27° C, α-stat, n = 8). Systemic hemodynamics, and cerebral cortical, esophageal, and arterial perfusate temperatures were recorded every 10 min for the first hour of bypass and again at 90 min. CBF and masseter blood flow (radiolabeled microspheres) were determined at 30, 60, and 90 min of bypass, while the cerebral metabolic rate for oxygen (CMR_{O_2}) was determined at 60 and 90 min. Groups were comparable with respect to mean arterial pressure, central venous pressure, hematocrit, and arterial oxygen content throughout bypass. Cortical temperature was stable in normothermic (group 1) animals, and there was no significant change in CBF between 30 and 90 min of bypass: 68 ± 18 *versus* 73 ± 20 ml · 100 g^{-1} · min^{-1} (mean ± SD). In the hypothermic groups (2 and 3), cortical temperature equilibration (95% of the total change) required 41 ± 6 min. In agreement with our hypothesis, once brain temperature had stabilized in hypothermic animals, we found no significant change in CBF between 60 and 90 min of bypass—37 ± 6 *versus* 37 ± 7 ml · 100 g^{-1} · min^{-1} (*p*H-stat) and 31 ± 6 *versus* 30 ± 3 ml · 100 g^{-1} · min^{-1} (α-stat). There was no significant change in CMR_{O_2} between 60 and 90 min of bypass in any group—3.8 ± 1.4 *versus* 3.4 ± 1.1 ml · 100 g^{-1} · min^{-1} (37°C); 1.4 ± 0.4 *versus* 1.2 ± 0.3 ml · 100 g^{-1} · min^{-1} (*p*H-stat); and 1.3 ± 0.4 *versus* 1.3 ± 0.5 ml · 100 g^{-1} · min^{-1} (α-stat). We conclude that at constant brain temperature, CBF and CMR_{O_2} are stable during cardiopulmonary bypass, and if progressive cerebral vasoconstriction and/or embolic obstruction occur, such events occur either during the early phase of bypass or, if later, at levels below the resolution of this study. (Key words: Anesthesia: cardiovascular. Brain: blood flow; hypothermia; metabolism. Surgery, cardiac: cardiopulmonary bypass. Temperature: hypothermia.)

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BECAUSE NEUROLOGIC COMPLICATIONS are common following cardiac surgery,[1] it is important to better characterize the cerebral physiology of cardiopulmonary bypass and to understand how it may influence neurologic outcome. Of particular interest, Rogers *et al.* observed that cerebral blood flow (CBF) decreased 4 ± 4 ml · 100 g^{-1} · min^{-1} (mean ± SD) over a period of 26 ± 15 min during human hypothermic bypass, despite stable nasopharyngeal temperature.[2,**] The same workers later reported that CBF responses to changing Pa_{CO_2} ($\Delta CBF/\Delta Pa_{CO_2}$) decreased with time during stable hypothermic bypass.[3] They proposed a progressive decline in CBF to account for these findings, ranging from 0.1 ± 0.1 to 0.4 ± 0.5 ml · 100 g^{-1} · min^{-1} per minute. The authors suggested that CBF reductions might be attributed to progressive cerebral vasoconstriction and/or microvascular (embolic) obstruction, potentially resulting in cerebral hypoperfusion and neurologic injury.

Both CBF and the cerebral metabolic rate for oxygen (CMR_{O_2}) are influenced by temperature. In a prior study using a rabbit model of cardiopulmonary bypass, we proposed that brain temperature equilibration during hypothermic bypass is much slower than generally appreciated and that brain temperature lags considerably behind that of the esophagus.[4] We hypothesized that CBF reductions during apparently stable hypothermic bypass might be due to continued, but undetected, brain cooling. The current experiment was therefore designed to answer the following questions: 1) How quickly does the brain cool during hypothermic bypass? 2) At constant, directly measured, brain temperature, do CBF and/or CMR_{O_2} actually change during cardiopulmonary bypass? 3) Are there differences in the stabilities of CBF and/or CMR_{O_2} as functions of temperature (normothermic *vs.* hypothermic bypass) and/or blood gas management (α-stat *vs.* *p*H-stat)?

Materials and Methods

The experimental protocol was approved by the Animal Care Committee of the University of Iowa. Anesthesia was induced with halothane in oxygen in 25 New Zealand White rabbits (weight 4.2 ± 0.7 kg). A tracheotomy was

** Calculated from data presented in figure 1 of Rogers *et al.*[2]

performed and the lungs ventilated to achieve normocarbia using a gas mixture containing 1.5% halothane in 33% oxygen/balance nitrous oxide. The animals were paralyzed with a succinylcholine infusion and placed prone. After a midline sagittal scalp incision, a 2-mm burr hole was drilled over the right frontoparietal cortex, and a calibrated 1 mm thermocouple (K-type, L-08419-02, Cole Palmer Instrument Co., Chicago, IL) was introduced under the cranium so as to rest on the dural surface. A posterior midline craniotomy was then performed, exposing the confluens sinuum. A loading dose of heparin was administered (200 U/kg intravenously), and heparin was added to the succinylcholine infusion to give a maintenance dose of 200 $U \cdot kg^{-1} \cdot h^{-1}$. The tip of a polyethylene catheter (PE-90, Intramedic, Parsippany, NJ) was then placed in the confluens sinuum, permitting collection of venous blood originating from the cerebral hemispheres.[5] The cortical thermocouple and cerebral venous catheter were secured with bone wax and fast-drying cyanoacrylate cement and the animals turned supine.

Esophageal temperature was monitored *via* calibrated thermocouple (same model as above) placed in the midesophagus. Central venous pressure was measured *via* the right external jugular vein (PE-90). Both brachial arteries were cannulated (PE-160) for microsphere reference blood samples. Teflon catheters (14-G, 32 mm long) were inserted into each femoral artery, and, after sternotomy and supplemental heparin (300 U/kg intravenously), an 18-Fr right atrial catheter was secured using a purse-string suture. Approximately 30 min before cardiopulmonary bypass was started, halothane, nitrous oxide, and the succinylcholine/heparin infusion were discontinued. Anesthesia was thereafter maintained with fentanyl (100-μg/kg loading dose, 2.5-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion) and midazolam (1-mg/kg loading dose, 33-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion). Muscle relaxation was achieved with pancuronium (0.2 mg/kg).

The bypass circuit consisted of a venous reservoir, a centrifugal blood pump (Biomedicus, Eden Prairie, MN), a membrane oxygenator/heat exchanger (Terumo, Piscataway, NJ), and a variable-temperature water pump. A continuous in-line blood gas analysis sensor, which also measured arterial perfusate temperature (model 200, Cardiovascular Devices Inc., Irvine, CA), was placed distal to the oxygenator and was calibrated against blood samples analyzed *via* standard blood gas analysis (see below).†† The priming fluid consisted of 300 ml 6% (wt/vol) hydroxyethyl starch in 0.72% sodium chloride, 15 mEq sodium bicarbonate, 250 mg $CaCl_2$, 1 mEq KCl, and 1,000 U heparin. The priming fluid was circulated through a 40-μm filter for at least 60 min prior to the addition of ~150 ml filtered rabbit packed red blood cells, achieving a priming hematocrit of 23 ± 2%.

Animals were randomly assigned to one of three groups: group 1 (37° C, n = 8), group 2 (27° C, *p*H-stat management, n = 9), or group 3 (27° C, α-stat management, n = 8); the water temperature to the heat exchanger was preequilibrated accordingly. Cardiopulmonary bypass was initiated (bifemoral inflow, right atrial return) and maintained at a flow of ~100 $ml \cdot kg^{-1} \cdot min^{-1}$ monitored with a calibrated in-line electromagnetic flow meter, with systemic cooling in groups 2 and 3 beginning immediately with initiation of bypass. The pulmonary artery was clamped, and a 16-G catheter was placed in the left ventricle to permit drainage to the venous reservoir. Arterial pressure was measured from the left brachial arterial catheter. No pharmacologic or mechanical method was used to control arterial pressure. With both group 1 (37° C) and group 3 (27° C, α-stat) animals, the oxygenator was ventilated with a variable mixture of oxygen and nitrogen to maintain Pa_{CO_2} near 40 mmHg and Pa_{O_2} near 250 mmHg when measured at 37° C. With group 2 (27° C, *p*H-stat), oxygen and nitrogen flows were adjusted to keep Pa_{CO_2} near 40 mmHg when corrected to arterial perfusate temperature.

The following variables were recorded every 10 min for 60 min of bypass, and then again at 90 min: mean arterial pressure, central venous pressure, bypass flow rate, brain (cortical) temperature, esophageal temperature, arterial perfusate temperature, hematocrit, and arterial blood gases (values measured at 37° C and temperature-corrected values). CBF determinations (see below) were made at 30, 60, and 90 min of bypass. At 60 and 90 min of bypass, arterial and cerebral venous blood was collected for measurement of oxygen content via the extraction/galvanic cell method. (Lex-O_2-Con, Lexington Instruments Corporation, Waltham, MA).[6,7]‡‡ Sodium bicarbonate was given to maintain base deficit of not greater than 4 mEq/l, measured at 37° C (1.5 ± 1.0 $mEq \cdot kg^{-1} \cdot h^{-1}$). At experiment completion, animals were killed by discontinuation of bypass and intracardiac administration of saturated KCl solution.[8]

†† All blood gases were measured on an IL1304 *p*H/blood gas analyzer (Instrumentation Laboratory, Lexington, MA) with an electrode temperature of 37° C. Values were corrected to the animal's perfusate temperature using the internal blood gas correction program of IL1304 (National Committee for Clinical Laboratory Standards: Definition of quantities and conventions related to blood *p*H and gas analysis. Catalog #C12-T).

‡‡ The specific aim of this study was to assess the stability of cerebral blood flow and metabolism at constant brain temperature. Because sampling from the confluens sinuum was technically difficult and pilot studies indicated that brain temperature equilibration would not be achieved by 30 min of bypass, cerebral venous blood was not collected at 30 min of bypass.

CBF was measured by the radioactive microsphere technique. Isotopes used included ^{141}Ce, ^{95}Nb, ^{46}Sc, and ^{85}Sr (New England Nuclear, Boston, MA), although only three isotopes were used in each experiment. Two hundred microliters of stock microspheres (~900,000 microspheres), vigorously mixed for 5 min prior to withdrawal, were diluted in 1.5 ml suspending solution (10% dextran 40 in normal saline with 0.5% [vol/vol] Tween-80) and mixed an additional 60 s. Microspheres were injected over 30 s into the arterial perfusion tubing just proximal to its bifurcation into the two femoral inflow cannulae. Starting 15 s before microsphere injection, and continuing 90 s thereafter, blood was simultaneously withdrawn from each brachial arterial catheter *via* calibrated withdrawal pump (1.96 ml/min). After the experiment, the brain was removed and dissected into the following regions: right and left cerebral hemispheres, cerebellum, midbrain, and medulla. Right and left masseter muscles were also sampled. Fresh tissue samples were weighed and placed in counting tubes, and, with reference blood samples, each was counted for 5 min in a γ counter. Isotope separation, background and overlap corrections, and organ blood flow calculations ($ml \cdot 100\ g^{-1} \cdot min^{-1}$) were performed by standard techniques.[9-11] Weight-averaged values for right and left masseter and right and left cerebral hemispheric blood flow were used to calculate mean masseter blood flow and mean hemispheric CBF. Weight-averaged values for each brain region were used to calculate global CBF.

CMR_{O_2} ($ml \cdot 100\ g^{-1} \cdot min^{-1}$) was calculated as the product of mean hemispheric CBF ($ml \cdot 100\ g^{-1} \cdot min^{-1}$) and the arterial − cerebral venous oxygen content difference (milliliters oxygen per 100 ml blood). Cerebral oxygen extraction ratio (OER) was calculated as the arterial − cerebral venous oxygen content difference divided by the arterial oxygen content.

Statistics

Right and left microsphere counts were distributed normally, permitting linear regression analysis to test adequacy of microsphere mixing and distribution. Box plots showed systemic physiologic variables to be normally distributed. Thus, these variables were expressed as mean ± standard deviation. Time to achieve 95% of the total change in temperature (cerebral cortex and esophagus) was calculated by linear interpolation of the temperature *versus* time data for each hypothermic animal.

Changes in CBF and CMR_{O_2} over time were analyzed for each group independently by linear regression.[12] (See Appendix.) Because CBF followed a normal distribution, we analyzed differences in CBF. On the other hand, because CMR_{O_2} was log-normally distributed, we tested whether the ratio of CMR_{O_2} values at 60 and 90 min was significantly different than 1. Statistical power was calculated at the 80% level to detect a change in CBF or CMR_{O_2} with an α of 0.05.[13]

Results

Paired right and left microsphere reference counts were well matched ($r^2 = 0.94$, slope = 0.98, intercept [921 cpm] not significantly different than zero), indicating excellent microsphere mixing and uniform distribution. There were no right–left blood flow asymmetries between either the cerebral hemispheres or masseter muscles.

Systemic physiologic variables are shown in table 1. There were no physiologically meaningful intra- or intergroup differences at 30, 60, and 90 min of bypass with respect to the following variables: mean arterial pressure, central venous pressure, Pa_{O_2}, hematocrit, and arterial oxygen content. As intended, arterial *p*H and P_{CO_2} differed between α-stat and *p*H-stat management, but values were constant within all groups at 30, 60, and 90 min of bypass.

Cortical temperature as a function of group assignment and bypass duration is shown in figure 1. Cortical temperature was constant over the entire 90 min of bypass in group 1 (37° C). There were no differences in cortical temperature between group 2 (*p*H-stat) and group 3 (α-stat) at any time, nor any difference in the time required to achieve 95% of the total change in temperature (39 ± 6 *vs.* 42 ± 6 min, respectively). Only 1 of 17 hypothermic animals achieved 95% cortical temperature equilibration in 30 min or less. Thus, CBF and CMR_{O_2} comparisons in groups 2 (*p*H-stat) and 3 (α-stat) are made only on data obtained at 60 and 90 min of bypass, during which time cortical temperature was constant. Esophageal temperature achieved 95% equilibration by 29 ± 4 min. The median difference between cortical and esophageal temperature exceeded 1° C for the first 30 min of cooling (fig. 2).

Cerebral physiologic variables are shown in table 2. For clarity, *P* values and power analyses for the following comparisons are shown in table 3. There was no significant change in global CBF between 30 and 90 min of bypass in group 1 (37° C): 68 ± 18 *versus* 73 ± 20 $ml \cdot 100\ g^{-1} \cdot min^{-1}$. There were no significant changes in global CBF between 60 and 90 min of bypass in either group 2 (*p*H-stat; 37 ± 6 *vs.* 37 ± 7 $ml \cdot 100\ g^{-1} \cdot min^{-1}$) or group 3 ($\alpha$-stat; 31 ± 6 *vs.* 30 ± 3 $ml \cdot 100\ g^{-1} \cdot min^{-1}$). There was no significant change in CMR_{O_2} between 60 and 90 min of bypass in any group: group 1 (37° C): 3.8 ± 1.4 *versus* 3.4 ± 1.1 $ml \cdot 100\ g^{-1} \cdot min^{-1}$; group 2 (*p*H-stat): 1.4 ± 0.4 *versus* 1.2 ± 0.3 $ml \cdot 100\ g^{-1} \cdot min^{-1}$; and group 3 ($\alpha$-stat): 1.3 ± .04 *versus* 1.3 ± 0.5 $ml \cdot 100\ g^{-1} \cdot min^{-1}$. Masseter blood flow was equivalent among groups and measurement intervals, averaging 16 $ml \cdot 100\ g^{-1} \cdot min^{-1}$.

TABLE 1. Systemic Physiologic Variables during Cardiopulmonary Bypass

Group	Bypass Time (min)	Mean Arterial Presure (mmHg)	Central Venous Pressure (mmHg)	Hematocrit (%)	Arterial O_2 Content (ml/dl)	pH_a		$Paco_2$		Pao_2	
						37° C	Corrected*	37° C	Corrected*	37° C	Corrected*
1: 37° C	30	88 ± 6	5 ± 3	25 ± 2	—	7.37 ± .05		37 ± 3		234 ± 55	
	60	90 ± 6	5 ± 2	24 ± 2	11.1 ± 0.7	7.35 ± .04		39 ± 1		270 ± 121	
	90	88 ± 8	5 ± 2	25 ± 2	10.9 ± 0.5	7.33 ± .05		38 ± 2		264 ± 126	
2: 27° C, *p*H-stat	30	86 ± 20	5 ± 2	24 ± 2	—	7.24 ± .04	7.37 ± .03	58 ± 5	37 ± 3	349 ± 157	295 ± 144
	60	94 ± 21	5 ± 2	24 ± 2	10.8 ± 1.1	7.22 ± .02	7.36 ± .02	63 ± 3	40 ± 2	315 ± 73	266 ± 68
	90	98 ± 21	5 ± 2	24 ± 2	10.5 ± 1.2	7.23 ± .03	7.37 ± .03	63 ± 3	40 ± 2	314 ± 74	265 ± 70
3: 27° C, α-stat	30	99 ± 14	5 ± 2	24 ± 3	—	7.35 ± .03	7.49 ± .03	41 ± 2	27 ± 2	360 ± 87	311 ± 82
	60	103 ± 18	5 ± 2	24 ± 1	11.2 ± 0.7	7.37 ± .02	7.52 ± .02	40 ± 2	26 ± 2	297 ± 53	250 ± 51
	90	107 ± 15	6 ± 2	24 ± 1	11.6 ± 0.9	7.37 ± .02	7.52 ± .03	38 ± 2	24 ± 1	276 ± 42	230 ± 40

Mean ± SD. Group 1 (37° C, n = 8); group 2 (27° C, *p*H-stat, n = 9); group 3 (27° C, α-stat, n = 8). * Corrected to arterial perfusate temperature.

Discussion

In a study of 12 patients undergoing hypothermic cardiopulmonary bypass, Rogers *et al.* observed spontaneous reductions in CBF ranging from 0 to 14 ml · 100 $g^{-1} \cdot min^{-1}$ (mean = 4 ml · 100 $g^{-1} \cdot min^{-1}$) over a period of 16 to 70 min (mean = 26), corresponding to a rate of decline of 0.2 ± 0.2 ml · 100 $g^{-1} \cdot min^{-1}$ per minute.[2] The authors used the data to time-correct CBF data in subsequent studies of cerebrovascular responses to phenylephrine and sodium nitroprusside during bypass.[14,15] Recently, Prough *et al.* presented additional evidence for a reduction in CBF during stable hypothermic bypass, with estimated rates of decline between 0.1 ± 0.1 and 0.4 ± 0.5 ml · 100 $g^{-1} \cdot min^{-1}$ per minute over a measurement interval of 20–30 min.[3] In the latter study, nasopharyngeal temperature and CMR_{O_2} were unchanged over the measurement interval. Based on this, the authors suggested that CBF reductions were unlikely due to continued undetected brain cooling but more likely due to progressive cerebral vasoconstriction and/or microvascular (embolic) obstruction.[3] In a prior investigation using our rabbit bypass model, we also found a significant inverse correlation between CBF and bypass duration.[4] When the earliest time points were omitted (CBF measured at 23 ± 5 min of bypass), the correlation between CBF and time disappeared. This suggested to us that the early dependency of CBF on bypass duration was most likely due to incomplete brain cooling in the early phase of bypass, which was undetected by esophageal thermometry. We hypothesized that if decline in CBF during cardiopulmonary bypass was due to progressive cerebral vasoconstriction and/or embolic obstruction, such a decline would occur at stable brain temperature and would also be observed during later periods of bypass. If, on the other hand, both CBF and CMR_{O_2} were unchanged over time at constant brain temperature, then progressive cerebral vasoconstriction and/or microvascular obstruction would be essentially ruled out.

In this experiment, with unchanging, directly measured, cortical temperature, there were no significant changes in either CBF or CMR_{O_2} over time during either normothermic or hypothermic bypass. Power analysis (table 3) indicated an 80% probability of detecting a CBF change of 2 ml · 100 $g^{-1} \cdot min^{-1}$ in the α-stat group and 5 ml · 100 $g^{-1} \cdot min^{-1}$ in the *p*H-stat group. Over the 30-min measurement interval, this would correspond to the ability to detect a decline of CBF of 0.07 and 0.17 ml · 100 $g^{-1} \cdot min^{-1}$ per minute, respectively; values less than or equal to those reported by Rogers *et al.*[2] and Prough *et al.*[3] During normothermic bypass, due to larger intraindividual CBF variation, 80% power of detecting a CBF change was considerably weaker, 19 ml · 100 $g^{-1} \cdot min^{-1}$. Over the longer measurement interval in this group (60 min), this corresponds to the ability to detect a CBF de-

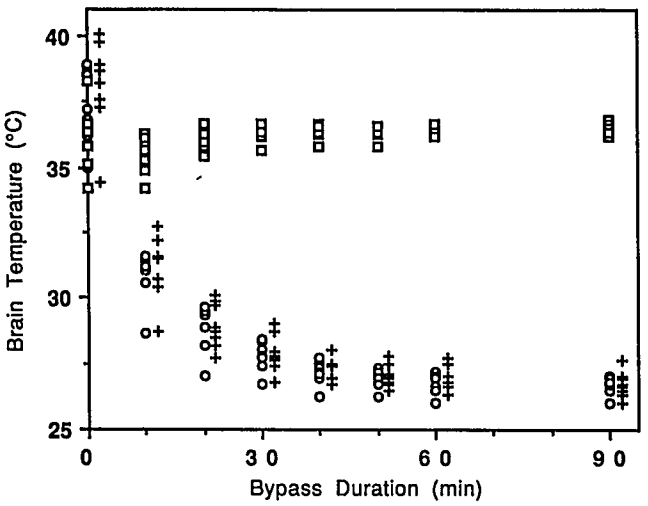

FIG. 1. Brain temperature during cardiopulmonary bypass. Squares = group 1 (37°C, n = 8); circles = group 2 (27°C, *p*H-stat, n = 9); crosses = group 3 (27°C, α-stat, n = 8). Missing data points are due to overlap. Group 3 data points are right-shifted for clarity.

crease of 0.32 ml · 100 g^{-1} · min^{-1} per minute. A similar pattern was noted with respect to CMR_{O_2}. Over the measurement interval, we had sufficient power to detect declines of 23% and 6% in groups 2 (*p*H-stat) and 3 (α-stat) respectively, corresponding to absolute changes in CMR_{O_2} of 0.32 and 0.08 ml · 100 g^{-1} · min^{-1}. Again, during normothermia, due to larger intraindividual variation, 80% power of detecting a CMR_{O_2} change was markedly weaker, corresponding to a change in CMR_{O_2} of 1.4 ml · 100 g^{-1} · min^{-1}. Overall, we observed neither reductions in CBF or CMR_{O_2} nor any evidence for a differential effect of either temperature or blood gas management upon stability of CBF or CMR_{O_2}. Thus, we find no evidence of either embolic obstruction or progressive cerebral vasoconstriction during cardiopulmonary bypass, as indicated by changes in CBF and CMR_{O_2}. If either is present, it occurs at levels below detection with current methodology. This is consistent with studies in humans wherein CBF and/or CMR_{O_2} were stable during hypothermic bypass and, in the absence of circulatory arrest, returned to prebypass values with warming and separation from bypass.[16–21]

What can account for the differences between the findings of Rogers *et al.*[2] and Prough *et al.*[3] and those of this experiment? Because membrane oxygenators were used in both the aforementioned studies and this experiment, differences in cerebral embolization based on oxygenator type are unlikely. Prough *et al.* and Rogers *et al.* did not report the duration of hypothermic bypass at which initial (control) CBF measurements were taken, stating only that nasopharyngeal temperature had been stable for at least 5 min.[2,3] Based on this description, it seems likely that control measurements were made earlier in the course of hypothermic bypass than our control measurements (60 min). Thus, if cerebral vasoconstriction and/or embolic obstruction occur primarily in the early phase of bypass, our experiment would not have detected it, whereas evidence for such a process might be observed by Rogers *et al.* and Prough *et al.* Nevertheless, we believe that the most likely explanation for the decrements in CBF previously reported from human studies is, simply, continued brain cooling in the early phase of bypass, despite stable nasopharyngeal temperatures.

There are few studies comparing nasopharyngeal and brain temperature in humans or primates during hypothermia. In a study of 13 adults undergoing neurosurgery with hypothermia (29° C, using surface cooling), Whitby and Dunkin found that nasopharyngeal temperature underestimated brain temperature by 0.5–1.0° C.[22] In that study, temperature measurements were made under fairly

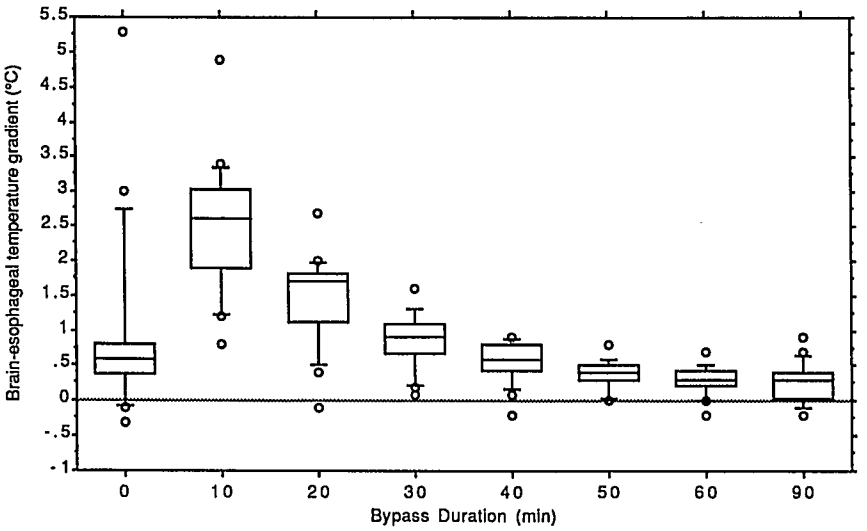

FIG. 2. Box plot of brain–esophageal temperature gradient during cardiopulmonary bypass in hypothermic groups 2 (n = 9) and 3 (n = 8). The 10th and 90th percentiles are delimited by the bars, and the 25th and 75th percentiles by the ends of the boxes. The median is marked by the horizontal line within the box. Circles represent values outside the 10th and 90th percentiles.

TABLE 2. Cerebral Physiologic Variables during Cardiopulmonary Bypass

Group	Bypass Time (min)	Cortical Temperature (° C)	Global Cerebral Blood Flow (ml · 100 g^{-1} · min^{-1})	Hemispheric Blood Flow (ml · 100 g^{-1} · min^{-1})	Sagittal Sinus O_2 Content (ml/dl)	Cerebral Arterial–Venous O_2 Content Difference (ml/dl)	O_2 Extraction Ratio	Cerebral Metabolic Rate for O_2 (ml · 100 g^{-1} · min^{-1})	Masseter Blood Flow (ml · 100 g^{-1} · min^{-1})
1: 37° C	30	36.3 ± 0.3	68 ± 18	66 ± 19	—	—	—	—	18 ± 10
	60	36.5 ± 0.2	73 ± 12	73 ± 17	6.0 ± 1.0	5.2 ± 1.3	0.46 ± 0.10	3.8 ± 1.4	17 ± 10
	90	36.5 ± 0.2	73 ± 20	72 ± 26	6.0 ± 1.1	4.9 ± 0.9	0.45 ± 0.09	3.4 ± 1.1	15 ± 9
2: 27° C, *p*H-stat	30	27.8 ± 0.5	38 ± 9	34 ± 9	—	—	—	—	14 ± 8
	60	26.8 ± 0.4	37 ± 6	33 ± 5	6.6 ± 1.2	4.2 ± 1.1	0.39 ± 0.09	1.4 ± 0.4	18 ± 11
	90	26.7 ± 0.3	37 ± 7	32 ± 7	6.6 ± 1.3	3.9 ± 1.3	0.37 ± 0.11	1.2 ± 0.3	20 ± 14
3: 27° C, α-stat	30	27.9 ± 0.7	38 ± 9	34 ± 7	—	—	—	—	13 ± 7
	60	26.9 ± 0.6	31 ± 6	28 ± 6	6.5 ± 1.4	4.7 ± 1.6	0.42 ± 0.12	1.3 ± 0.4	14 ± 5
	90	26.7 ± 0.5	30 ± 3	26 ± 4	6.6 ± 1.7	5.0 ± 2.0	0.43 ± 0.15	1.3 ± 0.5	16 ± 7

Mean ± SD. Group 1 (37° C, n = 8); group 2 (27° C, *p*H-stat, n = 9); group 3 (27° C, α-stat, n = 8).

stable thermal conditions. In contrast, with rapid cooling of arterial blood as occurs with cardiopulmonary bypass, nasopharyngeal temperatures probably more accurately indicate the temperature of the blood entering the Circle of Willis, with brain temperature lagging behind. Based on a Q_{10} of 2.8, a reduction of brain temperature of ~1.5° C would be sufficient to account for the CBF reductions reported by Rogers *et al.*[2] and Prough *et al.*[3] In light of Whitby and Dunkin's observations, we believe such a reduction in brain temperature, without a change in nasopharyngeal temperature, is possible during systemic ("core") cooling with cardiopulmonary bypass.

In our rabbit model, brain temperature equilibration during systemic cooling was remarkably slow, requiring about 40 min. This observation is in agreement with those of Harper *et al.*,[23] Civalero *et al.*,[24] and Kramer *et al.*,[25] who observed comparable rates of brain cooling and large brain − esophageal temperature gradients in dogs perfused *via* the femoral artery. Civalero and co-workers[24] found that brain temperature decreased more quickly with perfusion *via* the subclavian artery. Ongoing studies with our preparation have found 1) that carotid blood temperature is significantly warmer than arterial perfusate temperature during cooling (temperature gradients of ~3° C, 2° C, and 1° C at 10, 20, and 30 min of cooling, respectively), and 2) that brain temperature more closely follows carotid blood temperature, with carotid − brain temperature gradients less than 0.5° C after 20–25 min of systemic cooling. In total, these observations suggest that brain cooling should be more rapid with perfusion techniques using the ascending aorta relative to techniques using alternative perfusion sites. Clearly, as shown in figure 2, large thermal gradients persist for relatively long periods during cooling, rendering indirect methods of brain temperature monitoring, most notably esophageal thermometry, seriously inaccurate. This finding is particularly important for animal studies using species having a carotid rete, such as dogs, cats, and sheep (but not the rabbit), wherein brain blood temperature follows neither carotid nor core temperature because of cooling of cerebral blood in the cavernous sinus.[26] Future investigations of cerebral physiology during hypothermic cardiopulmonary bypass, in both humans and animals, must 1) account for differences in arterial perfusion technique, 2) use methods that reliably estimate brain temperature, and/or 3) allow sufficient time to ensure brain temperature equilibration.

By increasing CBF, hypercarbia has long been advocated as a method to increase the rate of brain cooling during cardiopulmonary bypass.[27–29] Accordingly, we anticipated that brain cooling would be more rapid with *p*H-stat management than with α-stat management. It was

TABLE 3. Comparisons and Power Analysis of Cerebral Blood Flow and Metabolism

Group	Comparison	*P*	80% Power to Detect a Difference
1: 37° C	$CBF_{(30)}$ *vs.* $CBF_{(90)}$	0.45	$\Delta CBF = 19$ ml · 100 g^{-1} · min^{-1}
	$CMR_{O_2(60)}$ *vs.* $CMR_{O_2(90)}$	0.50	$CMR_{O_2(90)}/CMR_{O_2(60)} = 0.63$
2: 27° C *p*H-stat	$CBF_{(60)}$ *vs.* $CBF_{(90)}$	0.70	$\Delta CBF = 5$ ml · 100 g^{-1} · min^{-1}
	$CMR_{O_2(60)}$ *vs.* $CMR_{O_2(90)}$	0.11	$CMR_{O_2(90)}/CMR_{O_2(60)} = 0.77$
3: 27° C α-stat	$CBF_{(60)}$ *vs.* $CBF_{(90)}$	0.45	$\Delta CBF = 2$ ml · 100 g^{-1} · min^{-1}
	$CMR_{O_2(60)}$ *vs.* $CMR_{O_2(90)}$	0.50	$CMR_{O_2(90)}/CMR_{O_2(60)} = 0.94$

CBF = cerebral blood flow; CMR_{O_2} = cerebral metabolic rate for O_2. Subscripts refer to bypass duration in minutes. See Appendix for complete discussion of statistical techniques.

not (fig. 1). As shown in table 2, there was, in fact, no difference in CBF between *p*H-stat and α-stat groups at 30 min of systemic cooling, although at later time points, in this and prior experiments,[4,30] CBF responses to carbon dioxide were present. Watanabe and associates recently made compatible observations, finding little to no increase in the rate of brain cooling despite the use of marked hypercarbia (Pa_{CO_2} 70–110 mmHg measured at 37° C).[31] Further experiments are required to confirm this phenomenon, but it appears that in our experiment the cerebral vasculature was rendered temporarily unresponsive to the vasodilatory effect of carbon dioxide during the cooling phase. Mechanistic possibilities include cerebral vasoconstriction in response to cold arterial blood and/or diminution of vascular responsiveness as a result of neurogenic mechanisms.[32]

As in prior investigations, hypothermia was associated with reductions in CMR_{O_2}, with a Q_{10} of 2.8 (95% confidence interval 2.3–3.4).§§ Although Murkin and coworkers found no difference in CMR_{O_2} between α-stat and *p*H-stat management,[33] Prough *et al.* recently reported that *p*H-stat management reduced CMR_{O_2} by 50% compared to α-stat management during cardiopulmonary bypass at 27° C.[34] Inspection of our CMR_{O_2} data indicate no major difference in CMR_{O_2} between α-stat and *p*H-stat groups in this experiment (table 2). The discrepancy between our findings and those of Prough *et al.*[34] is unexplained, except for potential methodological differences, as discussed below.

Reported values for cerebral OER during hypothermic cardiopulmonary bypass in humans approximate 0.25 with α-stat management[3,21,33,35,36] and 0.10 with *p*H-stat management.[3,20,33,37] These values are substantially lower than normal normothermic OERs, approximating 0.40.[21,33,35–37] Consequently, some authors have characterized the cerebral circulation as having an excess of perfusion relative to metabolic demand during hypothermic bypass, particularly when *p*H-stat management is used.[18,33,38] In contrast, our data, in agreement with the work in animals by Michenfelder and Theye,[39] Rosomoff and Holaday,[40] and Lafferty *et al.*,[41] shows cerebral OER during hypothermia (27° C) to be virtually indistinguishable from that during normothermia, indicating that cerebral oxygen supply/demand relationships are essentially normal at 27° C. CMR_{O_2} and OER calculations depend on accurate determination of cerebral venous oxygen content. Studies in humans have used jugular bulb catheters, introduced retrograde from the internal jugular vein, to obtain cerebral venous blood. Under normothermic conditions, only 3–6% of the blood in the jugular bulb is derived from extracranial sources,[42,43] such that sampling from this site yields a reliable cerebral venous specimen. Data from this and a prior study[30] indicate that although intracranial blood flow decreases dramatically during hypothermic bypass, extracranial blood flow (in the masseter muscle) does not. Consequently, it is possible that extracranial contributions to jugular bulb venous flow may increase as a percentage of the total during hypothermia. If so, this would artifactually increase venous oxygen content and decrease the calculated OER and CMR_{O_2} values. In this experiment and in the other animal studies cited above, cerebral venous blood was obtained from the sagittal sinus[39–41] or confluens sinuum, obviating the issue of extracranial contamination.

In summary, in our rabbit model of cardiopulmonary bypass, we conclude: 1) brain temperature equilibration during systemic cooling is remarkably slow; 2) indirect (esophageal) thermometry, as an estimate of brain temperature, is seriously inaccurate, with brain temperature lagging behind during cooling; 3) at constant, directly measured, brain temperature, CBF and CMR_{O_2} are stable during cardiopulmonary bypass; and 4) cerebral oxygen supply/demand relationships are essentially normal at 27° C and are minimally affected by blood gas management. We find no evidence that either progressive cerebral embolization or cerebral vasoconstriction occurred over 90 min of bypass in this experiment.

Appendix

Performing linear regression, rather than a *t* test, to examine change in CBF and CMR_{O_2} over time, increased our power significantly.[12] Using linear regression to analyze change in each animal, we found a substantial portion of the variance in the 90-min data could be accounted for by knowing an earlier value. For example, the mean-square error of the linear regression for α-stat CMR_{O_2} was 22% of the variance of the measurements themselves. Analysis of covariance on CBF and CMR_{O_2} data, which might have improved our power to detect change, was not possible for two reasons: 1) normothermic CBF measurements had substantially higher variance than did hypothermic measurements (although we did not find a clear dependency of CBF variance on CBF), and 2) CMR_{O_2} slopes and groups interacted significantly.

We analyzed CBF differences and the relative change in CMR_{O_2}. We analyzed CBF differences because CBF followed a normal distribution. For CBF analyses, the independent variable was the difference between CBF at the earlier time and the arithmetic mean CBF at the earlier time, and the dependent variable was CBF at the later time. CMR_{O_2}, on the other hand, appeared to be log-normally distributed. Therefore, we tested whether the ratio was significantly different than 1 or, more precisely, whether the logarithm was different than 0. For CMR_{O_2} analyses, the independent variable was the difference between the logarithm of the CMR_{O_2} at the earlier time and the arithmetic mean of the logarithms of CMR_{O_2} at the earlier time,

§§ Q_{10} = antilog ($10 \times \Delta[\log CMR_{O_2}]/\Delta T$). $\Delta[\log CMR_{O_2}]/\Delta T$ was calculated by linear regression of the pooled CMR_{O_2} *versus* temperature (T) data from all groups.

and the dependent variable was the logarithm of the CMR_{O_2} at the later time.

Standard regression diagnostics were used. First, no studentized residuals or Cook's statistics were statistically significant at the $P = 0.05$ criteria; *i.e.*, no data were statistically significant outliers. Second, studentized residuals showed no evidence for correlation with the independent variable or estimates of the dependent variable, as assessed graphically.[44] Thus, the assumption of linearity is reasonable. Third, probability plots and Liliefor's test indicated that studentized residuals were not inconsistent with normal distribution,[45] which is required for P and power values to be accurate.

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