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pH-Stat Management Reduces the Cerebral Metabolic Rate for Oxygen during Profound Hypothermia (17°C)

A Study during Cardiopulmonary Bypass in Rabbits

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Background: **Greater cerebral metabolic suppression may increase the brain's tolerance to ischemia. Previous studies examining the magnitude of metabolic suppression afforded by profound hypothermia suggest that the greater arterial carbon dioxide tension of *p*H-stat management may increase metabolic suppression when compared with α-stat management.**

Methods: **New Zealand White rabbits, anesthetized with fentanyl and diazepam, were maintained during cardiopulmonary bypass (CPB) at a brain temperature of 17°C with α-stat (group A, n = 9) or *p*H-stat (group B, n = 9) management. Measurements of brain temperature, systemic hemodynamics, arterial and cerebral venous blood gases and oxygen content, cerebral blood flow (CBF) (radiolabeled microspheres), and cerebral metabolic rate for oxygen (CMR_{O_2}) (Fick) were made in each animal at 65 and 95 min of CPB. To control for arterial pressure and CBF differences between techniques, additional rabbits underwent CPB at 17°C. In group C (α-stat, n = 8), arterial pressure was decreased with nitroglycerin to values observed with *p*H-stat management. In group D (*p*H-stat, n = 8), arterial pressure was increased with angiotensin II to values observed with α-stat management. In groups C and D, CBF and CMR_{O_2} were determined before (65 min of CPB) and after (95 min of CPB) arterial pressure manipulation.**

Results: **In groups A (α-stat) and B (*p*H-stat), arterial pressure; hemispheric CBF (44 ± 17 *vs.* 21 ± 4 ml · 100 g^{-1} · min^{-1} [median ± quartile deviation]; $P = 0.017$); and CMR_{O_2} (0.54 ± 0.13 *vs.* 0.32 ± 0.10 ml O_2 · 100 g^{-1} · min^{-1}; $P = 0.0015$) were greater in α-stat than in *p*H-stat animals, respectively. As a result of arterial pressure manipulation, in groups C (α-stat) and D (*p*H-stat) neither arterial pressure (75 ± 2 *vs.* 78 ± 2 mmHg) nor hemispheric CBF (40 ± 10 *vs.* 48 ± 6 ml · 100 g^{-1} · min^{-1}; $P = 0.21$) differed between α-stat and *p*H-stat management, respectively. Nevertheless, CMR_{O_2} was greater in α-stat than in *p*H-stat animals (0.71 ± 0.10 *vs.* 0.45 ± 0.10 ml O_2 · 100g^{-1} · min^{-1}, respectively; $P = 0.002$).**

Conclusions: **At 17°C, CMR_{O_2} with *p*H-stat management is 35–40% less than that with α-stat management and is independent of CBF or arterial pressure differences between the techniques.**
(Key words: Anesthesia: cardiovascular. Brain: blood flow; hypothermia; metabolism. Surgery: cardiac; cardiopulmonary bypass. Temperature: hypothermia.)

WITHIN limits, as the brain's temperature decreases, its tolerance to ischemia increases. By reducing metabolic rate, hypothermia slows the rate of high-energy phosphate depletion[1,2] and the development of intracellular acidosis during cerebral ischemia.[2] In this way, hypothermia delays or prevents neuronal energy failure and terminal membrane depolarization during periods of greatly reduced or absent blood flow.[3,4] For this reason, profound hypothermia (14–19°C), with or without circulatory arrest, is routinely used during repair of congenital heart defects in children[5] and in aortic arch procedures in adults.[6]

Q_{10} is defined as the ratio of metabolic rates over a 10°C temperature interval. Greater values for Q_{10} indicate a greater degree of metabolic suppression. As shown in table 1, the magnitude of cerebral metabolic suppression afforded by profound hypothermia varies as much as twofold among studies. Determining the cause of this variation could be of major clinical importance. Techniques augmenting hypothermic meta-

This article is accompanied by a Highlight. Please see this issue of ANESTHESIOLOGY, page 24A.

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Table 1. Variation in Pa_{CO_2}, and Cerebral Q_{10} among Studies

Reference	Brain Temperature (°C)	Pa_{CO_2}, as Measured with Temperature Correction (mmHg)	Pa_{CO_2}, as Measured at 37°C (mmHg)	Q_{10}	Temperature Range (°C)
Steen *et al.*[7]	18.0	~35*	~80	4.9	28–18
Michenfelder *et al.*[8]	17.9	27	62	4.4†	27–18
Tanaka *et al.*[9]	20.0	~19	~40*	2.9†	37–20
Astrup *et al.*[10]	18.0	11	25	2.5	37–18

* Numeric values not reported. Pa_{CO_2} estimates based on equations of Andritsch *et al.*[11]

† Calculated from experimental data. Q_{10} = antilog ($10 \times \Delta[\log CMR_{O_2}]/\Delta T$) where T denotes brain temperature (°C).

bolic suppression may confer a greater degree of brain protection during ischemia.

We observed that a different hypothermic acid–base technique was used in each of the studies cited in table 1. Steen *et al.* (Q_{10} = 4.9) used *p*H-stat technique,[7] in which temperature-corrected arterial carbon dioxide tension (Pa_{CO_2}) was maintained at approximately 40 mmHg.[12] Tanaka *et al.* (Q_{10} = 2.9) used α-stat technique,[9] wherein Pa_{CO_2} was maintained at approximately 40 mmHg as measured at 37°C.[12] Michenfelder and Milde (Q_{10} = 4.4) used an acid–base strategy that resulted in Pa_{CO_2} values intermediate between *p*H-stat and α-stat values,[8] and Astrup *et al.* (Q_{10} = 2.5) used a strategy that resulted in Pa_{CO_2} values even less than α-stat ideals.[10]

Viewed collectively, these studies suggest that greater Pa_{CO_2} decreases the cerebral metabolic rate for oxygen (CMR_{O_2}), increasing the degree of metabolic suppression (*i.e.*, Q_{10}) produced by profound hypothermia. Therefore, we hypothesized that during profoundly hypothermic (17°C) cardiopulmonary bypass (CPB), α-stat management would result in a greater CMR_{O_2} than would *p*H-stat management. This hypothesis was tested in our rabbit model of CPB.

Materials and Methods

Experimental protocols were approved by the Animal Care and Use Committee of the University of Iowa in accordance with the *Guide for the Care and Use of Laboratory Animals* of the National Institutes of Health.§

Preparation

Anesthesia was induced in New Zealand white rabbits (weight, 4.1–5.0 kg) by inhalation of halothane in oxygen. After local infiltration with 1% lidocaine, a tracheotomy was performed and the trachea intubated with a 3.0 cuffed endotracheal tube. Thereafter, the animals' lungs were mechanically ventilated to achieve normocapnia, and anesthesia was maintained with 1.5% halothane in oxygen for the remainder of pre-CPB preparation. Animals were paralyzed with an infusion of succinylcholine–lactated Ringer's (4 $ml \cdot kg^{-1} \cdot h^{-1}$) and were placed prone. After a midline sagittal scalp incision, a 2-mm burr hole was drilled over the right frontoparietal cortex, and a 1-mm thermocouple (K type, L-08419-02, Cole Parmer, Chicago, IL) was introduced under the cranium to rest on the dural surface. A posterior midline craniectomy was performed, exposing the confluens sinuum. Heparin was administered as a bolus (200 U/kg intravenously) and was added to the infusion of succinylcholine–lactated Ringer's to give a maintenance dose of 200 $U \cdot kg^{-1} \cdot h^{-1}$. The tip of a saline-filled polyethylene catheter (PE-90, Intramedic, Parsippany, NJ) was placed in the confluens sinuum, permitting collection of cerebral venous blood. The cortical thermocouple and cerebral venous catheter were secured with bone wax and fast-drying cyanoacrylate cement and the animals placed supine.

The tip of a saline-filled catheter (PE-90), introduced *via* the right external jugular vein, was advanced to the superior vena cava to measure central venous pressure. Both brachial arteries were cannulated (saline-filled PE-160 tubing) for microsphere reference blood sampling. The left brachial arterial catheter was also used for arterial pressure monitoring and collection of arterial blood. Teflon catheters (14-G, 32 mm long) were inserted into each femoral artery for arterial inflow during CPB. The sternum was divided in midline, the thymus retracted, and a Teflon-pledgeted 4-0 silk purse-

§ *Guide for Care and Use of Laboratory Animals*. Publication 85-23. Bethesda, MD, Public Health Services, National Institutes of Health, revised 1985.

string suture was placed in the right atrium. After systemic anticoagulation with heparin (300 U/kg, intravenously), either a 18- or 21-French venous cannula (Polystan, Ballerup, Denmark) was placed in the right atrium. The right atrial and arterial cannulas were connected to the perfusion circuit and CPB initiated as described below. Approximately 30 min before CPB, halothane, maintenance fluids, and the succinylcholine–heparin infusion were discontinued. Anesthesia was maintained for the rest of the experiment with fentanyl (100-μg/kg bolus, 150-$\mu g \cdot kg^{-1} \cdot h^{-1}$ infusion) and diazepam (2-mg/kg bolus, 3-$mg \cdot kg^{-1} \cdot h^{-1}$ infusion). Muscle relaxation was achieved with pancuronium (0.2 mg/kg).

Cardiopulmonary Bypass

The CPB circuit consisted of a venous reservoir, a membrane oxygenator–heat exchanger (Capiox 308, Terumo, Piscataway, NJ), a variable-temperature water pump (VWR Scientific, San Francisco, CA), and a nonpulsatile centrifugal pump (540, pump head BP-50, Biomedicus, Eden Prairie, MN). A continuous in-line blood gas analysis sensor, which also measured arterial perfusate temperature (300, Cardiovascular Devices, Irvine, CA), was placed distal to the oxygenator and was calibrated against standard blood gas analysis (see below). The perfusate temperature sensor was calibrated against the cortical thermocouple. Circuit priming fluid consisted of 350 ml 6% (weight in volume) hydroxyethyl starch in normal saline (Hetastarch, E. I. du Pont, Bannockburn, IL), 15 mEq sodium bicarbonate, 250 mg calcium chloride, and 1,000 U heparin. The priming fluid was circulated through a 40-μm filter for 15–20 min before addition of approximately 150 ml fresh, filtered, packed rabbit erythrocytes, achieving a priming hemoglobin concentration of 7–9 g/dl (OSM3 (rabbit coefficients), Radiometer, Copenhagen, Denmark).

CPB was initiated a systemic flow rate of 100 $ml \cdot kg^{-1} \cdot min^{-1}$, monitored with a calibrated in-line electromagnetic flow meter (TX-40P, Biomedicus). The pulmonary artery was clamped to ensure complete venous outflow to the CPB circuit. To prevent left ventricular ejection or distension, the tip of a 14-G catheter was placed transapically in the left ventricle to permit drainage to the venous reservoir. For the first five min of CPB, no active heating or cooling measures were taken. Thereafter, systemic cooling was initiated with a water bath at approximately 27°C, which, during the next 30 min, was cooled to approximately 16°C. When a brain temperature of 27.0°C was achieved, systemic flow was reduced to 80 $ml \cdot kg^{-1} \cdot min^{-1}$, and the fentanyl–diazepam infusion rate was halved. Shed blood from the surgical field was returned to the venous reservoir after passing through a 40-μm filter. Sodium bicarbonate was given to maintain a base excess greater than −4 mEq/l, calculated at 37°C (median = 2.0 $mEq \cdot kg^{-1} \cdot h^{-1}$). Rabbit erythrocytes were given to maintain hemoglobin concentration between 6.4–8.4 g/dl. Hypertension (systemic arterial pressure >100 mmHg) was treated with supplemental doses of fentanyl and diazepam, but systemic flow was kept constant. (See Results).

Experimental Protocol (Groups A and B)

Twenty-five animals were randomly assigned to one of two groups: α-stat management (group A) and *p*H-stat management (group B). With α-stat animals, the oxygenator was ventilated with a variable mixture of oxygen and nitrogen to maintain Pa_{CO_2} near 40 mmHg and arterial oxygen tension (Pa_{O_2}) near 250 mmHg when measured at an electrode temperature 37°C. With *p*H-stat animals, 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 65 min of CPB and then again at 95 min: systemic arterial pressure, central venous pressure, CPB flow rate, brain (epidural) temperature, arterial perfusate temperature, arterial hemoglobin concentration, and arterial blood gases (measured at 37°C and temperature-corrected values). Cerebral blood flow (CBF) determinations (see below) were made at 65 and 95 min of CPB,# and arterial and cerebral venous blood was simultaneously collected for blood gas analysis and measurement of oxygen content (Lex-O_2-Con, Lexington Instruments Corporation, Waltham, MA). At the completion of experimentation, animals were killed by discontinuation of CPB and intracardiac administration of saturated potassium chloride solution.

‖ All blood gases were measured on a *p*H–blood gas analyzer (IL1304, 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).

Pilot studies with this preparation showed 65 min was the average time required to achieve a stable brain temperature of approximately 17°C, with less than 1°C additional cooling over an ensuing 30-min period.

Measurements of Cerebral Blood Flow and Cerebral Metabolic Rate for Oxygen

CBF was measured by the radioactive microsphere technique. Isotopes included strontium 85, niobium 95, cerium 141, and gadolinium 153 (New England Nuclear, Boston, MA), although only two isotopes were used in each experiment. Stock microspheres (400 μl, approximately 1.8 million microspheres), vigorously mixed for 5 min before withdrawal, were diluted in 1.5 ml suspending solution (10% dextran-40 in normal saline with 0.5% [volume in volume] Tween-80) and mixed an additional 60 s. Microspheres were injected over a 30-s period into the arterial perfusion tubing just proximal to its bifurcation into the two femoral inflow cannulas. Starting 15 s before microsphere injection, and continuing 2 min thereafter, blood was simultaneously withdrawn from each brachial arterial catheter by means of a 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. Fresh tissue samples were weighed, placed in counting tubes and, with reference blood samples, each counted for 5 min in a sodium iodide well-type gamma counter (Minaxiγ Auto-Gamma 5000, Packard Instruments, Meriden, CT). Isotope separation, background, and overlap corrections, and organ blood flow calculations ($ml \cdot 100\ g^{-1} \cdot min^{-1}$) were performed by standard techniques.[13–15] Weight-averaged values for right- and left-hemispheric CBF were used to calculate mean hemispheric CBF.

CMR_{O_2} ($ml\ O_2 \cdot 100\ g^{-1} \cdot min^{-1}$) 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. Cerebral oxygen extraction ratio was calculated as the arterial-cerebral venous oxygen content difference, divided by arterial oxygen content.

Additional Experiments (Groups C and D)

As described in Results, CMR_{O_2} was significantly greater with α-stat (group A) than with *p*H-stat management (group B). However, both systemic arterial pressure and hemispheric CBF were also greater with α-stat management. We could not rule out the possibility that the lesser CMR_{O_2} of *p*H-stat animals was the result of their tendency toward lesser CBF (see Discussion). If CMR_{O_2} was CBF dependent at 17°C, CMR_{O_2} differences between α-stat and *p*H-stat management might have been the result of CBF differences, which in turn were mediated by differences in arterial pressure. Two address this possibility, 23 additional animals were subsequently studied, wherein the effect of arterial pressure on CBF and CMR_{O_2} could be examined.

In group C, animals underwent CPB with α-stat technique, and CBF and CMR_{O_2} were determined at 65 min of CPB as described above. Thereafter, keeping systemic flow constant, nitroglycerin (5 mg/ml, Tridil, du Pont Pharmaceuticals, Manati, Puerto Rico) was infused into the venous return line of the CPB circuit to decrease arterial pressure to a target value of 59 mmHg (median systemic arterial pressure under *p*H-stat conditions at 95 min of CPB in group B, see table 2). At 95 min of CPB, CBF, and CMR_{O_2} determinations were repeated. In group D, animals underwent CPB with *p*H-stat technique, and CBF and CMR_{O_2} were determined at 65 min of CPB. Thereafter, keeping systemic flow constant, angiotensin II (0.5 μg/ml, Sigma, St. Louis, MO) was infused into the venous return line of the CPB circuit to increase arterial pressure to a target value of 101 mmHg (median systemic arterial pressure under α-stat conditions at 95 min of CPB in group A, see table 2). At 95 min of CPB, CBF and CMR_{O_2} determinations were repeated. The conduct of CPB in groups C and D was as described for groups A and B, except that arterial inflow was achieved with a single 10-French pediatric arterial perfusion catheter (Biomedicus) placed retrograde in the descending aorta, 5–8 mm superior to the distal aortic bifurcation. This protocol change was made because of a high frequency of femoral arterial dissection with the bifemoral technique and because of improved microsphere mixing with use of descending aortic cannulation. Microspheres were injected into the arterial perfusion line approximately 25 cm proximal to distal tip of the aortic cannula.

Statistics

Right and left microsphere counts appeared to be normally distributed, permitting linear regression analysis to test adequacy of microsphere mixing and distribution. In contrast, box-and-whisker plots indicated that many physiologic variables did not appear to be normally distributed. Consequently, all physiologic variables are summarized using their median ± quartile deviation, the latter equaling half the difference between the first and third quartiles.

Analyses were performed using Systat statistical software.[16] CBF appeared to follow a normal distribution, whereas CMR_{O_2} appeared to follow a log-normal distribution. Two-measurement, two-group repeated-

Table 2. Systemic Physiologic Variables: Groups A and B

Variable	Group	Technique	Bypass Duration (min) 65	95
Systemic arterial pressure (mmHg)	A	α-stat	83 (16)	101 (10)
	B	*p*H-stat	59 (2)	59 (9)
Central venous pressure (mmHg)	A	α-stat	4 (1)	4 (1)
	B	*p*H-stat	4 (1)	4 (1)
Systemic flow ($ml \cdot kg^{-1} \cdot min^{-1}$)	A	α-stat	78 (8)	75 (7)
	B	*p*H-stat	83 (3)	83 (4)
Hemoglobin (g/dl)	A	α-stat	7.7 (0.3)	7.6 (0.2)
	B	*p*H-stat	7.4 (0.2)	7.6 (0.2)
pH_a (37°C)	A	α-stat	7.40 (0.01)	7.38 (0.01)
	B	*p*H-stat	7.10 (0.01)	7.09 (0.01)
Pa_{CO_2} (mmHg, 37°C)	A	α-stat	38 (1)	38 (1)
	B	*p*H-stat	98 (3)	96 (2)
Pa_{O_2} (mmHg, 37°C)	A	α-stat	259 (11)	251 (13)
	B	*p*H-stat	347 (8)	338 (8)
pH_a (mmHg, temperature corrected)	A	α-stat	7.69 (0.01)	7.68 (0.01)
	B	*p*H-stat	7.36 (0.01)	7.35 (0.01)
Pa_{CO_2} (mmHg, temperature corrected)	A	α-stat	16 (0)	16 (1)
	B	*p*H-stat	41 (1)	40 (1)
Pa_{O_2} (mmHg, temperature corrected)	A	α-stat	179 (10)	171 (11)
	B	*p*H-stat	256 (7)	250 (7)
Arterial oxygen content (ml O_2/dl)	A	α-stat	11.4 (0.4)	11.3 (0.3)
	B	*p*H-stat	11.2 (0.4)	11.3 (0.2)

Values are median and quartile deviation (parentheses); n = 9 in each group.

measures analysis of variance could not be used for data analysis (for either CBF or CMR_{O_2}) because of unequal variance among groups and times.[17] Therefore, for CBF analysis, the mean value of CBF at 65 and 95 min in each animal was compared between α-stat and *p*H-stat groups using independent-sample *t* tests, with separate within-group variances.[16,17] For CMR_{O_2} analysis, the mean value of $\ln(CMR_{O_2})$ at 65 and 95 min was compared between α-stat and *p*H-stat groups using independent-sample *t* tests, with separate within-group variances.[16,17]

Results

Groups A and B

Data from seven of 25 animals were rejected. In five cases, microspheres were not evenly distributed (making CBF determination unreliable), in one case the sagittal sinus catheter failed, and in one case brain damage occurred during craniotomy. Data from the remaining animals, group A (α-stat, n = 9) and group B (*p*H-stat, n = 9) were analyzed.

Microsphere Validation. Paired right and left microsphere reference counts were adequately matched (slope = 0.92, r^2 = 0.81, intercept not significantly different than zero), indicating adequate microsphere mixing and uniform distribution. There were no right–left CBF asymmetries between the cerebral hemispheres.

Systemic Variables. Despite equivalent systemic flow rates, arterial pressure increased in α-stat (group A) animals and decreased in *p*H-stat (group B) animals (fig. 1). In no *p*H-stat animal did systemic arterial pressure exceed 100 mmHg, whereas arterial pressure exceeded 100 mmHg in five of nine α-stat animals. Supplemental diazepam and fentanyl in the five hypertensive α-stat rabbits was 1–6 mg/kg and 0–180 μg/kg, respectively, over the entire 95 min of CPB. No supplemental anesthetic was given to nonhypertensive α-stat rabbits or to *p*H-stat rabbits. Systemic variables at 65 and 95 min of CPB are summarized in table 2. Systemic arterial pressure was greater in α-stat animals than in *p*H-stat animals at both 65 and 95 min of CPB. Arterial hemoglobin concentration and oxygen content, systemic flow rate, and central venous pressure were equivalent between groups and over time. As intended, pH_a and Pa_{CO_2} differed between α-stat and *p*H-stat groups and were essentially constant between measurements. Pa_{O_2} was 75–100 mmHg greater in *p*H-stat animals.

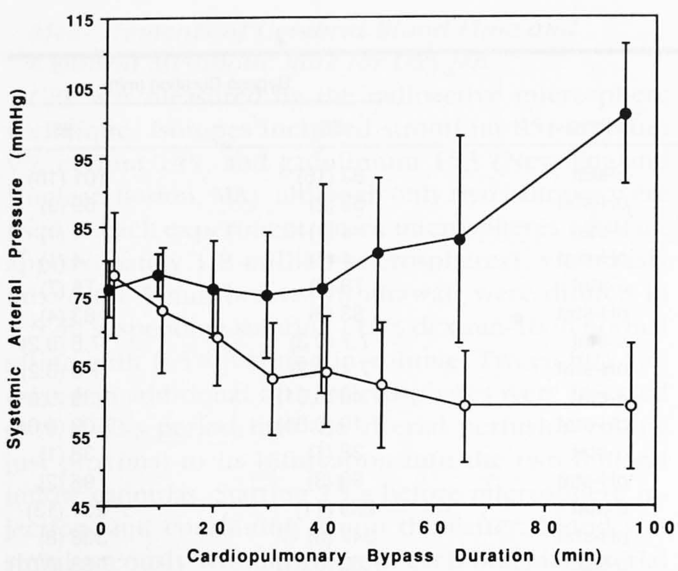

Fig. 1. Systemic arterial pressure over time in α-stat (group A, solid circles) and *p*H-stat animals (group B, open circles) Values are medians ± quartile deviation; n = 9 in each group. Data are time shifted for clarity.

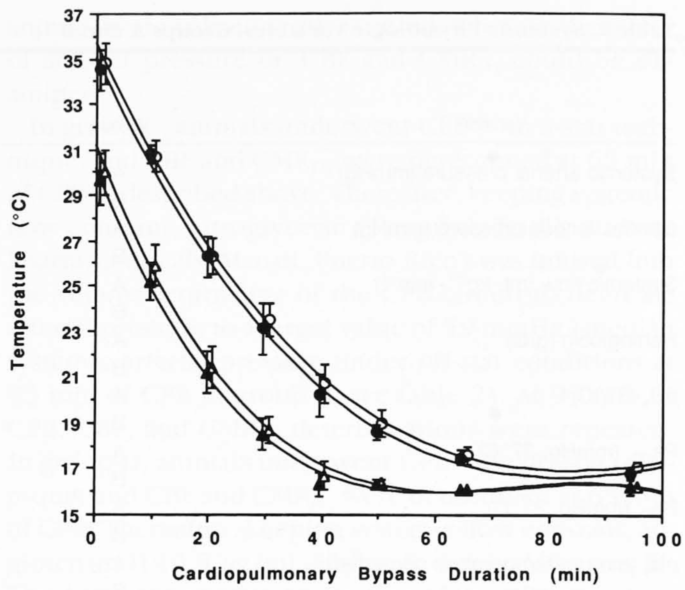

Fig. 2. Brain (circles) and perfusate (triangles) temperatures over time in α-stat (group A, solid symbols) and *p*H-stat (group B, open symbols) animals. Values are medians ± quartile deviation; n = 9 in each group. Data are time shifted for clarity.

Cerebral Physiologic Variables. Cerebral physiologic variables at 65 and 95 min of CPB are summarized in table 3. There were no differences between groups in the rates of perfusate or brain cooling (fig. 2). Mean hemispheric CBF was greater in α-stat than in *p*H-stat animals (44 ± 17 *vs.* 21 ± 4 ml · 100 g^{-1} · min^{-1}, respectively; $P = 0.017$). This CBF difference between groups must be interpreted with some caution, however, because, when corrected for multiple comparisons, $P = 0.017$ is not statistically significant. Mean CMR_{O_2} was significantly greater in α-stat than in *p*H-stat animals (0.54 ± 0.13 *vs.* 0.32 ± 0.10 ml O_2 · 100 g^{-1} · min^{-1}, respectively; $P = 0.0015$). (See fig. 3.) CMR_{O_2} did not differ between the five hypertensive α-stat animals receiving supplemental fentanyl and diazepam, and the four nonhypertensive α-stat animals (0.60 ± 0.13 *vs.* 0.54 ± 0.19 ml O_2 · 100 g^{-1} · min^{-1}, respectively).

Table 3. Cerebral Physiologic Variables: Groups A and B

Variable	Group	Technique	Bypass Duration (min) 65	95
Brain temperature (°C)	A	α-stat	17.4 (0.3)	16.8 (0.2)
	B	*p*H-stat	17.6 (0.4)	17.1 (0.2)
Cerebral venous oxygen content (ml O_2/dl)	A	α-stat	9.2 (0.8)	9.8 (0.5)
	B	*p*H-stat	10.0 (0.3)	9.8 (0.1)
Cerebral arterial-venous oxygen content difference (ml O_2/dl)	A	α-stat	1.8 (0.4)	1.0 (0.7)
	B	*p*H-stat	1.3 (0.5)	1.3 (0.7)
Cerebral oxygen extraction ratio	A	α-stat	0.16 (0.03)	0.09 (0.06)
	B	*p*H-stat	0.12 (0.04)	0.12 (0.03)
Hemispheric cerebral blood flow* (ml · 100 g^{-1} · min^{-1})	A	α-stat	37 (13)	48 (17)
	B	*p*H-stat	21 (5)	22 (3)
Cerebral metabolic rate for oxygen† (ml O_2 · 100 g^{-1} · min^{-1})	A	α-stat	0.59 (0.09)	0.52 (0.23)
	B	*p*H-stat	0.25 (0.12)	0.24 (0.12)

Values are median and quartile deviation (parentheses); n = 9 in each group.

* α-stat cerebral blood flow greater than *p*H-stat ($P = 0.017$).

† α-stat cerebral metabolic rate greater than *p*H-stat ($P = 0.0015$).

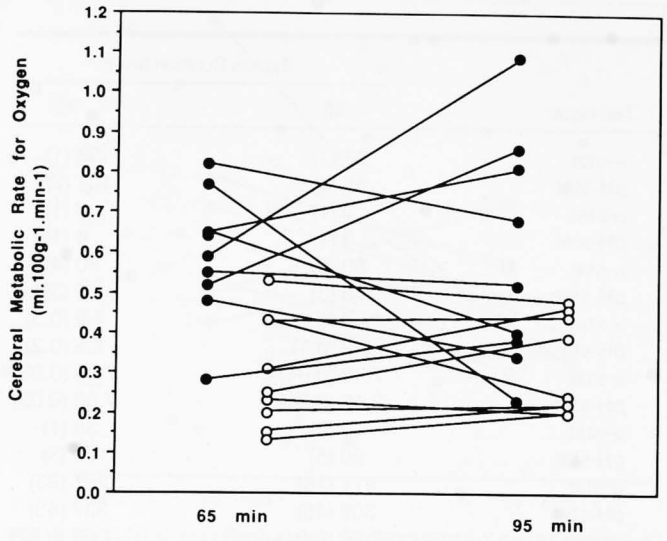

Fig. 3. Cerebral metabolic rate for oxygen in α-stat (group A, solid circles) and *p*H-stat animals (group B, open circles) at 65 and 95 min of cardiopulmonary bypass.

Groups C and D

Data from seven of 23 animals were rejected. In four cases, microspheres were not adequately mixed, in one case the animal was accidentally rewarmed before data collection, in one case Lex-O_2-Con measurements were unreliable, and in one case brain damage occurred during craniotomy. Data from the remaining animals, group C (α-stat, n = 8) and group D (*p*H-stat, n = 8) were analyzed.

Microsphere Validation. Paired right and left microsphere reference counts were adequately matched (slope = 1.02, $r^2 = 0.98$, intercept not significantly different than zero), indicating adequate microsphere mixing and uniform distribution. Right-hemispheric CBF was slightly but significantly ($P = 0.01$) less than left-hemispheric CBF (7 ± 13%), perhaps because of trauma from thermocouple placement.

Systemic Variables. Before the 65-min time point, three of eight α-stat animals required supplemental diazepam (1–7 mg/kg) or fentanyl (0–170 μg/kg) for arterial pressures greater than or equal to 100 mmHg. Supplemental anesthetics were not given to nonhypertensive α-stat rabbits or to *p*H-stat rabbits. Systemic physiologic variables at 65 and 95 min of CPB are summarized in table 4. As before, at 65 min of CPB, systemic arterial pressure was greater in α-stat (group C) animals than in *p*H-stat (group D) animals (93 ± 7 *vs.* 55 ± 4 mmHg, respectively). In α-stat animals, target systemic arterial pressure at 95 min of CPB (58 ± 1 mmHg) was achieved using 469 ± 586 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroglycerin. In *p*H-stat animals, target systemic arterial pressure at 95 min of CPB (101 ± 2 mmHg) was achieved using 18 ± 8 $ng \cdot kg^{-1} \cdot min^{-1}$ angiotensin II. The average of arterial pressure over time (65 and 95 min of CPB) did not differ between α-stat (group C) and *p*H-stat (group D) animals (75 ± 2 *vs.* 78 ± 2 mmHg, respectively). Arterial hemoglobin concentration and oxygen content, systemic flow rate, and central venous pressure were equivalent between groups and over time. Arterial *p*H and Pa_{CO_2} differed between α-stat and *p*H-stat groups and were essentially constant between measurements. As before, Pa_{O_2} was 75–100 mmHg greater in *p*H-stat animals.

Cerebral Physiologic Variables. Cerebral physiologic variables at 65 and 95 min of CPB are summarized in table 5. In *p*H-stat animals, with the increase in arterial pressure, there was a large increase in hemispheric CBF, from 30 ± 9 to 62 ± 10 $ml \cdot 100\ g^{-1} \cdot min^{-1}$. In α-stat animals, with the decrease in arterial pressure, there was no change in hemispheric CBF (40 ± 20 to 32 ± 8 $ml \cdot 100\ g^{-1} \cdot min^{-1}$). Mean CBF (65 and 95 min of CPB) did not differ between α-stat (group C) and *p*H-stat (group D) animals (40 ± 10 *vs.* 48 ± 6 $ml \cdot 100\ g^{-1} \cdot min^{-1}$, respectively; $P = 0.21$). As before, mean CMR_{O_2} was significantly greater in α-stat than in *p*H-stat animals (0.71 ± 0.10 *vs.* 0.45 ± 0.10 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$; $P = 0.002$). (See fig. 4.) CMR_{O_2} did not differ between the three hypertensive α-stat animals receiving supplemental anesthetics, and the five nonhypertensive α-stat animals (0.72 ± 0.17 *vs.* 0.71 ± 0.10 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$, respectively).

Discussion

Cerebral Metabolism and Blood Flow

These experiments show *p*H-stat management results in CMR_{O_2} values 35–40% less than those with α-stat management during profoundly hypothermic (17°C) CPB.

In the first experiment (groups A and B), systemic arterial pressure, hemispheric CBF, and CMR_{O_2} were all greater in α-stat than in *p*H-stat animals. We were surprised that α-stat animals tended to have greater CBF because, at moderate hypothermia (25–27°C), the greater Pa_{CO_2} of *p*H-stat technique results in greater CBF compared with that by the α-stat technique, in humans[18] and in this animal model.[19] However, at profound hypothermia, cerebral autoregulation appears to be completely inhibited, such that CBF varies directly with arterial pressure.[20–22] Thus, we believe the greater

Table 4. Systemic Physiologic Variables: Groups C and D

Variable	Group	Technique	Bypass Duration (min) 65	95
Systemic arterial pressure (mmHg)	C	α-stat	93 (7)	58 (1)
	D	*p*H-stat	55 (4)	101 (2)
Central venous pressure (mmHg)	C	α-stat	3 (1)	3 (1)
	D	*p*H-stat	3 (1)	4 (1)
Systemic flow ($ml \cdot kg^{-1} \cdot min^{-1}$)	C	α-stat	80 (5)	80 (4)
	D	*p*H-stat	78 (3)	78 (3)
Hemoglobin (g/dL)	C	α-stat	7.7 (0.2)	7.2 (0.3)
	D	*p*H-stat	7.2 (0.1)	7.5 (0.2)
pH_a (37°C)	C	α-stat	7.40 (0.01)	7.39 (0.02)
	D	*p*H-stat	7.10 (0.01)	7.08 (0.02)
Pa_{CO_2} (mmHg, 37°C)	C	α-stat	40 (2)	38 (1)
	D	*p*H-stat	90 (5)	100 (3)
Pa_{O_2} (mmHg, 37°C)	C	α-stat	271 (16)	267 (23)
	D	*p*H-stat	309 (46)	337 (43)
pH_a (mmHg, temperature corrected)	C	α-stat	7.69 (0.01)	7.69 (0.02)
	D	*p*H-stat	7.36 (0.01)	7.33 (0.02)
Pa_{CO_2} (mmHg, temperature corrected)	C	α-stat	17 (1)	16 (1)
	D	*p*H-stat	41 (3)	42 (1)
Pa_{O_2} (mmHg, temperature corrected)	C	α-stat	193 (16)	186 (22)
	D	*p*H-stat	230 (38)	251 (38)
Arterial oxygen content (ml O_2/dl)	C	α-stat	11.2 (0.2)	10.3 (0.4)
	D	*p*H-stat	10.9 (0.4)	11.2 (0.5)

Values are median and quartile deviation (parentheses); n = 8 in each group.

CBF of α-stat management was most likely the result of the greater systemic arterial pressure that occurred with this technique (see below).

Because of this unexpected CBF difference, it was not clear whether the difference in CMR_{O_2} between α-stat and *p*H-stat management occurred because of a difference in Pa_{CO_2} (as hypothesized) or might actually have occurred as a result of the CBF difference. Some non-CPB studies suggest that oxygen transfer from blood to tissue may be impaired during hypothermia

Table 5. Cerebral Physiologic Variables: Groups C and D

Variable	Group	Technique	Bypass Duration (min) 65	95
Brain temperature (°C)	C	α-stat	17.4 (0.2)	16.8 (0.2)
	D	*p*H-stat	17.5 (0.2)	16.7 (0.4)
Cerebral venous oxygen content (ml O_2/dl)	C	α-stat	9.1 (0.4)	8.3 (0.9)
	D	*p*H-stat	9.5 (0.8)	10.5 (0.4)
Cerebral arterial-venous oxygen content difference (ml O_2/dl)	C	α-stat	2.2 (0.3)	2.1 (0.5)
	D	*p*H-stat	1.6 (0.6)	0.7 (0.1)
Cerebral oxygen extraction ratio	C	α-stat	0.20 (0.03)	0.21 (0.04)
	D	*p*H-stat	0.15 (0.08)	0.06 (0.01)
Hemispheric cerebral blood flow ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	C	α-stat	40 (20)	32 (8)
	D	*p*H-stat	30 (9)	62 (10)
Cerebral metabolic rate for oxygen* ($ml\ O_2 \cdot 100\ g^{-1} \cdot min^{-1}$)	C	α-stat	0.79 (0.17)	0.61 (0.10)
	D	*p*H-stat	0.46 (0.18)	0.39 (0.04)

Values are median and quartile deviation (parentheses); n = 8 in each group.

* α-stat cerebral metabolic rate greater than *p*H-stat ($P = 0.002$).

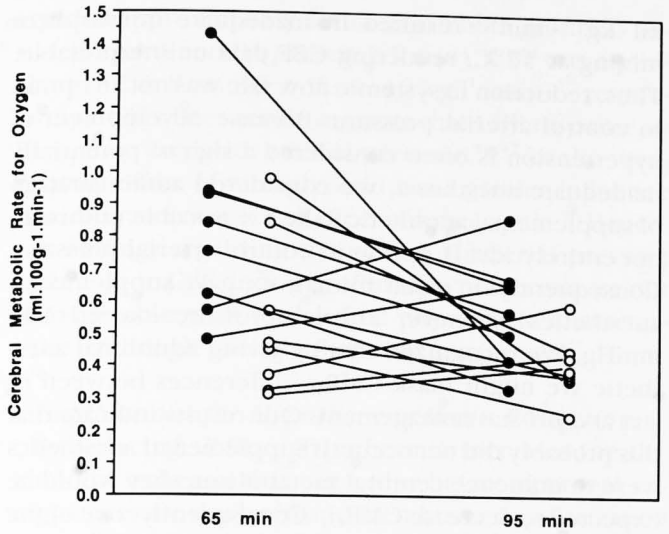

Fig. 4. Cerebral metabolic rate for oxygen in α-stat (group C, solid circles) and *p*H-stat animals (group D, open circles) at 65 and 95 min of cardiopulmonary bypass.

because of increased hemoglobin oxygen affinity or impaired erythrocyte capillary transit.[23–25] With impaired oxygen transfer from blood to brain, it is possible CMR_{O_2} may become flow limited, that is, CBF dependent. If so, our observation of lesser CMR_{O_2} in *p*H-stat animals may have been the result of their tendency toward lesser CBF relative to α-stat animals.

To address this possibility, additional experiments were performed where arterial pressure (and CBF) were altered. In a subsequent set of *p*H-stat animals (group D), arterial pressure was increased to α-stat levels using angiotensin II, which has no direct effect on CMR_{O_2}.[26] As expected, CBF increased. However, a concomitant decrease in oxygen extraction kept CMR_{O_2} constant. Thus, CMR_{O_2} was not CBF-dependent in *p*H-stat animals. In an additional set of α-stat animals (group C), arterial pressure was decreased to *p*H-stat levels using nitroglycerin, which has no direct effect on CMR_{O_2}.[27] The CBF response was variable. In some animals CBF decreased and in others it increased. The net result was an insignificant decrease in CBF, an insignificant increase in oxygen extraction, and an insignificant decrease in CMR_{O_2}. As a result of arterial pressure manipulation, systemic arterial pressure averaged over time (65 and 95 min of CPB) did not differ between α-stat (group C) and *p*H-stat (group D) animals. As a probable result, hemispheric CBF averaged over time (*i.e.*, mean CBF) also did not differ substantively between groups. Despite equivalence in mean arterial pressure and CBF, mean CMR_{O_2} was still significantly less in *p*H-stat (group D) animals than in α-stat animals. We conclude, therefore, CMR_{O_2} differences between α-stat and *p*H-stat management at 17°C were not because of CBF or arterial pressure differences between techniques.

Instead, we postulate that *p*H-stat–induced CMR_{O_2} reduction resulted from suppression of cerebral metabolism by the greater Pa_{CO_2} of *p*H-stat management. Most enzyme reaction rates are *p*H-dependent, and many enzymes have *p*H optima that follow the predictions of α-stat theory.[28,29] Because *p*H-stat management creates a relatively acidic intracellular environment, this would be expected to decrease enzyme reaction rates, adenosine triphosphate consumption, and, consequently, CMR_{O_2}. In fact, this process has been proposed as the mechanism by which hibernating species, which follow *p*H-stat strategy, reduce oxygen consumption in nonessential organs to the lowest possible values.[29–31] Our finding of additional cerebral metabolic suppression in *p*H-stat groups at 17°C provides a possible explanation for differences among the aforementioned studies in the CMR_{O_2}–temperature relation (table 1).

Our findings are in contrast to the work of Aoki *et al.*, who reported no difference in CMR_{O_2} between α-stat and *p*H-stat management in piglets undergoing CPB at 15°C.[32] Aoki *et al.* used samples from a retrograde internal jugular vein catheter to represent cerebral venous blood. Rudinsky and Meadow have shown that in the pig, internal jugular blood does not accurately represent cerebral venous blood because of extracranial venous contamination.[33] We have previously shown that although CBF decreases during hypothermic CPB, extracranial blood flow (masseter muscle) does not.[19] Data from the study by Aoki *et al.*[32] also showed that extracranial blood flow decreased far less than CBF during profound hypothermia. Therefore, during hypothermic CPB in the pig, the extracranial contribution to jugular venous blood is likely to further increase. Thus, samples from an internal jugular catheter will not represent cerebral venous blood and, as a consequence, CMR_{O_2} calculations using the Fick principle will not be accurate. In our experiments, cerebral venous blood was obtained from the confluens sinuum. Blood from this site is derived from the cerebral hemispheres and is free of extracranial venous contamination.[34]

Absolute CMR_{O_2} values appeared to differ between groups A and B and between groups C and D, with greater values in the latter groups. The most likely explanation for this difference is that bifemoral arterial

inflow was used in groups A and B, and descending aortic inflow was used in groups C and D. A similar pattern in this model can also be seen at 27°C.[19,35] Nevertheless, the relation between α-stat and *p*H-stat remained the same in both sets of experiments, specifically, *p*H-stat management resulted in CMR_{O_2} values 35–40% less than those with α-stat management.

Systemic Arterial Pressure

Unlike our experience at moderate hypothermia (27°C),[19] we noted major differences in systemic arterial pressure between α-stat and *p*H-stat management at profound hypothermia (17°C). α-Stat animals had a progressive increase in arterial pressure during cooling whereas *p*H-stat animals tended to have a progressive decrease. Because carbon dioxide is a known vasodilator,[36] we postulate the greater Pa_{CO_2} of *p*H-stat management prevented the arterial pressure increase observed in α-stat animals. Arterial pressures observed with α-stat management in these experiments greatly exceed those reported in other species (pigs,[37] sheep,[38] and dogs[39]) and in human infants[40,41] cooled to 15–20°C with α-stat management at equivalent systemic flow rates. Therefore, hypertension with α-stat management at 17°C differs significantly from the clinical situation and makes the rabbit a less attractive species for studies of cerebral physiologic variables during profoundly hypothermic CPB. Therefore, we believe our CMR_{O_2} findings should be confirmed in other species, with appropriate care to ensure accurate CBF determinations (such as paired microsphere reference samples), reliable cerebral venous blood samples, and constant brain temperature.

We did not consider a complete lack of arterial pressure control in α-stat animals (groups A and C) a tenable option because clinically unacceptable, supraphysiologic values of arterial pressure would have often occurred. Some studies of profoundly hypothermic CPB using α-stat technique, both in animals[32,42] and humans,[43–45] report the administration of vasodilators (phentolamine, phenoxybenzamine) with onset of perfusion cooling, suggesting these agents are necessary to prevent systemic arterial vasoconstriction. In pilot studies, we found neither phentolamine nor trimethaphan, antihypertensive agents having little direct effect on CBF and CMR_{O_2}, to effectively control hypertension during profound hypothermia. Pilot studies also showed reduction in systemic flow rate to less than 80 $ml \cdot kg^{-1} \cdot min^{-1}$ resulted in inadequate microsphere mixing at 17°C, rendering CBF data uninterpretable. Thus, reduction in systemic flow rate was not an option to control arterial pressure. Because development of hypertension is often considered a sign of potentially inadequate anesthesia, we considered administration of supplemental anesthetic to be a reasonable (although not entirely ideal) option to control arterial pressure. Consequently, in α-stat animals we gave supplemental anesthetics whenever arterial pressure exceed 100 mmHg. We recognized that by giving additional anesthetic we might mask CMR_{O_2} differences between α-stat and *p*H-stat management. Our results indicate that this probably did not occur. If supplemental anesthetics were to influence cerebral metabolism, they would be expected to decrease CMR_{O_2}. Consequently, one of the following may be expected: a lesser CMR_{O_2} in α-stat animals compared with *p*H-stat animals or a lesser CMR_{O_2} in α-stat animals that received supplemental anesthetic compared with α-stat animals that did not. In fact, neither was the case. Thus, we believe anesthetic differences between animals and groups at 17°C had little if any effect on CMR_{O_2}.

Opposing Effects of Systemic Arterial Pressure and Pa_{CO_2} on Cerebral Blood Flow

Given that *p*H-stat management results in much greater Pa_{CO_2} than does α-stat management, we were surprised that in the first set of experiments, CBF was greater in α-stat (group A) than in *p*H-stat (group B) animals. This finding might appear to be a radical departure from established physiologic characteristics: normally, increasing Pa_{CO_2} increases CBF. However, groups A and B differed not only in Pa_{CO_2}, but systemic arterial pressure as well, with α-stat animals having markedly greater systemic arterial pressure than *p*H-stat animals. Because profound hypothermia abolishes cerebral autoregulation,[20–22] it was not possible to discern the extent to which the CBF difference between groups A and B was the result of arterial pressure or Pa_{CO_2} differences. In the second set of experiments (groups C and D), we altered arterial pressure within each group, maintaining constant Pa_{CO_2}. When arterial pressure equaled approximately 100 mmHg in both groups C (α-stat, 65 min) and D (*p*H-stat, 95 min), CBF was, as expected, greater in the *p*H-stat group (40 ± 20 *vs.* 62 ± 10 $ml \cdot 100\ g^{-1} \cdot min^{-1}$, respectively). This finding is consistent with normothermic physiologic characteristics and with our studies** at 17°C in which acute increases in Pa_{CO_2} (α-stat to *p*H-stat conditions) were found to increase CBF. When arterial pressure

** Hindman BJ, Cutkomp J, Smith T: Unpublished data. 1992.

equaled approximately 58 mmHg in both groups C (α-stat, 95 min) and D (*p*H-stat, 65 min), CBF was equivalent (32 ± 8 *vs.* 30 ± 9 ml · 100 g^{-1} · min^{-1}, respectively). This later result suggests that CBF response to Pa_{CO_2} may vary with arterial pressure,[46,47] or the vasodilatory effect of nitroglycerin has a greater influence than the vasoconstricting effect of hypocapnia.[48] Hence, our findings regarding the effects of arterial pressure and Pa_{CO_2} on CBF during profound hypothermia are not incompatible with established physiologic characteristics, although initially they may appear so.

Implications for Hypothermic Brain Protection

By reducing CMR_{O_2}, hypothermia increases the duration of ischemia that can occur before neuronal energy stores are depleted and membrane depolarization occurs. By this and other mechanisms,[49–51] hypothermia provides a measure of brain protection during periods of cerebral ischemia. In these experiments we have shown *p*H-stat management significantly increases the suppressive effect of hypothermia on CMR_{O_2}. It is possible the additional CMR reduction of *p*H-stat management may significantly increase the allowable duration of cerebral ischemia before onset of terminal membrane depolarization and, thereby, provide an extra measure of brain protection.

Although membrane depolarization is the first step in the ischemic cascade, it is not the sole determinant of neurologic outcome. Once depolarization occurs, many subsequent events and processes (calcium influx, excitatory neurotransmitter release, reperfusion injuries) play critical roles in determining the final extent of neurologic injury.[49–51] How, or if, hypothermic acid–base management affects each of these processes and, consequently, net neurologic outcome in the setting of complete global cerebral ischemia (*i.e.*, circulatory arrest) is currently unclear. In a retrospective study, Jonas *et al.* reported better postoperative developmental outcome in children undergoing circulatory arrest with *p*H-stat as opposed to α-stat technique.[45] However, whether outcome differences were related to Pa_{CO_2} differences, or instead to differences in prearrest brain temperature cannot be ascertained. Animal studies are contradictory. Aoki *et al.* observed less brain water and a more prompt recovery of intracellular *p*H and adenosine triphosphate concentration after circulatory arrest (1 h at 15°C) in piglets cooled, arrested, and reperfused with *p*H-stat rather than α-stat management.[32] In stark contrast, Watanabe *et al.* found recovery of brain *p*H and P_{O_2} was more complete in dogs after circulatory arrest (1 h at 18°C) when animals were cooled, arrested, and reperfused under α-stat conditions as compared with hypercapnic (*p*H-stat) conditions.[52] Therefore, additional laboratory work and randomized clinical trials will be necessary to determine which hypothermic acid–base strategy provides optimal cerebral protection, and under what conditions (continuous flow *vs.* circulatory arrest).

In summary, during steady-state CPB at 17°C, *p*H-stat management reduced CMR_{O_2} 35–40% relative to α-stat management. The additional metabolic suppression of *p*H-stat management may explain previous discrepancies in the literature regarding the effect of profound hypothermia on CMR_{O_2}.

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