

Hypothermic Acid-Base Management Does Not Affect Cerebral Metabolic Rate for Oxygen at 27° C

A Study during Cardiopulmonary Bypass in Rabbits

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Background: It has been contended that, during cardiopulmonary bypass at 27° C, pH-stat management decreases cerebral metabolic rate for oxygen (CMR_{O₂}) more than α-stat management. In contrast, other studies have not found CMR_{O₂} to differ between techniques. Using each animal as its own control, the authors assessed the effect of α-stat *versus* pH-stat management on CMR_{O₂}, cerebral blood flow (CBF), and brain oxygen extraction during cardiopulmonary bypass at 27° C.

Methods: Fourteen New Zealand White rabbits, anesthetized with fentanyl and diazepam, underwent cardiopulmonary bypass at 27° C (membrane oxygenator, centrifugal pump, and bifemoral arterial perfusion). Group 1 animals (n = 7) had α-stat management for the initial 65–70 min of bypass, and were then changed to pH-stat management for the remaining 30 min of bypass. Group 2 animals (n = 7) had pH-stat management for the initial 65–70 min of bypass, and were then changed to α-stat management for the remaining 30 min. Measurement of CBF (radiolabeled microspheres), CMR_{O₂} (CBF × brain arterial-venous oxygen content difference), brain temperature, systemic hemodynamics, and arterial blood gases were made in each animal under both α-stat and pH-stat conditions.

Results: CMR_{O₂} did not differ between α-stat and pH-stat conditions ($1.4 \pm 0.3 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$; median ± quartile deviation), and was independent of order of determination. Changes in CBF between α-stat and pH-stat conditions were associated with proportional opposite changes in cerebral oxygen extraction. Cerebral blood flow was significantly greater with pH-stat management than with α-stat management (37 ± 5 vs.

$30 \pm 3 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, respectively). The CBF response to changing PaCO₂ was significantly greater when going from α-stat to pH-stat conditions (group 1) than in the reverse order (group 2).

Conclusions: During cardiopulmonary bypass at 27° C, hypothermic acid-base management has no measurable effect on CMR_{O₂}. CMR_{O₂} was neither extraction limited nor dependent on either PaCO₂, CBF, or hemoglobin oxygen affinity differences between α-stat and pH-stat management. Cerebral blood flow responses to changing CMR_{O₂} depend on the “starting” conditions, with α-stat management appearing to better preserve CBF reactivity than pH-stat management. (Key words: Anesthesia; cardiovascular. Brain: blood flow; carbon dioxide response; hypothermia; metabolism. Cardiopulmonary bypass. Temperature: hypothermia.)

NEUROLOGIC and neuropsychologic changes often follow procedures using cardiopulmonary bypass.^{1,2} It is important, therefore, to determine how the conduct of cardiopulmonary bypass affects cerebral physiology; either contributing to or modifying the brain's response to neurologic insults.

To date, studies examining the effect of α-stat *versus* pH-stat hypothermic acid-base management on cerebral oxygen metabolism have yielded inconsistent results. Prough *et al.* reported that the hypercarbia of pH-stat management reduced cerebral oxygen metabolism (CMR_{O₂}) 25–50% relative to α-stat management in patients undergoing cardiopulmonary bypass at 27° C.³ In contrast, Murkin *et al.*⁴ and Stephan *et al.*,⁵ in humans, and Hindman *et al.*, in rabbits,⁶ reported CMR_{O₂} values that were indistinguishable between groups managed with either α-stat or pH-stat technique at 26–27° C. Comparisons between groups are susceptible to greater variability because of interindividual variation, whereas comparisons within the same subject are not. For this reason, small, yet real, differences in CMR_{O₂} between α-stat and pH-stat management may have gone undetected in these latter investigations. This experiment, using each animal as its own control, was,

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therefore, designed to assess whether: (1) during cardiopulmonary bypass at 27° C, acid-base management influences CMR_{O_2} , and (2) the effect (if present) is reversible. The design of this study also permitted an assessment of whether cerebral blood flow (CBF) and hemoglobin oxygen affinity differences between α -stat and pH-stat technique may influence brain oxygen availability.

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 14 New Zealand White rabbits (4.1–5.1 kg). A tracheotomy was performed and the rabbits' lungs were ventilated with 1.5% halothane in oxygen to achieve normocarbica. The animals were paralyzed with a succinylcholine infusion and placed in the prone position. 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 so as to rest on the dural surface. A posterior midline craniectomy was then performed, exposing the confluens sinuum. Heparin (200 U/kg) was administered intravenously, and heparin was added to the succinylcholine infusion so as to give a maintenance dose of $200 \text{ U} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. The tip of a polyethylene catheter (PE-90; Intramedic, Parsippany, NJ) was then placed in the confluens sinuum, permitting the collection of cerebral venous blood.⁷ The cortical thermocouple and cerebral venous catheter were secured with bone wax and fast-drying cyanoacrylate cement, and the animals were turned to the supine position.

The tip of a catheter (PE-90), introduced *via* the right external jugular vein, was advanced to the superior vena cava to measure central venous pressure (CVP). Both brachial arteries were cannulated (PE-190) 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 and the succinylcholine/heparin infusion were discontinued. Anesthesia was maintained thereafter with fentanyl ($100\text{-}\mu\text{g/kg}$ bolus, $150\text{-}\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ infusion) and diazepam (2-mg/kg bolus, $3\text{-mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$

infusion). Muscle relaxation was achieved with 0.2 mg/kg pancuronium.

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 300, Cardiovascular Devices, Irvine, CA) was placed distal to the oxygenator and was calibrated against blood samples analyzed *via* standard blood gas analysis (see below). Circuit priming fluid consisted of 350 ml 6% (wt/vol) hydroxyethyl starch in normal saline (Hetastarch, E.I. Du Pont, Bannockburn, IL), 15 mEq sodium bicarbonate, 250 mg CaCl_2 , and 1,000 U heparin. The priming fluid was circulated through a $40\text{-}\mu\text{m}$ filter for 15–20 min before the addition of $\sim 150 \text{ ml}$ fresh filtered rabbit packed red blood cells, achieving a priming hematocrit of $\sim 25\%$. Cardiopulmonary bypass was initiated (bifemoral inflow, right atrial outflow) and maintained at a systemic flow of $100 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ monitored with a calibrated in-line electromagnetic flow meter (Biomedicus TX-40P). The pulmonary artery was clamped to ensure complete venous return to the bypass circuit. To ensure absence of pulsatile flow and to prevent ventricular distention, a 14-G catheter was placed in the left ventricle, which was then drained to the venous reservoir. For the first 5 min of bypass, no active heating or cooling measures were taken. Thereafter, animals were perfusion cooled to 27° C. Arterial pressure was measured from the left brachial arterial catheter. No pharmacologic or mechanical method was used to control arterial pressure.

To assess potential reversibility of CMR_{O_2} responses to hypothermic acid-base management, each animal was exposed to both α -stat and pH-stat conditions. The order of determination was randomized. Group 1 animals ($n = 7$) had α -stat management for the initial 65–70 min of bypass, and pH-stat management for the remaining 30 min of bypass. Group 2 animals ($n = 7$) had pH-stat management for the initial 65–70 min of bypass, and α -stat management for the remaining 30 min. With α -stat management, 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 pH-stat management, oxygen and nitrogen flows were adjusted to keep Pa_{CO_2} near 40 mmHg when

corrected to arterial perfusate temperature.^{||} Cerebral blood flow determinations (see below) were made in each animal under both α -stat and pH -stat conditions (*i.e.*, at both 70 and 95 min of bypass), and the following variables were simultaneously recorded: mean arterial pressure (MAP), CVP, bypass flow rate, brain (epidural) temperature, hematocrit, arterial blood gases (measured at 37° C and temperature-corrected values), and arterial and cerebral venous oxygen content (Lex-O₂-Con; Lexington Instruments Corporation, Waltham, MA). Sodium bicarbonate was given to increase the base excess to -4 mEq/l, or greater, calculated at 37° C (median = 1.4 mEq · kg⁻¹ · h⁻¹). At experiment completion, animals were killed by discontinuation of bypass and intracardiac administration of saturated KCl solution.

Cerebral blood flow was measured by the radioactive microsphere technique. Isotopes used included ¹⁴¹Ce, ⁹⁵Nb, ⁴⁶Sc, ⁸⁵Sr, ¹⁵³Gd, and ¹¹³Sn (New England Nuclear, Boston, MA), although only two isotopes were used in each experiment. Two hundred microliters of stock microspheres (~900,000 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% (vol/vol) Tween-80) and mixed for 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. Fresh tissue samples were weighed, placed in counting tubes, and, with reference blood samples, each counted for 5 min in a NaI well-type gamma counter. Isotope separation, background and overlap corrections, and organ blood flow calculations (ml · 100 g⁻¹ · min⁻¹) were performed by standard techniques.⁸⁻¹⁰ Weight-averaged values for right and left cerebral

hemispheric blood flow were used to mean hemispheric CBF.

CMR_{O₂} (ml · 100 g⁻¹ · min⁻¹) was calculated as the product of mean hemispheric cerebral blood flow (ml · 100 g⁻¹ · min⁻¹) and the arterial-cerebral venous oxygen content difference (ml 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 reference counts were normally distributed, permitting linear regression analysis to test adequacy of microsphere mixing and distribution. Some physiologic variables did not appear to be normally distributed. Consequently, physiologic variables are summarized using their median and quartile deviation (QD); the latter equaling one-half the difference between the first and third quartiles.

Analyses were performed using Systat (Evanston, IL) statistical software.¹¹ Differences in CBF and CMR_{O₂} between α -stat and pH -stat management were analyzed by one-way ANOVA. Because CMR_{O₂} appeared to follow a log-normal distribution, the logarithm of CMR_{O₂} was used for analysis. We tested whether the difference of the logarithms of the two CMR_{O₂} values in each animal (α -stat *vs.* pH -stat) was different than zero. The independent variable (group) was a binary variable. Statistical power (at the 80% level) to detect a change in CMR_{O₂} with an α of 0.05 was calculated *post hoc*¹² with log transformed data (see Appendix). Because CBF followed a normal distribution, we tested whether CBF differences between α -stat and pH -stat conditions in each animal were different than zero. The independent variable (group) was a binary variable. Standard regression diagnostics were used (see Appendix).

Results

Paired right and left microsphere reference counts were well matched ($r^2 = 0.96$, slope = 0.96, Y-intercept not significantly different than zero), indicating adequate microsphere mixing and uniform distribution. There were no right-left blood flow asymmetries between the cerebral hemispheres.

Systemic physiologic variables are shown in table 1. There were no physiologically meaningful differences between groups, or over time, with respect to the following: systemic flow, CVP, pH_a , hematocrit, PaO₂, and

^{||} All blood gases were measured on an IL1304 pH /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 pH and gas analysis. Catalog no. C12-T).

α -STAT VERSUS pH-STAT EFFECTS ON CMR_{O₂}

Table 1. Systemic Physiologic Variables

Variable	Group	α -stat	pH-stat
Bypass duration (min)	1	70 (0)	95 (5)
	2	95 (2)	67 (2)
Systemic flow	1	100 (1)	100 (3)
(ml · kg ⁻¹ · min ⁻¹)	2	100 (3)	100 (4)
Mean arterial pressure	1	80 (4)	84 (5)
(mmHg)	2	89 (2)	80 (5)
Central venous pressure	1	3 (1)	4 (1)
(mmHg)	2	4 (1)	4 (1)
Hematocrit (%)	1	24 (1)	23 (1)
	2	23 (2)	24 (2)
pH _a (37° C)	1	7.39 (0.01)	7.22 (0.02)
	2	7.37 (0.02)	7.24 (0.02)
Pa _{CO₂} (mmHg, 37° C)	1	38 (1)	63 (2)
	2	40 (3)	61 (2)
Pa _{O₂} (mmHg, 37° C)	1	249 (12)	288 (33)
	2	238 (19)	259 (39)
pH _a (mmHg, temperature	1	7.54 (0.01)	7.36 (0.02)
corrected)	2	7.52 (0.02)	7.39 (0.02)
Pa _{CO₂} (mmHg, temperature	1	24 (1)	40 (2)
corrected)	2	25 (2)	39 (1)
Pa _{O₂} (mmHg, temperature	1	203 (15)	243 (33)
corrected)	2	192 (21)	213 (15)
Arterial oxygen content (ml	1	11.9 (0.5)	11.4 (0.2)
O ₂ /dl)	2	11.4 (0.5)	11.5 (0.5)

Values are median and quartile deviation (parentheses); Group 1 (n = 7, α -stat to pH-stat); Group 2 (n = 7, pH-stat to α -stat).

arterial oxygen content. Mean arterial pressure tended to increase over time in both groups. As intended, pH_a and Pa_{CO₂} differed between α -stat and pH-stat management within each group. Mean arterial pressure and Pa_{CO₂} values during α -stat and pH-stat conditions varied slightly between groups. The time interval between measurements did not differ between groups (median = 27 min).

Cerebral physiologic variables are shown in table 2. Although brain temperature decreased, on average, 0.2° C between the first and second measurements, this decrease is physiologically inconsequential. CMR_{O₂} did not differ between α -stat (1.4 ± 0.3 ml · 100 g⁻¹ · min⁻¹; median \pm QD) and pH-stat conditions (1.4 ± 0.3 ml · 100 g⁻¹ · min⁻¹; $P = 0.68$; fig. 1). There was no effect of order of determination (group 1 *vs.* group 2) on CMR_{O₂} differences between α -stat and pH-stat conditions ($P = 0.41$). This study had sufficient power (at the 0.80 level) to detect a proportional change in CMR_{O₂} between α -stat and pH-stat conditions or be-

tween groups of less than 0.85 or greater than 1.20 (n = 14, SD = 0.22). Thus, this experiment had sufficient power to detect at least a 15% reduction in CMR_{O₂} under pH-stat conditions relative to α -stat conditions.

Cerebral blood flow differed between pH-stat management (37 ± 5 ml · 100 g⁻¹ · min⁻¹) and α -stat management (30 ± 3 ml · 100 g⁻¹ · min⁻¹; $P < 0.002$). Order of administration of the two acid-base strategies (*i.e.*, α -stat to pH-stat *vs.* pH-stat to α -stat) had a significant effect on the magnitude of the CBF differences ($P < 0.001$). Cerebral blood flow responses to changing Pa_{CO₂} were much greater when going from α -stat to pH-stat (group 1) than when Pa_{CO₂} changes were made in the reverse order (group 2; fig. 2).

Discussion

In this cardiopulmonary bypass model at 27° C, CMR_{O₂} is unaffected by acid-base management (α -stat *vs.* pH-stat). This finding is in contrast to the work of Prough *et al.*³ and Rogers *et al.*,¹³ wherein, at 27° C, pH-stat management resulted in CMR_{O₂} values 20–50% less than those measured in patients with α -stat management. Prough *et al.*³ proposed that the relative hypercarbia of pH-stat management reduced CMR_{O₂} in a manner analogous to hypercarbia-induced CMR_{O₂} suppression observed in normothermic animal studies. Reviews of the literature indicate that, at normothermia, CMR_{O₂} reductions are not detectable until Pa_{CO₂} exceeds 80–100 mmHg.^{14,15} We, therefore, consider it unlikely that the moderate hypercarbia of pH-stat management at 27° C (Pa_{CO₂} = 62 mmHg (pH-stat) *vs.* 40 mmHg (α -stat)*) would be sufficient to reduce CMR_{O₂}. Marked hypercarbia, Pa_{CO₂} > 100 mmHg, does reduce both cerebral metabolic rate for glucose (CMRg) and CMR_{O₂} at normothermia.^{14,15} Although CMRg is reduced *via* inhibition of phosphofructokinase, hypercarbia-induced reductions in CMR_{O₂} are believed to be the result of a net inhibitory effect of carbon dioxide on neuronal electrical activity.^{14,15} The greater inhibitory effects of hypothermia or anesthetics on brain electrical activity may be expected to overwhelm the comparatively small effect of mild to moderate hypercarbia on these processes at 27° C, and, hence, to eliminate CMR_{O₂} differences between α -stat and pH-stat management at 27° C.

We cannot readily explain the discrepancy between our findings and those of Prough *et al.*³ and Rogers *et al.*¹³ Because our results are consistent with the human

* Pa_{CO₂} measured at 37° C. If measured at 27° C, pH-stat Pa_{CO₂} = 40 mmHg, α -stat Pa_{CO₂} = 26 mmHg.¹⁶

Table 2. Cerebral Physiologic Variables

Variable	Group	α -stat	pH-stat
Brain temperature ($^{\circ}$ C)	1	26.7 (0.1)	26.5 (0.2)
	2	26.5 (0.1)	26.7 (0.3)
Confluens sinuum oxygen content (ml O_2 /dl)	1	6.6 (0.9)	8.3 (0.4)
	2	7.1 (0.6)	6.9 (0.5)
Cerebral arterial-venous oxygen difference (ml O_2 /dl)	1	5.1 (0.8)	3.4 (0.7)
	2	4.3 (0.9)	3.8 (0.8)
Cerebral oxygen extraction ratio	1	0.42 (0.07)	0.29 (0.05)
	2	0.38 (0.06)	0.36 (0.06)
Hemispheric cerebral blood flow*† (ml \cdot 100 g $^{-1}$ \cdot min $^{-1}$)	1	29 (3)	42 (8)
	2	31 (3)	33 (2)
Cerebral metabolic rate for oxygen (ml \cdot 100 g $^{-1}$ \cdot min $^{-1}$)	1	1.7 (0.3)	1.4 (0.1)
	2	1.4 (0.2)	1.3 (0.3)

Values are median and quartile deviation (parentheses); Group 1 (n = 7, α -stat to pH-stat), Group 2 (n = 7, pH-stat to α -stat).

* pH-stat cerebral blood flow significantly greater than α -stat ($P < 0.002$).

† Difference in cerebral blood flow between α -stat and pH-stat significantly greater in Group 1 ($P < 0.001$).

studies of Murkin *et al.*⁴ and Stephan *et al.*,⁵ species differences alone do not seem a sufficient explanation. This experiment had 80% power to detect either a >15% reduction or >20% increase in CMR_{O_2} under pH-stat relative to α -stat conditions. Thus, our sample size was adequate to detect pH-stat-induced CMR_{O_2} reductions of the magnitude reported by Prough *et al.*³

Using nonbypass animal models, Cain and Bradely,¹⁷ Schumaker *et al.*,¹⁸ and Hersenson *et al.*¹⁹ have shown that systemic oxygen extraction reserves are limited during hypothermia, presumably because of decreased

hemoglobin P_{50} or impaired red blood cell capillary transit. Studies of cerebral metabolism during human hypothermic bypass consistently report cerebral oxygen extraction ratios (OER) that are considerably less (~ 0.1 pH-stat; ~ 0.25 α -stat)^{4,20-23} than normothermic values (~ 0.4).^{4,20-23} Although these findings have been interpreted as evidence of excess CBF relative to CMR_{O_2} , *i.e.*, "luxury perfusion,"^{20,24} the alternative possibility is that low cerebral OER observed during human hypothermic bypass may be caused, at least in part, by impaired oxygen off-loading. If true, this would

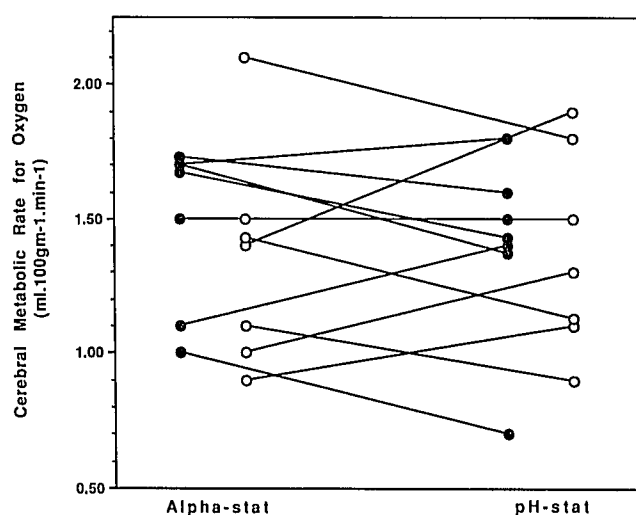


Fig. 1. Cerebral metabolic rate for oxygen under α -stat and pH-stat conditions. Solid circles = group 1 (α -stat to pH-stat, n = 7); open circles = group 2 (pH-stat to α -stat, n = 7).

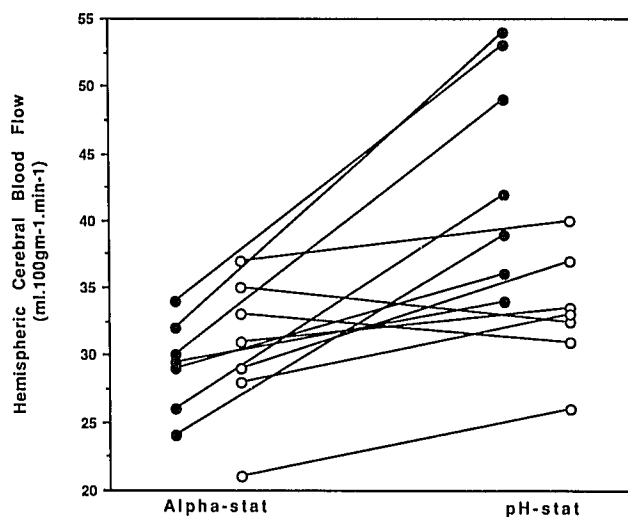


Fig. 2. Hemispheric cerebral blood flow under α -stat and pH-stat conditions. Solid circles = group 1 (α -stat to pH-stat, n = 7); open circles = group 2 (pH-stat to α -stat, n = 7).

suggest that: (1) the increased CBF and hemoglobin P₅₀ of pH-stat management may provide better oxygen availability to the brain, and (2) CMR_{O₂} may, therefore, be greater with pH-stat management than with α -stat management. Our experiment indicates that this is not the case. Figure 3 shows that, in each animal, a CO₂-induced change in CBF was associated with a proportional opposite change in OER, while CMR_{O₂} remained constant. This indicates that, during cardiopulmonary bypass at 27° C, given adequate systemic flow and arterial pressure, CMR_{O₂} is not extraction limited nor dependent on either CBF or hemoglobin oxygen affinity differences between α -stat and pH-stat management.^{**} Thus, during cardiopulmonary bypass at 27° C, there is no evidence of any difference between α -stat and pH-stat management in terms of either brain oxygen consumption or availability. Our findings indicate that neurologic outcome differences between patients managed with either α -stat or pH-stat technique, recently reported by Stephan *et al.*,⁵ are unlikely to be caused by differences in brain oxygen metabolism during cardiopulmonary bypass.

Animals maintained under α -stat conditions for the first 70 min of bypass had marked CBF increases when changed to pH-stat conditions (group 1). In contrast, animals initially maintained under pH-stat conditions had only small CBF decreases when subsequently changed to α -stat (group 2; fig. 2). Clearly, the cerebral blood flow response to changing PaCO₂ (Δ CBF/ Δ PaCO₂) depended on the starting conditions. Prior studies of CBF responses to changing PaCO₂ during hypothermic bypass have randomized order of determination (high to low PaCO₂ *vs.* low to high) to eliminate potential ordering effects on Δ CBF/ Δ PaCO₂.²⁶⁻³¹ In only two of the cited studies were data tested for evidence of an ordering effect. In an early study from our laboratory, we detected no evidence of an ordering effect on Δ CBF/ Δ PaCO₂, but, because of limitations in experimental design, our statistical power to detect such an effect was very low.²⁶ Prough *et al.* did detect an ordering effect: Δ CBF/ Δ PaCO₂ was greater when going from high to low PaCO₂ than when going from low to high²⁷ (the opposite of what we found in this experiment). They ascribed the ordering effect to a spontaneous decrease in CBF over time while on bypass. In this experiment, initial CBF values under steady-

^{**} Based on coefficients for change in P₅₀ with temperature and pH, at 27° C P₅₀ should equal ~12 mmHg with α -stat management and ~15 mmHg with pH-stat management.²⁵

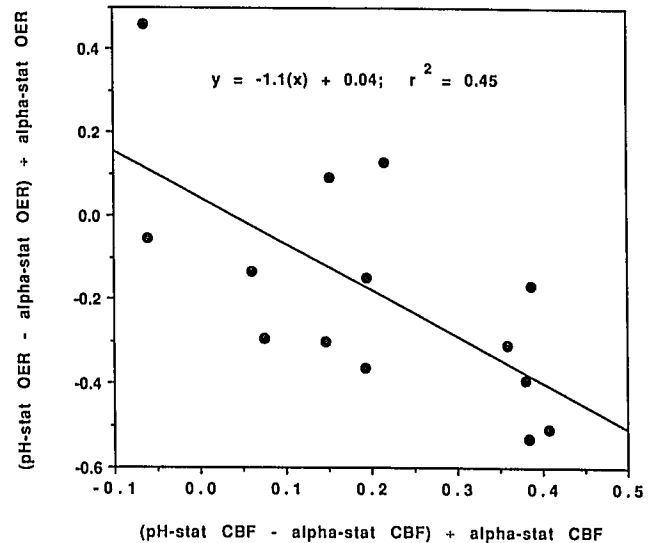


Fig. 3. Proportional change in cerebral oxygen extraction ratio *versus* proportional change in hemispheric cerebral blood flow under α -stat and pH-stat conditions for each animal. Slope = -1.1 ± 0.35 (SEM).

state α -stat and pH-stat conditions (70 min of bypass) are indistinguishable from CBF values obtained in a prior experiment in which, under steady state conditions, CBF remained unchanged between 60 and 90 min of bypass during both α -stat and pH-stat conditions.⁶ It, therefore, seems unlikely that spontaneous changes in CBF between measurements, independent of changing PaCO₂, can serve as an explanation for differences between groups in Δ CBF/ Δ PaCO₂ in this experiment, although it cannot be entirely ruled out.

Differences between steady-state α -stat and pH-stat CBF values were fairly small in this experiment. Compensatory increases in CSF bicarbonate concentration, the result of the relative hypercarbia of pH-stat conditions, would tend to increase CSF pH. This normalization of CSF pH would tend, over time, to minimize CBF differences between α -stat and pH-stat management. Indeed, Johnston *et al.* found no CBF differences between α -stat and pH-stat management in dogs maintained on cardiopulmonary bypass for greater than 90 min.³² Nevertheless, changes in CSF bicarbonate concentration cannot explain differing Δ CBF/ Δ PaCO₂ between groups exposed to acute PaCO₂ changes as produced in this experiment. Such PaCO₂ changes should have resulted in nearly equal changes in perivascular hydrogen ion concentration, although of opposite sign. Thus, differing Δ CBF/ Δ PaCO₂ between groups in our

experiment must be caused by differences in cerebrovascular smooth muscle responsiveness to CO_2 , with responsiveness being better preserved with chronic α -stat management than with chronic $p\text{H}$ -stat management.

Recently, nitric oxide has been found to play an important role in cerebral blood flow response to changing PaCO_2 . Inhibition of nitric oxide synthesis markedly diminishes $\Delta\text{CBF}/\Delta\text{PaCO}_2$.³³⁻³⁵ $\Delta\text{CBF}/\Delta\text{PaCO}_2$ has also been found to be diminished for hours following cortical spreading depression, a transient electrophysiologic response to brain injury.^{36,37} Although this experiment does not give insight into mechanisms whereby $p\text{H}$ -stat management inhibited cerebrovascular responsiveness to carbon dioxide, it clearly shows that choice of hypothermic acid-base management can have a marked influence on cerebrovascular responsiveness. Although cerebrovascular control mechanisms (autoregulation in other studies and CO_2 responsiveness in this experiment) appear to be better preserved with α -stat, it remains to be determined what effect, if any, preservation of vascular control mechanisms may have on the brain's tolerance to ischemic insults occurring during the course of cardiopulmonary bypass.

We conclude that, in our rabbit model of cardiopulmonary bypass at 27°C , hypothermic acid-base management (α -stat *vs.* $p\text{H}$ -stat) had no measurable effect on CMR_{O_2} . CMR_{O_2} was not extraction limited, CBF dependent, nor influenced by P_{50} differences between α -stat *vs.* $p\text{H}$ -stat management. In contrast, acid-base management differentially affected CBF and CBF responsiveness to PaCO_2 . Although CBF was greater with $p\text{H}$ -stat management than with α -stat management, chronic $p\text{H}$ -stat management diminished cerebrovascular responsiveness to PaCO_2 , whereas chronic α -stat management appeared to preserve it.

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Appendix

For power analysis, the sample standard deviation of the difference of the logarithm of CMR_{O_2} in each animal was used as the estimate for the population standard deviation.³⁸

For CMR_{O_2} and CBF analyses, standard regression diagnostics were used. First, no studentized residuals³⁹ or Cook's statistics³⁹ were statistically significant. Thus, no data were outliers or strongly influenced the results. Second, neither box plots nor Bartlett's tests⁴¹ showed evidence of heteroscedasticity. Third, probability plots and Lilliefors' tests⁴⁰ indicated that studentized residuals were not inconsistent with

being normally distributed. These criteria are required for P values and power analysis to be accurate.

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