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Differences in Cerebral Blood Flow between Alpha-stat and pH-stat Management Are Eliminated during Periods of Decreased Systemic Flow and Pressure

A Study during Cardiopulmonary Bypass in Rabbits

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Prior reports suggest cerebral blood flow (CBF) responses to changing bypass (systemic) flow rates may differ between alpha-stat and *p*H-stat management. To compare the effect of blood gas management upon CBF responses to changing systemic flow and pressure, 15 New Zealand White rabbits, anesthetized with fentanyl and diazepam, underwent nonpulsatile cardiopulmonary bypass at 25° C. One group of animals (n = 8) was randomized to alpha-stat blood gas management that maintained arterial carbon dioxide tension (Pa_{CO_2}) ≈ 40 mmHg when measured at 37° C. A second group (n = 7) was managed with *p*H-stat technique, maintaining Pa_{CO_2} ≈ 40 mmHg when corrected to the animal's actual temperature. Bypass was initiated at a flow rate of 100 ml · kg^{-1} · min^{-1} and, after ~20 min, control hemodynamic and CBF measurements (radioactive microspheres) were made. Thereafter, bypass flow rate was changed in random order at 15-min intervals to 50, 70, and 100 ml · kg^{-1} · min^{-1}. CBF and hemodynamic measurements were repeated at the end of each period of altered bypass flow. Groups differed significantly with respect to both *p*Ha and Pa_{CO_2}. There were no significant differences between groups with respect to bypass flow rate, mean arterial pressure (MAP), central venous pressure, temperature, hematocrit, arterial oxygen tension (Pa_{O_2}), or bypass duration at any measurement point. MAP decreased significantly, from ~ 80 to ~ 65 mmHg with decreasing bypass flow ($P = 0.0001$). Over the entire range of bypass flows, CBF decreased with decreasing bypass flow ($P = 0.001$), and the degree of change was equivalent among regions and between groups. *p*H-stat animals had significantly greater global CBF values compared with alpha-stat animals *only* at a bypass flow of 100 ml · kg^{-1} · min^{-1}. In addition, there was a strong suggestion ($P = 0.058$) that CBF responses to decreased systemic flow and pressure differed between groups at this level: CBF was unchanged in the alpha-stat group, whereas CBF decreased in the *p*H-stat group when bypass flow decreased from 100 to 70 ml · kg^{-1} · min^{-1}. At bypass flow rates of 50 and 70 ml · kg^{-1} · min^{-1}, there were no significant differences between groups in global CBF or in the CBF response to decreased systemic flow and pressure. Differences between alpha-stat and *p*H-stat management in both CBF and CBF dynamics can be eliminated under certain bypass conditions in rabbits. (Key words: Anesthesia: cardiovascular. Brain: autoregulation; blood flow; carbon dioxide response. Cardiopulmonary bypass: alpha-stat; blood gas management; *p*H-stat. Temperature: hypothermia.)

NEUROLOGIC AND NEUROPSYCHOLOGIC complications following surgery using cardiopulmonary bypass continue to be common.[1,2] For this reason, considerable research has been directed toward better understanding of cerebrovascular dynamics during bypass.

One aspect of this field that has received little attention concerns the effect of bypass flow rate upon cerebral blood flow (CBF). Govier and co-workers, using stepwise linear regression, found CBF to vary with temperature and carbon dioxide tension (Pa_{CO_2}) during bypass, with the effect of bypass flow rate nearly achieving statistical significance ($P = 0.06$).[3] In a subgroup of ten patients these authors randomly varied bypass flow while Pa_{CO_2} (33–45 mmHg), temperature (25.6–29.3° C), and arterial pressure (45–70 mmHg) were held relatively constant. They concluded that bypass flow of between 1.0 and 2.0 l · m^{-2} · min^{-1} had no effect upon CBF. In complete contrast, Soma and colleagues recently found CBF to vary linearly with a bypass flow rate of between 40 and 70 ml · kg^{-1} · min^{-1} (1.4–2.4 l · m^{-2} · min^{-1}) and found no significant change in arterial pressure over this flow range.[4]

A notable methodologic difference between these two studies is that Govier *et al.*'s patients had alpha-stat blood gas management whereas those of Soma *et al.* had *p*H-stat management.[5] The relative hypercarbia of *p*H-stat management is contended to induce cerebral vasodilation and to eliminate cerebral autoregulation.[6,7] We wondered whether hypothermic blood gas management might similarly affect CBF responses to changing bypass flow rate. We hypothesized that under alpha-stat conditions, CBF would be independent of bypass flow rate, whereas during *p*H-stat conditions, it would be dependent. This study compared CBF responses to changing bypass flow during hypothermic cardiopulmonary bypass, managed with either alpha-stat or *p*H-stat technique, using our previously described model of cardiopulmonary bypass in rabbits.[8]

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Materials and Methods

Basic Preparation

The experimental protocol was approved by the Animal Care Committee of the University of Iowa School of Medicine. Anesthesia was induced with halothane in oxygen in 15 New Zealand White rabbits (4.0 ± 0.4 kg, mean ± standard deviation [SD]). After ear vein cannulation and tracheal intubation with a 3.0-mm-ID cuffed tube (Mallinckrodt, Glens Falls, NY), the animals were paralyzed with 1 mg/kg succinylcholine and their lungs ventilated to achieve normocapnia (guided initially by capnography and later by arterial blood gas analysis) using a gas mixture containing 1.5% halothane in 33% oxygen/balance nitrous oxide. Paralysis was maintained with succinylcholine added to maintenance lactated Ringer's solution (4 $ml \cdot kg^{-1} \cdot h^{-1}$) in amounts sufficient to ensure delivery of 3 $mg \cdot kg^{-1} \cdot h^{-1}$. Temperature was measured *via* a thermistor placed in the mid-esophagus (Yellow Springs Instrument Co., Yellow Springs, OH).

Vascular Access

Via a branch of the right external jugular vein, a polyethylene catheter (PE-90, Intramedic, Parsippany, NJ) was advanced into the superior vena cava for central venous pressure monitoring. Both brachial arteries were cannulated (PE-160) for simultaneous withdrawal of microsphere reference blood samples, with the orifice of each catheter ~ 1 mm from the origin of the artery. Teflon catheters (14-G, 32 mm long) (Deseret, Sandy, UT) were inserted into each femoral artery. A median sternotomy was then performed; thymus and pericardium were reflected. Heparin (300 U/kg) was administered, achieving activated clotting times of greater than 900 s. An 18-Fr right atrial catheter (Polystan, Ballerup, Denmark) was placed *via* a purse-string suture. Ten to 15 min prior to bypass, halothane, nitrous oxide, and maintenance fluids were discontinued, and each animal received a loading dose of fentanyl and diazepam followed by a continuous infusion of each for the remainder of the experiment (fentanyl: 100 $\mu g/kg$ loading dose, 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion; diazepam: 2 mg/kg loading dose, 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion). Pancuronium (0.1 mg/kg) was used for subsequent muscle relaxation.

Cardiopulmonary Bypass

The bypass circuit consisted of a venous reservoir (model 400; Terumo Corporation, Piscataway, NJ), a centrifugal blood pump (model 540, with a BP-50 pump head; Biomedicus, Eden Prairie, MN), a membrane oxygenator/heat exchanger (Capiox II 08; Terumo), and a variable temperature water pump (VWR Scientific, San Francisco, CA). Priming fluid consisted of 300 ml 6% hydroxyethyl starch in normal saline (Hetastarch®, E. I. DuPont, Bannockburn, IL) to which was added 250 mg $CaCl_2$, 1000 U heparin, and ~150 ml filtered fresh packed donor rabbit red blood cells (collected in citrate/phosphate/dextrose) to achieve a total volume of ~450 ml and a hematocrit of ~20%. A continuous in-line blood gas analysis sensor (model 200; Cardiovascular Devices Inc., Irvine, CA), placed distal to the oxygenator, was calibrated against blood samples analyzed *via* standard blood gas analysis (IL1304, Instrumentation Laboratory, Lexington, MA).

The bilateral femoral arterial and the single atrial cannulas were connected to the circuit, and bypass was initiated at a flow rate of 100 $ml \cdot kg^{-1} \cdot min^{-1}$ monitored with a calibrated in-line electromagnetic flow meter (model TX40P, Biomedicus). Arterial pressure during bypass was measured from the left brachial arterial catheter. Because flow was the chosen independent variable, no attempt was made to control arterial pressure. The pulmonary artery was clamped to ensure complete venous return. *Via* purse-string suture, a 16-G left ventricular catheter allowed passive drainage to the venous reservoir.

Animals were randomly assigned to one of two blood gas management groups, alpha-stat (n = 8) or *p*H-stat (n = 7), and were cooled to 25° C. In the alpha-stat animals, Pa_{CO_2} was kept near 40 mmHg measured at 37° C (*i.e.*, not temperature-corrected), whereas with *p*H-stat animals Pa_{CO_2} was kept near 40 mmHg when corrected to the animal's actual temperature.‡‡ The oxygenator was ventilated with a mixture of oxygen and nitrogen varied so as to achieve an arterial oxygen tension (Pa_{O_2}) of near 250 mmHg and a Pa_{CO_2} appropriate to the assigned blood gas management strategy. Sodium bicarbonate was given to maintain a base deficit of not greater than 4 mEq/l, measured at 37° C. After 20–25 min of hypothermic perfusion at 100 $ml \cdot kg^{-1} \cdot min^{-1}$, hemodynamic and blood gas measurements were made and tissue blood flow measurements were made *via* the microsphere technique, described below. Next, bypass flow was serially changed, at 15-min intervals, to randomly assigned levels of 50, 70, and 100 $ml \cdot kg^{-1} \cdot min^{-1}$. At the end of each period of altered bypass flow, hemodynamic, blood gas, and organ blood flow measurements were repeated. Thus, all animals had initial (control) organ blood flow measurements made at a bypass flow of 100 $ml \cdot kg^{-1} \cdot min^{-1}$ (hereafter referred to as flow 100C) followed by additional organ blood flow

‡‡ 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 actual 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 number C12-T).

measurements at the end of each of the three subsequent randomly ordered bypass flows. At the completion of the experiment, animals were killed by discontinuation of bypass and intracardiac administration of saturated KCl solution.

Blood Flow Determinations

Tissue blood flows were determined by use of radioactive microspheres. Isotopes used included ^{141}Ce, ^{95}Nb, ^{153}Gd, ^{46}Sc, ^{85}Sr, and ^{113}Sn (New England Nuclear, Boston, MA). Two hundred microliters of stock 15-μm microspheres (~ 900,000 microspheres), vigorously mixed for 2–4 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 line just proximal to its bifurcation into the two inflow lines. Starting 15 s before injection of microspheres, and continuing 90 s afterward, blood was simultaneously withdrawn from each brachial arterial catheter *via* calibrated withdrawal pump at 1.96 ml/min (Harvard Apparatus, South Natick, MA). After the experiment, the brain was removed and dissected into the following regions: right and left cerebral hemispheres, cerebellum, midbrain (which included the thalamus, hypothalamus, pons, and cerebral peduncles), and medulla. Right and left masseter muscles also were sampled. Tissue samples were weighed, placed in counting tubes, and with reference blood samples, each was counted for 5 min in a gamma counter (Packard Instrument Co., Meriden, CT). The energy windows were as follows: ^{46}Sc, 862–1,200; ^{95}Nb, 626–800; ^{85}Sr, 418–600; ^{113}Sn, 344–416; ^{141}Ce, 126–170; and ^{153}Gd, 54–116 kiloelectron-volts. Corrections for background counts, isotope counting overlap, and tube geometry were performed by standard techniques.[9,10] Organ blood flow (milliliters per 100 grams per minute) was calculated by the following formula:

$$\text{blood flow} = 100 \times ([C_t \times RBF]/C_{rb})$$

where C_t = corrected counts per gram of tissue; RBF = reference blood flow (1.96 ml/min; see above); and C_{rb} = total corrected counts in reference blood. Corrected counts in the paired reference blood samples were averaged. Weight-averaged values for right and left hemispheric blood flows were used to calculate mean hemispheric CBF for each measurement point. Weight-averaged regional CBFs were used to calculate global CBF.

Statistics

All results are expressed as mean ± SD. Unless otherwise stated, hemodynamic, blood gas, and tissue blood flow measurements were compared using one (group), two (group and bypass flow), or three-way (group, bypass flow, and region) analysis of variance (ANOVA) using StatView 512$^+$ (BrainPower Inc., Calabasas CA) or SuperANOVA (Abacuss Concepts, Berkeley, CA) software. Significance was assumed for P values < 0.05.

Results

Hemodynamic and blood gas data are presented in table 1. As intended, alpha-stat and *p*H-stat animals differed significantly with respect to the independent variables, *p*Ha and Pa_{CO_2}. These variables remained constant within each group over the course of the study. Bicarbonate administered over the duration of bypass averaged 1.2 ± 0.7 mEq/kg with no difference between groups. There were no significant differences between alpha-stat and *p*H-stat groups with respect to bypass pump flow, mean arterial pressure (MAP), central venous pressure, temperature, hematocrit, Pa_{O_2}, or duration of bypass, at any measurement point. MAP decreased significantly with decreasing bypass flow in both groups ($F = 42.4$, $P = 0.0001$). Mixed venous oxygen tension ($P\bar{v}_{O_2}$) decreased significantly with decreasing bypass flow but was significantly greater in *p*H-stat animals as compared to alpha-stat animals. Animals in both groups were significantly colder during the latter three measurement points than they were at flow 100C ($P = 0.0025$). Mean temperature and mean duration of bypass were equivalent in the latter three measurement points, with no difference between alpha-stat and *p*H-stat animals.

Flow 100C was always studied first and, as noted above, temperature continued to decrease to a steady state after initial blood flow measurements were made. Consequently, when flow 100C data are included in the analysis, temperature and duration of bypass were inversely correlated ($r = 0.37$, $P = 0.004$), and global CBF varied significantly with *both* duration of bypass and with temperature in both groups. With exclusion of the flow 100C data, global CBF no longer correlated either with temperature ($P = 0.4$, $P = 0.7$) or with duration of bypass ($P = 0.4$, $P = 0.2$) in either the alpha-stat or *p*H-stat group respectively, and there was no longer a significant correlation between temperature and duration of bypass with subsequent data points ($r = 0.28$, $P = 0.06$). It therefore appears that flow 100C data points are not appropriate CBF controls because animals were significantly warmer at this measurement point, and CBF is known to be highly dependent on temperature. Thus, flow 100C data points were excluded from further analysis.

As shown in table 2, CBF decreased with decreasing bypass flow in both groups ($F = 8.6$, $P = 0.001$). Because there were no significant regional differences in the response of CBF to decreasing bypass flow ($F = 1.7$, $P = 0.14$), further analysis was limited to weight-averaged

TABLE 1. Physiologic Data During Cardiopulmonary Bypass with Varying Bypass Flow Rate

Variable	Bypass Flow (ml · kg^{-1} · min^{-1})							
	100C		100		70		50	
	Alpha-stat	*p*H-stat	Alpha-stat	*p*H-stat	Alpha-stat	*p*H-stat	Alpha-stat	*p*H-stat
Bypass flow (ml · kg^{-1} · min^{-1})	100 ± 0	100 ± 0	100 ± 1	100 ± 1	71 ± 1	71 ± 2	51 ± 1	50 ± 1
Mean arterial pressure (mmHg)*	74 ± 9	83 ± 7	80 ± 9	82 ± 6	76 ± 12	76 ± 7	62 ± 8	69 ± 6
Central venous pressure (mmHg)	4 ± 2	5 ± 1	5 ± 1	5 ± 1	4 ± 1	4 ± 1	4 ± 1	4 ± 1
Hematocrit (%)	22 ± 1	22 ± 3	22 ± 1	21 ± 3	22 ± 1	21 ± 2	21 ± 1	21 ± 2
Duration of bypass (min)	22 ± 3	24 ± 7	45 ± 14	60 ± 15	63 ± 9	51 ± 9	48 ± 10	56 ± 19
Temperature (° C)†	25.8 ± .9	25.5 ± .4	25.5 ± .5	25.1 ± .2	25.1 ± .2	25.1 ± .2	25.3 ± .5	25.0 ± .0
*p*Ha (37° C)‡	7.33 ± .05	7.22 ± .03	7.37 ± .05	7.21 ± .02	7.36 ± .03	7.21 ± .03	7.35 ± .04	7.21 ± .03
Pa_{CO_2} (37° C)‡	44 ± 5	63 ± 5	39 ± 5	63 ± 2	40 ± 4	65 ± 3	41 ± 3	65 ± 4
Pa_{O_2} (37° C)	247 ± 65	323 ± 187	296 ± 57	274 ± 90	229 ± 86	318 ± 120	260 ± 77	256 ± 75
$P\bar{v}_{O_2}$ (37° C)*‡	62 ± 3	79 ± 17	64 ± 4	80 ± 10	54 ± 7	71 ± 9	48 ± 4	59 ± 7
pHa (temp-cor)‡	7.51 ± .05	7.38 ± .02	7.55 ± .04	7.37 ± .02	7.53 ± .03	7.37 ± .02	7.52 ± .05	7.37 ± .04
Pa_{CO_2} (temp-cor)‡	26 ± 3	37 ± 3	23 ± 3	37 ± 2	23 ± 3	39 ± 2	24 ± 2	38 ± 2
Pa_{O_2} (temp-cor)	193 ± 67	261 ± 170	242 ± 54	218 ± 90	179 ± 80	260 ± 113	205 ± 77	255 ± 90
$P\bar{v}_{O_2}$ (temp-cor)*§	27 ± 1	37 ± 10	28 ± 2	36 ± 6	24 ± 3	32 ± 5	21 ± 2	26 ± 3

Mean ± SD. Alpha-stat, n = 8; *p*H-stat, n = 7. Blood gas tensions are expressed in mmHg. 37° C and temp-cor designate whether the measurement was performed at 37° C or the result was temperature-corrected, respectively.

* Decreased significantly with decreasing CPB flow, $P = 0.001$.

† Temperature significantly greater at flow 100C compared with other flows, $P = 0.0025$.

‡ Alpha-stat significantly different than *p*H-stat, $P = 0.0001$.

§ Alpha-stat significantly different than *p*H-state, $P = 0.003$.

TABLE 2. Cerebral Blood Flows (ml · 100 g^{-1} · min^{-1}) *versus* Bypass Flow Rate

Region	Bypass Flow (ml · kg^{-1} · min^{-1})							
	100C		100		70		50	
	Alpha-stat	*p*H-stat	Alpha-stat	*p*H-stat	Alpha-stat	*p*H-stat	Alpha-stat	*p*H-stat
Cerebral hemispheres	34 ± 8	45 ± 8	27 ± 5	35 ± 10	27 ± 6	28 ± 3	19 ± 5	25 ± 7
Midbrain	46 ± 12	49 ± 8	38 ± 6	46 ± 9	45 ± 12	38 ± 6	31 ± 7	32 ± 7
Cerebellum	54 ± 17	62 ± 11	43 ± 7	57 ± 16	47 ± 16	47 ± 10	36 ± 9	40 ± 16
Medulla	46 ± 10	48 ± 7	35 ± 3	45 ± 9	44 ± 14	39 ± 6	32 ± 9	32 ± 6
Global	40 ± 9	45 ± 8	32 ± 3	41 ± 9*	35 ± 9	34 ± 2	25 ± 5	29 ± 7

Mean ± SD. Alpha-stat, n = 8; *p*H-stat, n = 7. Cerebral blood flows at 100C excluded from analysis. Analysis performed only on global cerebral blood values. (See text for explanations).

* *p*H-stat significantly greater than alpha-stat, $P = 0.02$ (paired *t* test).

global CBF values (fig. 1). Over the *entire* range of bypass flows there was no significant difference in CBF between alpha-stat and *p*H-stat groups (F = 3.9, $P = 0.07$) or in the CBF response to decreasing bypass flow (F = 1.9, $P = 0.17$). At the lower bypass flow rates (50 and 70 $ml \cdot kg^{-1} \cdot min^{-1}$), there was no difference between alpha-stat and *p*H-stat animals in CBF or in the CBF response to changing bypass flow. In contrast, at the highest bypass flow rate (100 $ml \cdot kg^{-1} \cdot min^{-1}$), the difference in global CBF between *p*H-stat and alpha-stat groups achieved statistical significance ($P = 0.02$, unpaired *t* test). Likewise, the CBF response to decreasing bypass flow from 100 to 70 $ml \cdot kg^{-1} \cdot min^{-1}$ differed between alpha-stat and *p*H-stat animals at the P = 0.058 level (F = 4.3, two-way ANOVA).

Discussion

Methodology

For calculated blood flow values to be accurate with the microsphere technique, six conditions must be met[9,11]: 1) reference blood samples must be representative of arterial blood supplying the organ(s) of interest; 2) microspheres must be evenly distributed in the bloodstream so that concentrations reaching all branching sites are similar; 3) microspheres must distribute in the bloodstream proportional to actual blood flow; 4) sufficient numbers of spheres must be used as to achieve ≥ 400 spheres per gram of tissue; 5) microspheres must not disturb or decrease the circulation in the organ of interest; and 6) microspheres must be completely trapped on the first pass of the circulation.

In the current experiment, blood was sampled from both brachial arteries, which originate at the innominate artery and ascending aorta, as do the right and left common carotid arteries. Use of paired brachial arterial blood collection allowed verification of the uniformity of microsphere distribution in the blood supply of interest. The slope of a paired correlation of right and left references counts equalled 0.87 ± 0.08 (r = 0.81). In addition, there were no right–left asymmetries in either the cerebral hemispheres or masseter muscles in either group at any bypass flow rate (paired *t* tests). In pilot experiments using an arterial perfusion cannula in the ascending aorta, we observed wide disparity between right and left brachial arterial reference counts. This was most likely due to microsphere streaming and inadequate mixing. Use of two femoral perfusion cannulas probably creates some turbulence at the confluence of their streams such that microspheres are more adequately mixed and distributed.

Rosenberg and colleagues postulated anemia might be associated with a tendency for microspheres to flow in the axial portion of the arterial stream. In such cases small catheters lying against larger vessel walls might withdraw blood relatively poor in microspheres.[12] This would make the calculated organ blood flows artificially high. The authors[12] found that these errors could be eliminated by use of large catheters and relatively high withdrawal rates in animals with hematocrits as low as 15%. Accordingly, we used microsphere-withdrawal catheters that were greater than or equal to the size of the arteries (PE-160) and withdrew blood at three times the standard rate.[13,14] Large numbers (~ 900,000) of microspheres were used for each blood flow determination, such that even at the lowest CBF values obtained (~ 20 $ml \cdot 100\ gm^{-1} \cdot min^{-1}$), it was expected that cerebral tissue would contain ≥ 500 spheres per gram. Despite the use of these large numbers of microspheres, previous investigators have found even five serial injections of this quantity of spheres did not alter CBF in rabbits.[13] Finally, we performed pilot studies with this model, simultaneously withdrawing arterial and both systemic venous and cerebral venous reference samples. We found both systemic and cerebral shunting of 15-μm microspheres was less than 1% during both normothermic and hypothermic bypass (with both alpha-stat and *p*H-stat management). Thus, we believe we have satisfied all reported methodologic criteria for use of the microsphere technique and consider ours a valid model of regional and global cerebrovascular dynamics during cardiopulmonary bypass.

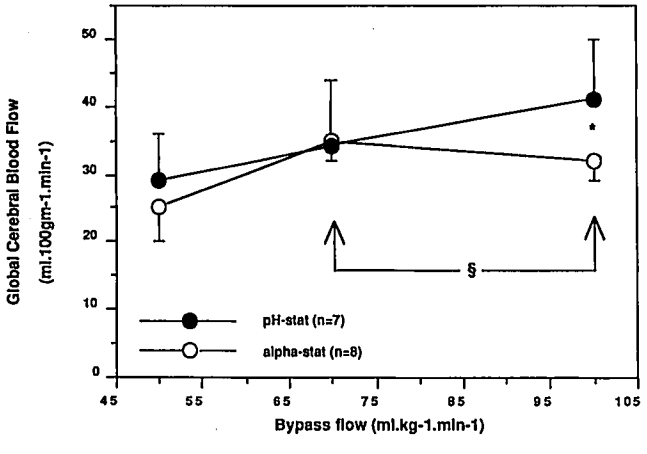

FIG. 1. Global cerebral blood flow (±SD) *versus* bypass flow rate. *pH-stat greater than alpha-stat at bypass flow of 100 $ml \cdot kg^{-1} \cdot min^{-1}$, $P = 0.02$ (paired *t* test). § Change in cerebral blood flow with changing bypass flow different between alpha-stat and *p*H-stat, $P = 0.058$ (two-way ANOVA).

Findings

Our data address two issues concerning cerebrovascular physiology during cardiopulmonary bypass: 1) time and temperature effects upon CBF during hypothermic bypass and 2) differences in CBF between alpha-stat and *p*H-stat

management as affected by bypass flow rate and arterial pressure.

In a study of the cerebrovascular effects of phenylephrine, Rogers and co-workers found CBF to decrease progressively over time on hypothermic bypass at a rate of $\sim 1 \pm 1$ %/min.[7] In the current experiment, when flow 100C points were included in the analysis (obtained at $\sim$ 20 min of hypothermic bypass), we also observed time-dependent decreases in CBF. In contrast, subsequent CBF measurements (after at least 40 min of hypothermic bypass) exhibited no such dependence. Temperature and duration of bypass were inversely correlated when flow 100C points were included in the analysis, but no such correlation was present when these points were excluded. From these observations we conclude that the brain lags somewhat in temperature equilibration, such that relatively long periods on hypothermic bypass are necessary before stable and reproducible conditions exist. Ongoing experiments with this preparation, using an epidural thermocouple to estimate brain temperature, have confirmed that $\sim$ 40 min are required for brain temperature equilibration to 25° C. Since brain cooling must be a flow-dependent process, we suggest that a similar duration of bypass may be necessary in humans before brain temperature equilibration with perfusate occurs.

Ideally, to study the effect of bypass flow rate upon CBF, one would vary bypass flow at constant arterial pressure. Although baseline arterial pressure could be maintained in the face of decreasing bypass flow by the use of vasopressors, Patel and Mutch have shown phenylephrine, norepinephrine, and angiotensin II have differential effects on CBF in the anesthetized rabbit, independent of their effect on arterial pressure.[15] To avoid the potentially confounding effect of vasopressors, we made no attempt to control arterial pressure with varying bypass flow, recognizing fully that independent effects of bypass flow rate and arterial pressure upon CBF could not be formally separated.

When perfused at the highest flow rate (100 $ml \cdot kg^{-1} \cdot min^{-1}$), our *p*H-stat animals had greater CBF values than did alpha-stat animals. Using group means, this implies that the slope of the CBF *versus* Pa_{CO_2} response curve at this bypass flow rate was $\sim$ 0.7 $ml \cdot 100\ gm^{-1} \cdot min^{-1} \cdot mmHg^{-1}$. This is in close agreement with composite data of previous human studies.[6,7,16–18] Unlike the situation at lower bypass flows, there is a strong suggestion ($P = 0.058$) that blood gas management affected the CBF response to decreased systemic flow and pressure. In the transition from 100 to 70 $ml \cdot kg^{-1} \cdot min^{-1}$, CBF was unchanged in the alpha-stat group, whereas CBF decreased in the *p*H-stat group. This observation suggests preserved autoregulatory responses to decreased systemic flow and pressure under alpha-stat conditions and an attenuation of these responses under *p*H-stat conditions. More specifically, since the decrease in arterial pressure was rather small in both groups (5 ± 4 mmHg), the data suggest that in *p*H-stat animals, bypass flow rate may have an effect on CBF independent of arterial pressure, whereas no such effect is present in alpha-stat animals. This finding reconciles the apparently contradictory results of Govier *et al.*[3] and Soma *et al.*[4] regarding the effect of bypass flow rate upon CBF.

In stark contrast, differences between alpha-stat and *p*H-stat animals were greatly diminished at lower bypass flow rates (50 and 70 $ml \cdot kg^{-1} \cdot min^{-1}$). Absolute CBF values as well as CBF variation with systemic flow and pressure were indistinguishable, with an apparent absence of autoregulation in both groups. This indicates that the effect of carbon dioxide on CBF and upon CBF responses to changing systemic flow and pressure (*i.e.*, differences between alpha-stat and *p*H-stat management) can be eliminated under certain bypass conditions. In normothermic animals, the CBF response to carbon dioxide decreases and finally is eliminated during progressive hemorrhagic hypotension,[19–22] wherein, as in this experiment, both systemic flow and pressure decrease. The presumed mechanism for this observation is that autoregulatory cerebral vasodilation mitigates any further vasodilatory response to carbon dioxide. It appears that a similar process can occur during hypothermic bypass.

It is impossible to directly compare the bypass flow rates used in this study to those clinically used. However, based on $P\bar{v}_{O_2}$ values (table 1), mixed venous oxyhemoglobin saturations of at least 70%[23] were present even at the lowest flow rate, suggesting adequate systemic oxygen delivery. Likewise, arterial pressure was not dramatically reduced and in most cases was well above the lower limit of cerebral autoregulation and carbon dioxide responsiveness in normothermic rabbits ($\sim$ 60 mmHg).[20] Consequently, the low flow conditions of this experiment were not unduly "challenging" and were physiologically comparable to bypass conditions often encountered in clinical practice.

Consistent with our findings, Lundar and co-workers, using transcranial Doppler to measure CBF velocity in humans during hypothermic bypass, found the cerebral vasodilatory effect of carbon dioxide to depend on arterial pressure. CBF responses to carbon dioxide decreased when cerebral perfusion pressure was less than 50 mmHg (and MAP was less than $\sim$ 60 mmHg).[24] Therefore, we contend that loss or attenuation of the effect of carbon dioxide on CBF, as well as the effect of carbon dioxide upon CBF–arterial pressure–bypass flow interactions, might occur during what appears to be adequate hypothermic bypass, and thus that the distinction between alpha-stat and *p*H-stat management is relatively unimportant. That biologically significant differences between alpha-stat and *p*H-stat management are small is supported

by the following observations: 1) there is considerable overlap in absolute CBF values between these patient groups;[25] and 2) a prospective randomized study of neurologic outcome following cardiac surgery was unable to find any difference between patients assigned to alpha-stat *versus* *p*H-stat blood gas management.[1]

In summary, using a rabbit model of cardiopulmonary bypass, we found that differences between alpha-stat and *p*H-stat management in CBF and in CBF dynamics were drastically reduced during periods of decreased systemic flow and pressure. Our findings suggest that differences between alpha-stat and *p*H-stat management may be slight or nonexistent during many clinical circumstances of hypothermic cardiopulmonary bypass. "Critical" values of systemic flow and pressure, below which carbon dioxide has no effect on CBF or CBF dynamics during human cardiopulmonary bypass, cannot be determined from this study.

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