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Response of Cerebral Blood Flow to Phenylephrine Infusion during Hypothermic Cardiopulmonary Bypass:

Influence of Pa_{CO_2} Management

Anne T. Rogers, M.B.Ch.B., F.R.C.P.(C.), David A. Stump, Ph.D.,† Glenn P. Gravlee, M.D.,‡ Donald S. Prough, M.D.,§ Kevin C. Angert, M.D.,* Stephen L. Wallenhaupt, M.D.,¶ Raymond C. Roy, M.D., Ph.D.,‡ Julia Phipps, R.N.***

Twenty-eight adult patients anesthetized with fentanyl, then subjected to hypothermic cardiopulmonary bypass (CPB), were studied to determine the effect of phenylephrine-induced changes in mean arterial pressure (MAP) on cerebral blood flow (CBF). During CPB patients managed at 28° C with either alpha-stat (temperature-uncorrected Pa_{CO_2} = 41 ± 4 mmHg) or *p*H-stat (temperature-uncorrected Pa_{CO_2} = 54 ± 8 mmHg) Pa_{CO_2} for blood gas maintenance received phenylephrine to increase MAP ≥ 25% (group A, n = 10; group B, n = 6). To correct for a spontaneous, time-related decline in CBF observed during CPB, two additional groups of patients undergoing CPB were either managed with the alpha-stat or *p*H-stat approach, but neither group received phenylephrine and MAP remained unchanged in both groups (group C, n = 6; group D, n = 6). For all patients controlled variables (nasopharyngeal temperature, Pa_{CO_2}, pump flow, and hematocrit) remained unchanged between measurements. Phenylephrine data were corrected based on the data from groups C and D for the effect of diminishing CBF over time during CPB. In patients in group A CBF was unchanged as MAP rose from 56 ± 7 to 84 ± 8 mmHg. In patients in group B CBF increased 41% as MAP rose from 53 ± 8 to 77 ± 9 mmHg ($P < 0.001$). During hypothermic CPB normocarbia maintained *via* the alpha-stat approach at a temperature-uncorrected Pa_{CO_2} of ≃40 mmHg preserves cerebral autoregulation; *p*H-stat management (Pa_{CO_2} ≃57 mmHg uncorrected for temperature, or 40 mmHg when corrected to 28° C) causes cerebrovascular changes (*i.e.*, impaired autoregulation) similar to those changes produced by hypercarbia in awake, normothermic patients. (Key words: Blood pressure: cerebral blood flow. Brain: cerebral blood flow. Carbon dioxide: cerebral blood flow; hypothermia. Hypothermia: blood gases; cerebral blood flow. Phenylephrine. Surgery: cardiovascular. Sympathetic nervous system: cerebral blood flow.)

IN NORMOTHERMIC, awake humans autoregulation maintains cerebral blood flow (CBF) at 50–55 ml · 100 $g^{-1} \cdot min^{-1}$ over a wide range of perfusion pressures.[1] In normotensive humans a mean arterial pressure (MAP) of 50–70 mmHg defines the lower limit of cerebral autoregulation,[1–3] with CBF declining abruptly as MAP falls below 50 mmHg.[1]

Studies of the relationship between MAP and CBF during hypothermic nonpulsatile cardiopulmonary bypass (CPB) in humans have yielded conflicting results.[4–7] Govier *et al.*[4] using xenon clearance techniques and multiple linear regression analysis, reported persistence of cerebral autoregulation during CPB, with leftward extension of the plateau to a MAP of 30 mmHg. In contrast, Lundar *et al.*[5] used a Doppler ultrasonic probe over the internal carotid artery to demonstrate that flow velocity, a variable that correlates with CBF, varied directly with changes in MAP. Methodologic differences between these two studies could explain the divergent findings. However, because Pa_{CO_2} profoundly influences CBF during CPB, differing acid–base management might account for these conflicting results.[8] Govier *et al.*[4] adjusted patient Pa_{CO_2} to approximately 40 mmHg, uncorrected for body temperature, and Lundar *et al.*[5] used a temperature-corrected Pa_{CO_2} of 37.5 mmHg. This concept is supported by Murkin *et al.*,[9] who measured CBF by clearance of xenon while MAP varied spontaneously and also determined the cerebral metabolic rate for oxygen ($CMRO_2$). They found that during hypothermic CPB cerebral autoregulation remained intact at a temperature-uncorrected Pa_{CO_2} of 40 mmHg (alpha-stat management), whereas maintenance of a temperature-corrected Pa_{CO_2} of 40 mmHg (*p*H-stat management) resulted in CBF becoming perfusion pressure-dependent. In the Murkin *et al.* study analysis of pooled data showed that CBF correlated significantly with $CMRO_2$ when Pa_{CO_2} was controlled by the alpha-stat approach and was independent of cerebral perfusion pressure over the range of 20–100 mmHg.[9]

Presently, the optimal MAP during CPB remains speculative. Many clinicians choose to maintain MAP in the range of 50–70 mmHg; however, MAP frequently falls below this range during hypothermic CPB, necessitating the use of a vasopressor, and phenylephrine administered by constant infusion is the agent most often employed. Precise evaluation of the response of CBF to phenyleph-

* Assistant Professor of Anesthesia.
† Associate Professor of Neurology.
‡ Associate Professor of Anesthesia.
§ Associate Professor of Anesthesia (Section on Critical Care) and Neurology.
¶ Assistant Professor of Surgery (Section on Cardiothoracic Surgery).
** Research Associate, Department of Anesthesia.

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Address reprint requests to Dr. Rogers: Department of Anesthesia, Wake Forest University Medical Center, Bowman Gray School of Medicine, 300 S. Hawthorne Road, Winston-Salem, NC 27103.

rine infusion requires determination of CBF at varying MAP levels for individual patients while holding other factors constant.

We examined the effect of phenylephrine infusion on CBF during hypothermic, nonpulsatile CPB for two different types of acid–base management, the alpha-stat and the *p*H-stat method. To control for the influence of elapsed time on CBF during CPB, we also assessed CBF in a group of CPB patients who received no pharmacologic intervention. CBF values for patients receiving phenylephrine were then corrected for this spontaneous decline in CBF, which occurred in the absence of any pharmacologic agent.

Methods

We studied CBF in 28 adult patients (18 males, 10 females) undergoing elective cardiac surgery, with a mean age of 61 years (range, 45–77 yr). The Institutional Clinical Research Practices Committee approved this study and all patients gave written informed consent. Preoperative exclusion criteria included uncontrolled arterial hypertension and clinical evidence of cerebrovascular disease. Premedication consisted of oral lorazepam 50 $\mu g \cdot kg^{-1}$ and intramuscular morphine 0.1 $mg \cdot kg^{-1}$. Anesthesia was induced and maintained with fentanyl 75 $\mu g \cdot kg^{-1}$ while nondepolarizing muscle relaxants (pancuronium or metocurine) facilitated endotracheal intubation. No additional agents other than oxygen and phenylephrine were administered until all measurements were completed.

All patients underwent nonpulsatile CPB through an ascending aortic cannula, with induction of hypothermia to approximately 28° C. A membrane oxygenator, an arterial line filter, and a crystalloid priming solution were used in each case. During CPB the perfusionist maintained within narrow limits each patient's nasopharyngeal temperature (NPT), Pa_{CO_2}, pump flow ($\dot{Q}$), and hematocrit under the direction of the supervising anesthesiologist.

We assessed the effect of phenylephrine infusion on CBF by randomizing patients into one of two groups according to acid–base management. For patients in group A (n = 10) the mean Pa_{CO_2}, uncorrected for temperature, was held at approximately 40 mmHg (alpha-stat) by varying fresh gas flow to the membrane oxygenator, whereas in group B patients (n = 6) an average uncorrected Pa_{CO_2} of 57 mmHg (*p*H-stat, 40 mmHg, corrected for temperature) was achieved by adding carbon dioxide to the inflow gas. In both groups of patients baseline CBF measurements proceeded once the aorta had been cross-clamped and once CPB conditions, including body temperature, had stabilized for approximately 5 min. After infusing phenylephrine into the venous reservoir of the extracorporeal circuit at a rate sufficient to increase MAP by at least 25% (patient doses varied from 40–300 $\mu g \cdot min^{-1}$), CBF determinations were repeated approximately 21–25 min after obtaining baseline CBF measurements. Central venous pressure was maintained close to zero by allowing unrestricted drainage to the venous reservoir of the pump circuit.

To account for decreasing CBF observed over time during CPB in the absence of phenylephrine, we randomized 12 additional patients into one of two additional groups, managed with either alpha-stat (group C, n = 6) or *p*H-stat (group D, n = 6) blood gases. Once CPB stabilized, as described above, a baseline CBF measurement was performed. This was repeated after an interval of approximately 20–30 min without changing any of the controlled variables or using any pharmacologic intervention. Time intervals, varying among patients, were a function of individual clinical settings.

For all patients CBF was measured in both hemispheres using a portable regional cerebral blood flow (rCBF) system developed at our institution, which consisted of 16 cadmium telluride gamma detectors positioned in a helmet around the patient's head. Data were processed and displayed in real time on a microcomputer terminal in the operating room. Simultaneously, CBF data were transferred *via* modem to a central Vax 730 computer for rapid analysis of individual brain regions. We obtained CBF measurements by injecting 3–5 mCi of ^{133}Xenon (^{133}Xe) dissolved in sterile saline into the arterial tubing of the pump circuit, proximal to the filter. The arterial inflow tubing was monitored with a separate cadmium telluride probe to detect recirculation of the radioactive tracer. If this had occurred, the washout curve would have been deconvoluted to take account of this. Recirculation was not observed in any patient. To eliminate artifacts due to residual ^{133}Xe during repeat injections, we planned to reject curves with baseline count rates exceeding 10% of the peak count rate. By waiting longer than 15 min before performing the second injection, no background count exceeded 2.5% of the peak count rate; therefore, no patients were rejected on that basis. Additionally, we increased the dose of ^{133}Xe by 50% for the repeat injection and consistently employed the maximum possible interstudy interval.

The CBF_{15} technique described by Obrist and Wilkinson[10] provided analysis of ^{133}Xe clearance. This is a noncompartmental analysis mathematically equivalent to the height/area method (the reference standard for calculation of rCBF by xenon washout), with integration of the clearance curve to 15 min. Elimination of the tail of the washout curve markedly diminishes the influence of extracerebral tissues as a source of error. As suggested by several authors,[10,11] we did not correct xenon clearance curves for extracerebral delivery and washout. Consequently, this is present as a small but consistent error in

TABLE 1. Correlation of Controlled Variables and MAP with CBF

	Group A (alpha-stat) (Elapsed Time = 21 ± 9 min)		Group B (*p*H-stat) (Elapsed Time = 25 ± 12 min)	
	Baseline	Postphenylephrine	Baseline	Postphenylephrine
CBF (ml · 100 g^{-1} · min^{-1})	15 ± 3.7	13 ± 4†	19 + 3	22 + 6†
CBF_{est} (ml · 100 g^{-1} · min^{-1})	—	16 ± 4	—	26 ± 5‡
MAP (mmHg)	56 ± 7	84 ± 8	53 ± 8	77 ± 9
NPT (° C)	26.8 ± 1.4	27.0 ± 1.3	27.3 ± 0.9	26.6 ± 2.4
Pa_{CO_2} (mmHg)*	41 ± 4	41 ± 3	54 ± 8	55 ± 7
*p*H*	7.42 ± 0.05	7.42 ± 0.05	7.27 ± 0.07	7.25 ± 0.05
$\dot{Q}$ (l · min^{-1} · m^{-2})	1.9 ± 0.4	1.9 ± 0.4	2.2 ± 0.4	2.2 ± 0.4
Hematocrit (%)	23.8 ± 4.0	23.8 ± 3.3	23.5 ± 2.9	23.3 ± 2.2

Values are given as mean ± SD.
* Uncorrected for temperature.
† $P < 0.05$, intragroup difference.
‡ $P < 0.001$, intragroup difference.

all CBF measurements (<5%). The tissue–blood partition coefficient for xenon was corrected for decreases in temperature and hematocrit according to the data of Chen *et al.*[12] A global CBF value for each measurement in each patient was then obtained by averaging the rCBF values for the 16 detector sites to obtain a mean value ± SD.

Controlled variables (NPT, hematocrit, Pa_{CO_2}, and $\dot{Q}$) were compared within groups to ensure good correlation. For patients receiving phenylephrine data for MAP within each group were compared by paired two-tailed *t* tests to ensure a statistically significant increase in the experimental variable ($P < 0.05$). CBF data for each group were analyzed by paired two-tailed *t* tests to determine whether a significant change in CBF had occurred ($P < 0.05$).

After averaging rCBF values to obtain a global CBF measurement, we compared mean rates of CBF. To determine the validity of using mean values, we tested the homogeneity of individual patient rCBF values by calculating the SD of each patient's mean CBF at each measurement interval from the measurements at all sites. All values are expressed as mean ± SD. In patients receiving phenylephrine (groups A and B), we corrected the postphenylephrine CBF values for the effect of elapsed time as predicted by our control patients (groups C and D), using the following calculation:

$$CBF_{est} = (CBF_b \times 0.0087) \times \text{time difference (min)} + CBF_p,$$

where CBF_{est} = estimated CBF, CBF_b = baseline CBF, CBF_p = postphenylephrine CBF, and 0.0087 = time correction coefficient. This equation assumes a linear decrease in CBF over time.

Results

Table 1 demonstrates that within the groups of patients receiving phenylephrine, the controlled variables NPT, Pa_{CO_2}, $\dot{Q}$, and hematocrit changed little during baseline and subsequent rCBF measurement intervals. The same held true for controlled variables measured in patients in groups C and D (table 2). Figure 1 depicts the effect of time on CBF during CPB for individual patients in groups C and D. All subjects had a fall in CBF with time during hypothermic CPB. In group C (alpha-stat, uncorrected $Pa_{CO_2} \simeq 40$ mmHg) CBF declined by an average of 0.7 ± 0.5%/min. Patients in group D (*p*H-stat, uncorrected $Pa_{CO_2} \simeq 60$ mmHg) demonstrated a decline of 1.0 ± 0.8%/min. There was no statistically significant difference in the rate of CBF decline between patients in groups C and D.

TABLE 2. Correlation of Controlled Variables and Elapsed Time with CBF

	Group C (alpha-stat) (Elapsed Time = 30 ± 20 min)		Group D (*p*H-stat) (Elapsed Time = 20 ± 4 min)	
	Baseline	Repeated	Baseline	Repeated
CBF (ml · 100 g^{-1} · min^{-1})	16 ± 4	13 ± 2†	27 ± 7	21 ± 4‡
MAP (mmHg)	68 ± 11	71 ± 10	67 ± 4	71 ± 13
NPT (° C)	26.5 ± 0.8	26.6 ± 0.8	27.3 ± 1.5	27.3 ± 1.4
Pa_{CO_2} (mmHg)*	41 ± 3	40 ± 4	58 ± 4	60 ± 6
*p*H*	7.42 ± 0.06	7.44 ± 0.04	7.33 ± 0.19	7.27 ± 0.05
$\dot{Q}$ (l · min^{-1} · m^{-2})	1.9 ± 0.1	1.8 ± 0.1	1.9 ± 0.2	1.9 ± 0.2
Hematocrit (%)	22.3 ± 3.4	22.7 ± 2.7	23.3 ± 2.9	22.3 ± 3.2

Values are given as mean ± SD.
* Uncorrected for temperature.
† Intragroup difference, $P < 0.02$.
‡ Intragroup difference, $P < 0.05$.

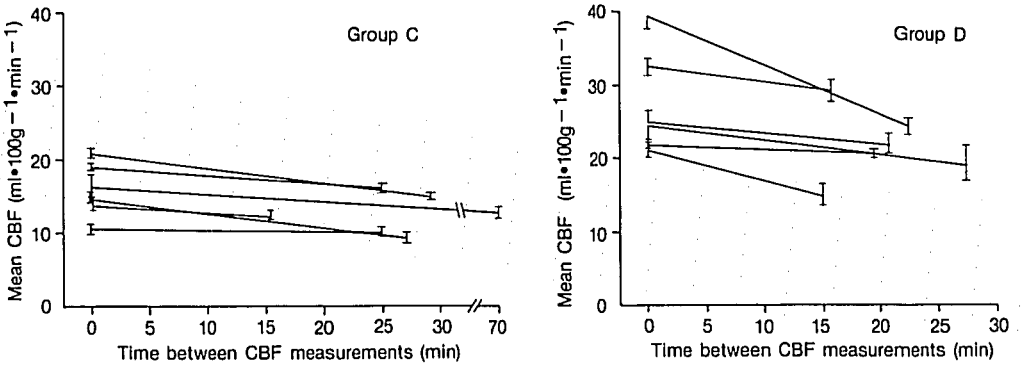

FIG. 1. Spontaneous decline in CBF during CPB for patients in group C (Pa_{CO_2} ≃ 40 mmHg, uncorrected for body temperature) and group D (Pa_{CO_2} ≃ 58 mmHg, uncorrected for body temperature). Data points represent mean global CBF for individual patients at each time interval, ±SD of the 16 regional values.

Figure 2 presents CBF responses to phenylephrine-induced changes in MAP for patients in groups A and B. After correcting for the decline in CBF associated with the duration of CPB, CBF in group A patients was unchanged after phenylephrine infusion, whereas in group B patients CBF increased by 41% (fig. 2; $P < 0.001$).

Discussion

Individual patient CBF responses to phenylephrine infusion during hypothermic CPB have not been previously reported. Clearly, acid–base management is a critical determinant of that response as evidenced by the observed difference between patients in groups A and B. Our group B patient management, similar to that of Lundar *et al.*,[5] used a mean uncorrected Pa_{CO_2} value of 55 mmHg (*p*H-stat method). Over the range of pressures studied, CBF in group B patients increased in a pressure-dependent manner during phenylephrine infusion. This direct correlation existed before and after correction for declining CBF with duration of CPB. The mean uncorrected Pa_{CO_2} value in group A patients (alpha-stat method) approximated that reported in the Govier *et al.*[4] study, which demonstrated persistence of cerebral autoregulation down to an MAP of 30 mmHg. Our data support the findings of Murkin *et al.*,[9] that in patients whose MAP varied spontaneously, cerebral autoregulation is preserved during hypothermic CPB under alpha-stat controlled normocarbic conditions.

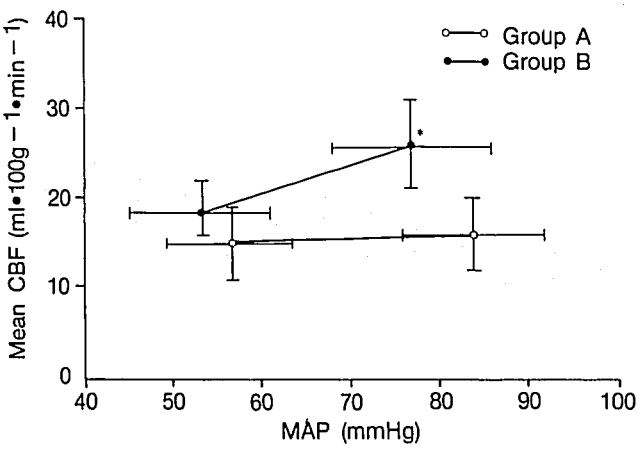

FIG. 2. CBF response to phenylephrine infusion in patients in group A (Pa_{CO_2} ≃ 41 mmHg, uncorrected for body temperature) and group B (Pa_{CO_2} ≃ 54 mmHg, uncorrected for body temperature) patients, corrected for the effect of elapsed time between measurement intervals. *$P < 0.001$ for CBF within group B.

Considerable controversy exists as to whether a temperature-uncorrected or a temperature-corrected Pa_{CO_2} of 40 mmHg is physiologically appropriate during hypothermia.[13,14] These two approaches to acid–base management have been termed, respectively, the alpha-stat and *p*H-stat methods.[15,16] Our data confirm that *p*H-stat management during hypothermia is associated with hypercarbia-induced cerebrovascular changes (*i.e.*, unequivocal impairment of autoregulation),[17,18] whereas alpha-stat management is analogous to normocarbia.

Perhaps differences in acid–base management could explain the diversity of conclusions reached by others concerning the relationship between mean arterial blood pressure and neurologic outcome following CPB[19–22] because cerebral circulatory responses vary according to whether the alpha-stat or *p*H-stat approach is used. Currently, no data are available to describe the influence of Pa_{CO_2} and CBF during CPB on the incidence of postoperative cerebral dysfunction.

To precisely characterize the effects of MAP changes on CBF during CPB, accurate data were required to document changes that usually occur in the absence of pharmacologic intervention. The effect of time on repeated measurements of CBF has been examined in both awake[23] and anesthetized[24] human subjects but not in patients undergoing CPB. Our observations in these patients (that CBF decreases over time) are consistent with the conclusions of these other studies.

We cannot explain why CBF should have declined with time in our patients undergoing CPB. Govier *et al.*[4] found a decrease in CBF during CPB but ascribed this to a concomitant decline in NPT. This does not explain the fall in CBF observed in our study because NPT remained

constant from one measurement to the next. Despite the fact that NPT was stable during our study, brain temperature may have fallen, with a concomitant decline in $CMRO_2$. Murkin *et al.*[9] used jugular venous samples to demonstrate that CBF correlates with $CMRO_2$ during CPB. Thus, in our study it is possible that during hypothermic CPB, when NPT, esophageal temperature, and blood temperature had stabilized, cerebral metabolic rate (hence CBF) may not have reached a steady state.

In conclusion, cerebral autoregulation persists in patients receiving phenylephrine during hypothermic nonpulsatile CPB when Pa_{CO_2} is interpreted by the alpha-stat approach, whereas blood gas maintenance that adds CO_2 to the inflow gas (*p*H-stat method) causes CBF to increase in response to rising MAP, a response consistent with hypercarbia.

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