Anesthesiology
64:576-581, 1986

Response of Cerebral Blood Flow to Changes in Carbon Dioxide Tension during Hypothermic Cardiopulmonary Bypass

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Changes in cerebral blood flow (CBF) in response to changes in Pa_{CO_2} were measured by intraaortic injection of ^{133}Xe in 12 patients during hypothermic (23–30° C) cardiopulmonary bypass. In each patient, CBF was determined at two randomly ordered levels of Pa_{CO_2} obtained by varying the rate of gas inflow into the pump oxygenator (Group I, n = 6) or by varying the percentage of CO_2 added to the gas inflow (Group II, n = 6). Nasopharyngeal temperature, mean arterial pressure, pump–oxygenator flow, and hematocrit were maintained within a narrow range. In group I, a Pa_{CO_2} (uncorrected for body temperature) of 36 ± 4 mmHg (mean ± SD) was associated with a CBF of 13 ± 5 ml · 100 g^{-1} · min^{-1}, while a Pa_{CO_2} of 42 ± 4 mmHg was associated with a CBF of 19 ± 10 ml · 100 g^{-1} · min^{-1}. In group II, a Pa_{CO_2} of 47 ± 3 mmHg was associated with a CBF of 20 ± 8 ml · 100 g^{-1} · min^{-1}, and a Pa_{CO_2} of 53 ± 3 mmHg was associated with a CBF of 26 ± 9 ml · 100 g^{-1} · min^{-1}. Within group I, the difference in CBF was significant ($P < 0.05$); within group II, the difference in CBF was significant at the $P < 0.002$ level. All CBF measurements were lower than those reported for normothermic, unanesthetized subjects of similar age. The response of the cerebral circulation to changes in CO_2 tension was well-maintained during hypothermic cardiopulmonary bypass. CBF increased by an average of 1.07 ± 1.19 (SD) ml · 100 g^{-1} · min^{-1} · $mmHg^{-1}$ increase in temperature-uncorrected Pa_{CO_2} in Group I, and by 1.05 ± 0.54 ml · 100 g^{-1} · min^{-1} · $mmHg^{-1}$ increase in group II. (Key words: Brain: cerebral blood flow. Carbon dioxide: cerebral blood flow; hypothermia. Hypothermia: blood gases; cerebral blood flow. Surgery: cardiovascular.)

STROKE OCCURS IN 5.2% of patients undergoing coronary artery bypass grafting (CABG) and is severe in 2.0%.[1] Transient cerebral dysfunction is even more common.[2] The mechanism of injury is not clear, but both embolic phenomena and inadequate cerebral perfusion have been implicated.[3,4] Anecdotal reports describe patients in whom postoperative neurologic deficits appear to be consistent with inadequate cerebral blood flow (CBF) during cardiopulmonary bypass.[5]

However, studies of directly measured CBF during cardiopulmonary bypass have produced conflicting data.[6,7] Henriksen *et al.* reported increased CBF during cardiopulmonary bypass, which they speculated was due to multiple small cerebral emboli surrounded by reactive hyperemia.[6] They also noted that the response of CBF to changes in Pa_{CO_2} was virtually absent during cardiopulmonary bypass. In contrast, Govier *et al.* found that: 1) CBF decreased during cardiopulmonary bypass in a manner that paralleled the reduction in body temperature; and 2) patients with higher levels of Pa_{CO_2} had higher CBF.[7] The latter data are consistent with preserved responsiveness of the cerebral circulation during cardiopulmonary bypass to changes in Pa_{CO_2}, and they agree with the data of Wollman *et al.* that demonstrated a reduction in the brain arteriovenous oxygen content difference when Pa_{CO_2} was increased during cardiopulmonary bypass in humans.[8]

Accurate determination of the response of CBF to changes in Pa_{CO_2} requires determination of CBF at more than one level of Pa_{CO_2} in each patient. Neither Henriksen nor Govier and their colleagues intentionally altered Pa_{CO_2} in individual patients. Rather, they inferred the response of CBF to changes in Pa_{CO_2} based on the regression relationship between those variables across their entire study populations.

We initiated this investigation to determine, in individual patients undergoing hypothermic cardiopulmonary bypass, whether CBF predictably increased in response to intentional changes in Pa_{CO_2}.

Methods

Cerebral blood flow was studied in 12 adult patients (11 men, one woman) undergoing CABG. Their mean age was 59 yr (range 46 to 75 yr). No patient had clinical evidence of cerebrovascular disease. The study was approved by the institutional Clinical Research Practices Committee, and informed consent was obtained from each patient.

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Received from the Departments of Anesthesia (Section on Critical Care), Neurology, and Surgery (Section on Cardiothoracic Surgery), Wake Forest University Medical Center, Bowman Gray School of Medicine, Winston-Salem, North Carolina. Accepted for publication December 4, 1985. Presented in part at the Annual Meeting of The American Society of Anesthesiologists, San Francisco, October 12–16, 1985.

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All patients were premedicated with lorazepam, 50 $\mu g \cdot kg^{-1}$ im and morphine sulfate 0.1 $mg \cdot kg^{-1}$ im. In the operating room, a radial artery catheter, two peripheral intravenous catheters, and a 7.5 French thermodilution pulmonary artery catheter were inserted. ECG leads II and V_5 were monitored continuously. Anesthesia was induced with fentanyl 75 $\mu g \cdot kg^{-1}$ iv; neuromuscular blockade was established with pancuronium 0.1 $mg \cdot kg^{-1}$ iv; and patients were intubated endotracheally and ventilated with 100% oxygen. No additional anesthetic drugs were given before or during cardiopulmonary bypass until after the CBF studies had been completed. Data from patients who required additional anesthetic drugs or required pharmacologic manipulation of blood pressure or heart rate before the conclusion of the study were omitted from statistical analysis.

Cardiopulmonary bypass was conducted using a bubble oxygenator and nonpulsatile perfusion through an ascending aortic cannula. A nonsanguineous priming solution was used. Each study was conducted in the period during which the aorta was cross-clamped and after the patient's body temperature had been reduced to a stable level appropriate for the intended duration of aortic cross-clamping (range 23–30° C). Nasopharyngeal temperature (NPT), hematocrit (Hct), mean arterial pressure (MAP), and systemic flow ($\dot{Q}$) were then maintained within 5.0% of baseline values by the extracorporeal technician under the direction of the supervising anesthesiologist. Any patient who required a greater change in any of those variables was excluded. Central venous pressure was maintained at 0 mmHg by allowing unrestricted venous drainage to the reservoir of the bypass circuit.

The only experimentally changed variable was Pa_{CO_2}. Pa_{CO_2} may be varied during extracorporeal circulation in two ways. Fresh gas flow may be varied or carbon dioxide may be added to the gas flow.[9] The former method is routinely employed in institutions where the surgical team prefers to maintain temperature-uncorrected Pa_{CO_2} near 40 mmHg. The latter method is employed if the team prefers to maintain temperature-corrected Pa_{CO_2} near 40 mmHg (approximately 60 mmHg before correction if the patient's body temperature is 27° C). Carbon dioxide usually must be added if the latter approach is used because, if gas flow is reduced sufficiently to produce that level of Pa_{CO_2}, hypoxemia is likely. The addition of carbon dioxide permits higher gas flows. In order to produce the widest possible range of Pa_{CO_2} values, we used both approaches. In Group I patients, two CBF determinations, one at a lower and one at a higher Pa_{CO_2} (uncorrected for body temperature) were made in random order, within a range of 32 to 46 mmHg, by varying the inflow rate of 100% oxygen into the pump oxygenator. In Group II patients, two CBF determinations were made in random order over a Pa_{CO_2} range of 42 to 58 mmHg (uncorrected for body temperature) made by varying the proportions of 100% oxygen and 3.0% CO_2 flowing into the pump oxygenator. Once flow or gas proportions had been adjusted, at least 5 min were allowed to elapse before a measurement was made.

Cerebral blood flow was measured in both hemispheres using a portable regional cerebral blood flow (rCBF) system constructed at the Wake Forest University Medical Center. The system consists of 16 solid-state cadmium telluride gamma-ray detectors mounted in a flexible helmet, which is secured to the operating room table. Data are initially processed and displayed on a color-graphic terminal mounted on a portable cart, which also contains a microcomputer connected to the detectors by a 25-foot (7.62 meter) RS232 cable. For rapid simultaneous analysis of individual brain regions, data are transferred *via* modem to a central Vax 730® computer, which maintains a file on each patient and maintains group averages. During cardiopulmonary bypass, measurements are obtained by the injection of 3–5 mCi of ^{133}Xe dissolved in sterile saline into the arterial line of the pump–oxygenator proximal to the bubble trap. This technique permits analysis of xenon clearance using the mathematical techniques developed for intraarterial injection without adding the risk of a separate arterial access site or of increased duration of surgery.

Although the computer performs multiple analyses of rCBF, the present study employed a modification of the initial slope index (ISI) method as originally described by Olesen *et al.*[10] using the formula

$$CBF = \text{slope} \cdot \lambda \cdot 100$$

where slope = the natural logarithm (ln) of the ^{133}Xe clearance curve from 6.0 to 66 s after the peak of the curve; λ = the tissue–blood partition coefficient for Xe (corrected for temperature and Hct by the method of Chen *et al.*[11]); and 100 converts $ml \cdot g^{-1} \cdot min^{-1}$ to $ml \cdot 100\ g^{-1} \cdot min^{-1}$. λ was calculated separately for each individual determination of CBF.

The mean CBF was determined by averaging rCBF values from individual detector locations. For individual studies, 12 to 16 probes were averaged, the differences being due to mechanical limitations in the prototype probe–computer interface that precluded use of one to four probe locations in three of the patients. To eliminate the need to correct clearance curves for residual xenon, subsequent measurements were begun when residual radioactivity had returned to baseline values (approximately 15 min after injection of xenon).

The mean CBF changes in each group in response to changes in Pa_{CO_2} were calculated from the slopes of the lines connecting the lower and higher Pa_{CO_2} data points for each patient within Group I and within Group II.

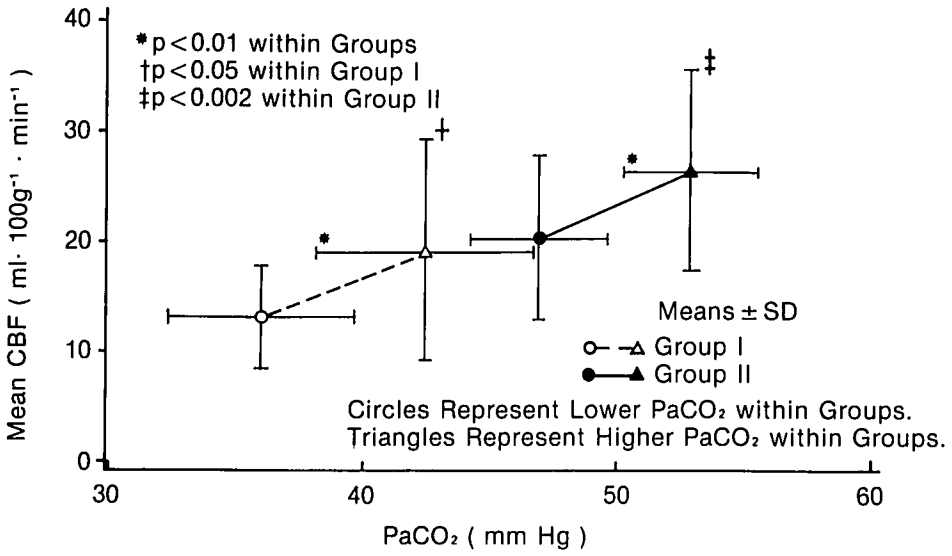

FIG. 1. CBF response (mean ± SD) to changes in Pa_{CO_2} in Group I and Group II. CBF increased significantly in both groups in response to changes in Pa_{CO_2}.

STATISTICAL ANALYSIS

To ensure comparability of the controlled variables (NPT, Hct, MAP and $\dot{Q}$), data for those variables within each group and between the two groups were analyzed by paired and unpaired *t* tests. No correction for multiple testing was employed in these comparisons, again to ensure that we would detect inadvertent differences. Data for Pa_{CO_2} within each group were then compared by two-tailed *t* tests to ensure that a significant ($P < 0.05$) change had occurred in the experimentally altered variable. Finally, data for CBF were analyzed by two-tailed *t* tests to determine whether the increase in Pa_{CO_2} had produced a significant ($P < 0.05$) increase in CBF.

We chose to compare mean CBF, obtained by averaging the rCBF values. To determine the validity of using mean values, we tested the homogeneity of rCBF values for each patient by calculating the standard deviation of each patient's mean CBF at each level of Pa_{CO_2} from the measurements at all sites. Mean rCBF ± SD was then calculated at each probe location at lower and higher levels of Pa_{CO_2} for the series as a whole.

Results

The relationship between Pa_{CO_2} (temperature-uncorrected) and mean global CBF is depicted in figure 1 and table 1. CBF was significantly greater ($P < 0.05$) at the higher Pa_{CO_2} in Group I, and the increase was 1.07 ± 1.19 (SD) ml · 100 g^{-1} · min^{-1} for every 1.0 mmHg increase in Pa_{CO_2}. CBF was also greater at the higher Pa_{CO_2} ($P < 0.002$) in Group II, and the increase averaged 1.05 ± 0.54 (SD) ml · 100 g^{-1} · min^{-1} · $mmHg^{-1}$. In both groups, the intentional increase in Pa_{CO_2} was significant from the lower to the higher values ($P < 0.01$). Table 1 also depicts NPT, MAP, $\dot{Q}$, and Hct for groups I and II at the lower and higher Pa_{CO_2} within each group. This table confirms that these variables were maintained at comparable values during cardiopulmonary bypass.

Mean CBF data ± SD of individual probe measurements in individual patients are displayed in figure 2 and demonstrate marked differences among patients in the magnitude of the change in CBF produced by changes in Pa_{CO_2}. There was little variability among probe locations in individual patients as is evident from the small standard

TABLE 1. Correlation of Clinical Conditions with CBF (Means ± SD)

	Group I		Group II	
Pa_{CO_2} (mmHg)	36 ± 4	42 ± 4*	47 ± 3	53 ± 3*
CBF (ml · 100 g^{-1} · min^{-1})	13 ± 5	19 ± 10	20 ± 8	26 ± 9
NPT (°C)	29.9 ± 0.8	28.6 ± 0.9	28.4 ± 2.6	27.1 ± 2.4
MAP (mmHg)	66 ± 9	68 ± 14	66 ± 19	71 ± 13
$\dot{Q}$(l · min^{-1} · m^{-2})	2.13 ± 0.40	2.22 ± 0.43	2.13 ± 0.48	2.03 ± 0.21
Hct (%)	22.1 ± 3.1	22.3 ± 3.3	23.7 ± 2.5	23.0 ± 2.4

CBF = cerebral blood flow; NPT = nasopharyngeal temperature; MAP = mean arterial pressure; $\dot{Q}$ = systemic flow; Hct = hematocrit.

* $P < 0.01$ between values within Group I or Group II.

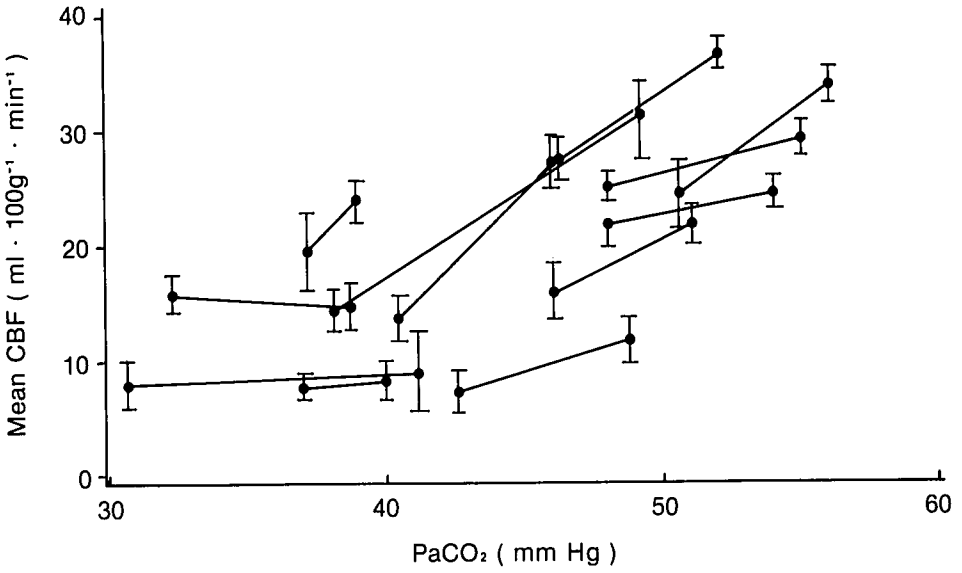

FIG. 2. Individual patient mean CBF ± SD of the mean when calculated from all probe locations. The mean CBF at the lower Pa_{CO_2} and the higher Pa_{CO_2} is shown for each subject.

deviations of the mean CBF values. The validity of using multiple probe locations to determine mean global CBF is further supported by the similarities in rCBF ± SD in figure 3, which depicts data from each individual probe location for all 12 patients at the lower and higher levels of Pa_{CO_2}.

Discussion

Our data demonstrate that CBF remains responsive to changes in Pa_{CO_2} during hypothermic, nonpulsatile cardiopulmonary bypass in patients anesthetized with high-dose fentanyl. These data are consistent with the data from the study by Wollman *et al.*, in which sustained cerebrovascular responsiveness during hypothermic cardiopulmonary bypass was inferred from the fact that the cerebral arteriovenous difference for oxygen decreased when Pa_{CO_2} was experimentally increased.[8] Data obtained in Group I are comparable to the data of Govier *et al.*, which demonstrated that CBF was lower than baseline during hypothermic cardiopulmonary bypass, and con-

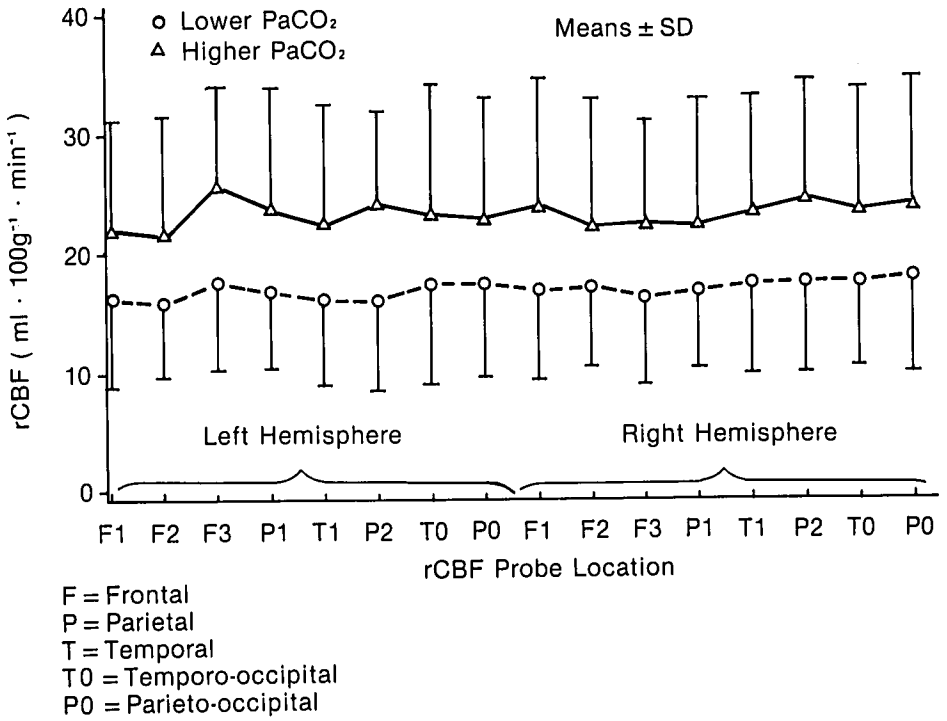

FIG. 3. Mean rCBF ± SD at individual detector locations for all 12 patients in both groups. Changes were consistent across all probe locations in response to changes in Pa_{CO_2} (*open circle* = lower levels of Pa_{CO_2}; *open triangle* = higher levels of Pa_{CO_2}).

TABLE 2. Reported Relationship of Pa_{CO_2} to CBF (Means ± SD)

	CBF ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	Temperature-uncorrected Pa_{CO_2} (mmHg)	Temperature-corrected Pa_{CO_2} (mmHg)	NPT (°C)
Govier *et al.*[7]	13 ± 7	37 ± 3	24*	28.0 ± 3.6
Prough *et al.*				
Group I (lower)	13 ± 5	36 ± 4	26*	29.9 ± 0.8
Group I (higher)	19 ± 10	42 ± 4	28*	28.6 ± 1.0
Group II (lower)	20 ± 8	47 ± 3	31*	28.4 ± 2.6
Group II (higher)	26 ± 9	53 ± 3	33*	27.1 ± 2.4
Henriksen *et al.*[6]	64 ± 29	57†	40 ± 10	29.3 ± 1.8
Murkin *et al.*[12]	30 ± 9	71†	42 ± 5	26.2 ± 1.4

See table 1 for abbreviations.

* For comparison among studies, mean temperature-corrected Pa_{CO_2} was calculated from reported mean temperature-uncorrected Pa_{CO_2}.

† Similarly, mean temperature-uncorrected Pa_{CO_2} was calculated from mean temperature-corrected Pa_{CO_2} using the Radiometer® Blood Gas Calculator, Type BGC-1.

firm the inference from those data that responsivity of CBF to Pa_{CO_2} was maintained[7] (table 2). The higher CBF in Group II is comparable to that reported by Murkin *et al.*[12] However, these data are in direct contrast to those from the study of Henriksen *et al.*, in which it was reported that, while CBF increased during hypothermic cardiopulmonary bypass, the responsiveness of CBF to changes in Pa_{CO_2} was nearly absent.[6]

Differences among the studies may be due to differences in anesthetic techniques or in methods of measuring CBF. Halothane was the primary anesthetic used by Wollman *et al.*[8]; diazepam and fentanyl were used by Govier *et al.*[7]; enflurane was used during the precardiopulmonary bypass period in Henriksen's study[6]; a high-dose fentanyl and diazepam technique was employed in Murkin's study,[12] and we employed high-dose fentanyl. Murkin *et al.* found that induction of anesthesia with fentanyl 100 $\mu g \cdot kg^{-1}$ and diazepam 0.4 $mg \cdot kg^{-1}$ iv decreased CBF from 37 ± 15 (SD) $ml \cdot 100\ g^{-1} \cdot min^{-1}$ to 27 ± 5 $ml \cdot 100\ g^{-1} \cdot min^{-1}$.[12] That decrease, comparable to the reduction in CBF produced by fentanyl in dogs and rats anesthetized with nitrous oxide,[13,14] occurred without a corresponding decrease in the cerebral metabolic rate for oxygen.[12] As for the method of measuring CBF, the use of arteriovenous differences for determination of the oxygen content of cerebral flow requires the assumption of a constant cerebral metabolic rate for oxygen, and xenon clearance techniques require accurate mathematical analysis of xenon clearance curves. Insufficient detail regarding the xenon[133] clearance method used by Henriksen *et al.* prevents analysis of the marked differences between that study and the others.

These data have clinical implications regarding the management of Pa_{CO_2} during cardiopulmonary bypass. Currently, there is strong disagreement on whether temperature-uncorrected Pa_{CO_2} or temperature-corrected Pa_{CO_2} should be maintained near 40 mmHg during cardiopulmonary bypass.[15] This controversy has been intensified by an increasing awareness that maintenance of temperature-corrected Pa_{CO_2} at 40 mmHg and *p*H at 7.40 during hypothermia may be physiologically inappropriate.[16,17] Because CO_2 is more soluble and therefore exerts a lower partial pressure at lower temperatures, a temperature-uncorrected Pa_{CO_2} of 61 mmHg measured at the standard blood-gas machine electrode temperature of 37° C would be equivalent to a Pa_{CO_2} of 40 mmHg when corrected for a body temperature of 28° C (Radiometer® Blood Gas Calculator Type BGC-1). Similarly, a temperature-uncorrected Pa_{CO_2} of 40 mmHg at 37° C is equivalent to a temperature-corrected Pa_{CO_2} of 26 mmHg at 28° C. As this and comparable studies have demonstrated, because CBF is strongly influenced by the level of Pa_{CO_2} during hypothermic cardiopulmonary bypass, the decision to maintain temperature-corrected Pa_{CO_2} rather than temperature-uncorrected Pa_{CO_2} near normal will result in a higher rate of CBF during hypothermic cardiopulmonary bypass. If temperature-uncorrected Pa_{CO_2} is maintained near 40 mmHg, one would expect the rate of CBF to be similar to that seen in our Group I patients. In fact, this technique was employed by Govier *et al.*, and their results were similar to ours (table 2). In contrast, a higher CBF would be expected if a temperature-corrected strategy were employed. The Pa_{CO_2} in our Group II patients approaches, although it remains somewhat less than, the levels of temperature-uncorrected Pa_{CO_2} that would be found if Pa_{CO_2} were maintained strictly at 40 mmHg when corrected for body temperature. Under similar conditions, Murkin *et al.* reported a CBF of 30 ± 9 $ml \cdot 100\ g^{-1} \cdot min^{-1}$.[12]

Our data cannot be used to compare the adequacy of CBF at the levels of Pa_{CO_2} studied. For that comparison, it would have been necessary to determine jugular bulb oxygen content and the cerebral metabolic rate for oxygen at the varying levels of Pa_{CO_2}. A partial answer may be supplied by Murkin *et al.*, who reported that the cerebral metabolic rate for oxygen was decreased during hypo-

thermic cardiopulmonary bypass and, therefore, that the CBF reported in their study represented hyperperfusion relative to cerebral oxygen demand.[12] This apparent hyperperfusion suggests that maintenance of temperature-corrected Pa_{CO_2} near 40 mmHg during cardiopulmonary bypass produces unnecessarily increased CBF in a manner analogous to the production of hypercarbia in normothermic patients. Certainly, in species other than humans, there is considerable evidence suggesting that a decrease in Pa_{CO_2} and an increase in *p*H are the appropriate responses to a decrease in body temperature.[15-17] In addition, for patients with cerebrovascular disease, the production of relative hypercarbia may risk the production of an intracerebral steal phenomenon, a phenomenon that has been demonstrated during carotid cross-clamping in patients undergoing carotid endarterectomy.[18] This question, as well as the possible effects of the different levels of Pa_{CO_2} on postoperative neurological outcome, deserves further study.

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