Hypercarbia Depresses Cerebral Oxygen Consumption During Cardiopulmonary Bypass

Donald S. Prough, MD, Anne T. Rogers, MBChB, FRCP(C), David A. Stump, PhD, Stephen A. Mills, MD, CM, Glenn P. Gravlee, MD, and Carol Taylor, MAS

No human studies have systematically examined the relations among PaCO₂, cerebral blood flow, and the cerebral metabolic rate for oxygen during hypothermic cardiopulmonary bypass. We varied PaCO₂ during hypothermic (26–28°C) cardiopulmonary bypass and estimated the cerebral metabolic rate for oxygen by multiplying cerebral blood flow (measured using xenon-133 clearance) by the cerebral arteriovenous difference in oxygen contents. Patients were randomly assigned to either of two methods of managing PaCO₂ (uncorrected for body temperature). In group 1 (PaCO₂ 32–48 mm Hg, n=13) the mean±SD cerebral metabolic rate for oxygen was 0.40±0.11 ml O₂/100 g·min⁻¹ at a mean±SD PaCO₂ of 36±2.0 mm Hg and 0.40±0.14 ml O₂/100 g·min⁻¹ at a mean±SD PaCO₂ of 45±2 mm Hg. In group 2 (PaCO₂ 49–72 mm Hg, n=12) the mean±SD cerebral metabolic rate for oxygen was 0.31±0.09 ml O₂/100 g·min⁻¹ at a mean±SD PaCO₂ of 55±3 mm Hg and 0.21±0.07 ml O₂/100 g·min⁻¹ at a mean±SD PaCO₂ of 68±2 mm Hg. Group 2 values differed significantly from those in Group 1 (p<0.05). In both groups, cerebral blood flow increased as PaCO₂ increased.

During cardiopulmonary bypass, increasing PaCO₂ increases cerebral blood flow and decreases the cerebral metabolic rate for oxygen.

Presently, two methods of acid-base management, α-stat and pH-stat, are used during hypothermic cardiopulmonary bypass.1 The α-stat method maintains PaCO₂ at 40 mm Hg and pH at 7.40 when measured at 37°C. The pH-stat method adds CO₂ to the gas inflow of the pump oxygenator to maintain PaCO₂ near 40 mm Hg and pH near 7.40 when corrected to body temperature. For example, a PaCO₂ measured to be 40 mm Hg in a blood gas analyzer at 37°C would be 27 mm Hg if corrected to a body temperature of 27°C. Clinical studies describing the cerebrovascular effects of PaCO₂ during cardiopulmonary bypass have examined the effect of changes in PaCO₂ on cerebral blood flow (CBF) but have not investigated the effect of systematic changes in PaCO₂ on the cerebral metabolic rate for oxygen (CMRO₂).2,3

Further characterization of human cerebrovascular responses during cardiopulmonary bypass is essential in the ongoing effort to limit neurologic injury following cardiac surgery. Despite the substantial improvement in neurologic outcome that accompanied early, aggressive efforts to reduce the incidence of embolic events,4 the incidence of frank stroke still exceeds 1%5,6 and may actually be increasing as progressively older patients are considered to be appropriate candidates for surgery.7 More significantly, subtle intellectual impairment may follow cardiac surgery in as many as 79% of patients.8 We performed the following study to characterize a broader range of the CO₂ response curve for CBF and to determine whether changes in CMRO₂ are associated with changes in PaCO₂ during hypothermic cardiopulmonary bypass.

Subjects and Methods

Twenty-five patients gave written, informed consent to a study approved by the Institutional Clinical Research Practices Committee. All study patients, scheduled for myocardial revascularization and free of clinical evidence of cerebrovascular disease or
hypertension, were screened using carotid Doppler ultrasound to exclude asymptomatic extracranial cerebrovascular occlusive disease. During hypothermic, nonpulsatile cardiopulmonary bypass, patients were randomly assigned either to the α-stat method of PaCO₂ management (group 1, n=13) or to the pH-stat method (group 2, n=12). In each patient, CBF and CMRO₂ were determined at two randomly ordered PaCO₂ levels. During each determination, mean arterial blood pressure, pump flow rate, nasopharyngeal temperature, and hematocrit were kept constant. An in-line blood gas analyzer (Bentley Gas-Stat, CDI, Inc., Irvine, Calif.) continuously monitored PaCO₂ during cardiopulmonary bypass, and these values were confirmed by intermittent arterial blood gas sampling.

Following premedication with 0.05 mg/kg p.o. lorazepam and 0.10 mg/kg i.m. morphine sulfate, anesthesia was induced with 0.075 mg/kg i.v. fentanyl. The patients were paralyzed with pancuronium or metocurine and ventilated with O₂ to maintain normocarbia before cardiopulmonary bypass. No other drugs were given prior to the completion of CBF determinations; any patient requiring additional drugs for clinical reasons would have been excluded from the study; however, exclusion was not necessary. During cardiopulmonary bypass, 3–4 mg/kg heparin was given as necessary to maintain the activated clotting time at >400 seconds. Extracorporeal circulation was conducted using a membrane oxygenator, a blood-free priming solution, and moderate hemodilution. All patients were cooled to a nasopharyngeal temperature of 25–30° C.

Once each patient’s temperature and PaCO₂ had been stable for at least 5 minutes, the first CBF determination proceeded by the injection of 3–5 mCi of xenon-133 dissolved in saline into the arterial line of the pump oxygenator. Eight cadmium-telluride gamma detectors per hemisphere measured gamma emissions, and a central VAX 730 computer analyzed the data after correcting each individual clearance curve for changes in the tissue-blood partition coefficient of xenon produced by hypothermia and hemodilution. Data from each detector were analyzed using the CBF₁₅ method, a noncompartmental calculation similar to the traditional height-over-area method. Data from all detectors in each patient were then averaged to obtain the mean global CBF. Blood samples were analyzed at 37° C in an IL 813 blood gas analyzer and at 37° C in an IL 282 CO-oximeter (Instrumentation Laboratory, Lexington, Mass.). We calculated arterial and jugular bulb venous oxygen contents from the temperature-uncorrected blood gas and CO-oximeter data using the standard formula C₅O₂=PxO₂×0.0031+S₁O₂×Hgb×1.34, where C₅O₂ is arterial or venous oxygen content, PₓO₂ is arterial or venous oxygen tension, Hgb is hemoglobin concentration, and S₁O₂ is measured oxygen saturation.

Data (expressed as mean±SD) were analyzed using multivariate repeated-measures analysis of variance (ANOVA) for the primary variables CBF, A–VDO₂, and CMRO₂. Three-way repeated-measures ANOVA was initially performed to confirm the necessity of randomly varying the order of the PaCO₂ levels. The factors analyzed were group, PaCO₂ level, and order of PaCO₂ level. Two-way repeated-measures ANOVA was then performed for the two variables group and PaCO₂ level. When an interaction occurred between the two variables, multivariate repeated-measures ANOVA was performed for each group to look for an effect of PaCO₂ level and for each PaCO₂ level to look for an effect of group. Where significant differences existed, Tukey’s multiple comparison procedure was applied to determine at what intervals these differences occurred. An α of 0.05 was used for all statistical procedures. Data for controlled variables were calculated for descriptive purposes only and were not analyzed statistically.

**Results**

All controlled variables except PaCO₂ were comparable at both PaCO₂ levels in both groups (Table 1). PaCO₂ differed by experimental design.

As demonstrated by a significant three-way interaction (p<0.02) among group, PaCO₂ level, and order of PaCO₂ level, the randomization of order was necessary. There was no significant effect of order alone. Changes in CBF with alterations in PaCO₂ are shown in Figure 1. CBF in group 2 was significantly greater than that in group 1 (p<0.05) at both PaCO₂ levels. Within each group, CBF was significantly greater at the high PaCO₂ level (p<0.05 in each group).

The increase in CBF as PaCO₂ increased was associated with a decrease in A–VDO₂ (Figure 2). Within each group, PaCO₂ level significantly influenced A–VDO₂ (p<0.05 in group 1 and p<0.001 in group 2).

Like CBF and A–VDO₂, CMRO₂ also depended on PaCO₂. There was no three-way interaction among group, PaCO₂ level, and order of PaCO₂ level for CMRO₂. In group 1, CMRO₂ did not differ between PaCO₂ levels (Figure 3). However, CMRO₂ in group 2
TABLE 1. Controlled and Experimental Variables in Patients During Cardiopulmonary Bypass

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n=13)</th>
<th>Group 2 (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>Low PaCO2</td>
<td>High PaCO2</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>36±2</td>
<td>45±2*</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>70±9</td>
<td>70±10</td>
</tr>
<tr>
<td>NPT (°C)</td>
<td>27.4±0.5</td>
<td>27.3±0.6</td>
</tr>
<tr>
<td>Q (l/min·m⁻²)</td>
<td>1.8±0.4</td>
<td>1.8±0.4</td>
</tr>
<tr>
<td>Hct (vol %)</td>
<td>23±3</td>
<td>23±3</td>
</tr>
<tr>
<td>Experimental</td>
<td>Low PaCO2</td>
<td>High PaCO2</td>
</tr>
<tr>
<td>CBF (ml·100 g⁻¹·min⁻¹)</td>
<td>11.6±2.8†</td>
<td>15.0±3.4‡</td>
</tr>
<tr>
<td>A—VDO₂ (ml·100 ml⁻¹)</td>
<td>3.7±1.3</td>
<td>2.8±1.2*</td>
</tr>
<tr>
<td>SjvO₂ (%)</td>
<td>69±10</td>
<td>77±9</td>
</tr>
<tr>
<td>CMRO₂ (ml·100 g⁻¹·min⁻¹)</td>
<td>0.4±0.1</td>
<td>0.4±0.1§</td>
</tr>
<tr>
<td>CVR (mm Hg·ml·100 g⁻¹·min⁻¹)</td>
<td>5.8±2.0</td>
<td>4.3±1.1</td>
</tr>
</tbody>
</table>

PaCO₂, partial pressure of CO₂ uncorrected for temperature; MABP, mean arterial blood pressure; NPT, nasopharyngeal temperature; Q, pump oxygenator blood flow rate; Hct, hematocrit; CBF, global mean cerebral blood flow; A—VDO₂, arteriovenous difference in oxygen contents; SjvO₂, oxygen saturation in jugular bulb; CMRO₂, cerebral metabolic rate for oxygen; CVR, cerebrovascular resistance. Data are mean±SD.

* p<0.05, ** p<0.001, respectively, different from low PaCO₂ within group by two-way repeated-measures ANOVA.

declined significantly as PaCO₂ increased (p<0.05). CMRO₂ at the high PaCO₂ level in group 2 was nearly 50% of that in group 1 (p<0.01).

Discussion

Poikilothermic animals regulate PaCO₂ during hypothermia in an α-stat fashion.12-15 Although no published data establish which method is preferable during hypothermic cardiopulmonary bypass, several investigators2,3,16-18 have shown that the α-stat method, but not the pH-stat method, preserves cerebral autoregulation.

Our data provide the first evidence demonstrating the dependency of CMRO₂ on PaCO₂ in humans during cardiopulmonary bypass. At 28°C, when PaCO₂ is 35–45 mm Hg (uncorrected for temperature), CMRO₂ is comparable to that reported by Murkin et al,17 approximately 10% of that in normal, awake humans.19 The surprisingly low CMRO₂ results from reductions in both CBF and A—VDO₂ to below those found in normothermic humans. Possible explanations for these levels include the effects of fentanyl, hypothermia, and hemodilution. In response to moderate hemodilution, CBF increases

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Relation between mean±SD cerebral blood flow (CBF) and mean±SD partial pressure of CO₂ uncorrected for temperature (PaCO₂) in patients during cardiopulmonary bypass. ●, Group 1 (n=13); ○, group 2 (n=12). *p<0.05 different from low PaCO₂ within group by two-way repeated-measures ANOVA.

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Relation between mean±SD cerebral arteriovenous difference in oxygen contents (A—VDO₂) and mean±SD partial pressure of CO₂ uncorrected for temperature (PaCO₂) in patients during cardiopulmonary bypass. ●, Group 1 (n=13); ○, group 2 (n=12). *p<0.05 different from low PaCO₂ within group by two-way repeated-measures ANOVA.
sufficiently to offset approximately 50% of the decline in arterial oxygen content. Therefore, in a hypothetical, spontaneously perfusing, normothermic human, a decline in arterial oxygen content from 20 to 10 ml×100 ml⁻¹ would be expected to increase CBF from 50 to 75 ml×100 g⁻¹×min⁻¹. If CMRO₂ remained constant at 3.5 ml×100 g⁻¹×min⁻¹, A−VDO₂ would decline from 7.0 to approximately 4.7 ml×100 ml⁻¹. Jugular venous oxygen saturation would also decline from 65% to approximately 53%. In our study, A−VDO₂ (which is multiplied by CBF to calculate CMRO₂) during cardiopulmonary bypass at any given PaCO₂ level is similar to that reported by Wollman et al²¹ two decades ago.

Our study further suggests that greater increases in PaCO₂ depress CMRO₂ by nearly 50%. The mechanism of this substantial reduction in CMRO₂ cannot be determined from this study but may involve the anesthetic/narcotic effect of CO₂. At a partial pressure of 245 mm Hg, CO₂ produces surgical anesthesia in normothermic dogs.²² Less severe hypercarbia depresses CMRO₂ in normothermic, anesthetized animals.²³⁻²⁵ Therefore, our data suggest that the pH-stat method of managing PaCO₂ and pH produces cerebral metabolic effects analogous to acute hypercarbia. Dependence of CMRO₂ on PaCO₂ in humans has also been suggested by Obrist et al²⁶ based on studies in patients with head injuries. However, our data do not clarify whether relative hypercarbia primarily reduces activity-related or basal CMRO₂.

Our data also suggest that cerebral metabolism is depressed to a surprisingly great extent in humans during hypothermic cardiopulmonary bypass. In animals undergoing cardiopulmonary bypass, systemic oxygen consumption declines by a factor of 2.8±0.3 for each 10°C decline in body temperature.²⁷ In rapidly cooled patients, systemic oxygen consumption changes similarly.²⁸ In nonhuman primates, CMRO₂ declined from 5.9 ml×100 g⁻¹×min⁻¹ at 37°C to 1.8 ml×100 g⁻¹×min⁻¹ at a body temperature of 27°C, with individual animals having CMRO₂ values as low as 0.5 and 0.9 ml×100 g⁻¹×min⁻¹ at body temperatures of 26.5°C and 25°C, respectively.²⁹

However, our calculation of CMRO₂, as those of Murkin et al,³⁰ Woodcock et al,³¹ and Obrist et al,²⁶ is based on the multiplication of mean cortical blood flow by the difference in oxygen contents of arterial and jugular bulb blood. Implicit in the use of that calculation is the assumption that CBF and CMRO₂ change in quantitatively similar manners in the cortex and deeper structures. Current technology does not permit validation of this concept in humans during cardiopulmonary bypass; however, measurements obtained using a modification of the Kety-Schmidt technique demonstrated a mean CMRO₂ during cardiopulmonary bypass of 0.49 ml×100 g⁻¹×min⁻¹ at a temperature-uncorrected PaCO₂ approximating 46 mm Hg at 26.9°C. The authors did not report adjustment of the argon tissue–blood partition coefficient for changes due to hemodilution and hypothermia. Analysis of xenon-133 clearance data during cardiopulmonary bypass demonstrates excellent correlation between the CBF₁₅ technique and the classical stochastic method.³²

No study has systematically evaluated neuropsychologic outcome as a function of CBF or CMRO₂ across the entire range of PaCO₂ values encompassed by the pH-stat and pH-stat methods. Although the pH-stat method simultaneously depresses CMRO₂ and increases CBF, the increase in CBF might increase the proportion of emboli directed to the cerebral circulation and might create intracerebral steals. Although they have been described in humans undergoing carotid endarterectomy,³³ intracerebral steals have not been demonstrated during cardiopulmonary bypass.

In summary, during hypothermic cardiopulmonary bypass (nasopharyngeal temperature of 25–30°C), a temperature-uncorrected PaCO₂ of 68 mm Hg reduces CMRO₂ to approximately one-half that at a PaCO₂ of 45 mm Hg. Our data additionally confirm a progressive increase in CBF as PaCO₂ increases. Further studies must clarify the significance and application of these findings to postoperative neurologic deficits following cardiac surgery.

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References


**Key Words**: cardiopulmonary bypass • cerebral blood flow • hypercapnia • oxygen consumption
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