Autoregulation and the CO₂ responsiveness of cerebral blood flow after cardiopulmonary bypass

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Cerebral blood flow (CBF) was measured by ¹³³Xe clearance to determine whether there were any residual effects of cardiopulmonary bypass (CPB) on the CBF response to changes in arterial PCO₂ or blood pressure in the early (3–8 hr) post-CPB period. During CPB, the nine patients studied were managed according to alpha-stat, temperature uncorrected, pH management. The mean $\pm$ SD increase in CBF resulting from an increase in PaCO₂ ($1.35 \pm 0.5 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ PaCO₂) was within the normal range, indicating appropriate CBF response to a change in PaCO₂. There were no significant differences in CBF, being $25.7 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ at a mean arterial blood pressure of 70 mmHg and $26.5 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ at 110 mmHg, demonstrating intact cerebral autoregulation over this pressure range. We conclude that cerebral autoregulation and CO₂ responsiveness are preserved in the immediate postoperative period after CPB using alpha-stat pH management.

Le flot sanguin cérébral (CBF) a été mesuré par Xe¹³³ afin de déterminer les effets résiduels de la circulation extracorporelle (CPB) sur les réponses due CBF aux changements de la PCO₂ ou de la pression artérielle dans la période précoce en post CPB (3–8 hres). Durant le CPB, les neuf patients étudiés et chez qui le pH ne fut pas corrigé selon la température, l'augmentation

moyenne $\pm$ SD de la CBF après une augmentation de la PaCO₂ ($1,35 \pm 0,5 \text{ ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ PaCO₂) était à l'intérieur des normes indiquant une réponse appropriée du CBF au changement de la PaCO₂. Il n'y avait aucune différence significative dans le CBF, étant $25,7 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ pour des pressions artérielles moyennes de 70 mmHg et $26,5 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ à 110 mmHg, démontrant une autorégulation cérébrale intacte pour cet écart de pression. On conclut que l'autorégulation cérébrale et la réponse au CO₂ est préservée dans la période postopératoire immédiate après CPB utilisant la conduite alpha-stat du pH.

Central nervous system (CNS) dysfunction following cardiopulmonary bypass (CPB) has been reported to occur in most patients in the early postoperative period, with new neurological signs demonstrable in approximately two-thirds of them.^{1,2} Although most of the abnormalities are transient and non-disabling, they are often present at the time of discharge from hospital.¹ At this time, clinically obvious stroke is found in five per cent and severe disability in one to two per cent of patients.^{1,3}

In a prospective study, Smith *et al.*² demonstrated a significant increase in (signs of) CNS dysfunction at 24 hr after CPB, but no significant differences in the incidence of CNS dysfunction at eight days or eight weeks compared with controls undergoing major vascular or thoracic procedures. Cerebral blood flow (CBF), however, was only measured on the latter two occasions and was no different from controls. In another study, CBF was shown to be reduced on the fourth and eighth day following CPB with the greatest reductions occurring at the earlier measurement period.⁴

These results may indicate a window of vulnerability of the CNS in the early post-CPB period. This time may also be associated with marked swings in blood pressure or PaCO₂. If CBF autoregulation were deranged, such swings could result in large changes in CBF that may contribute to postoperative neurological dysfunction.

Key words

ANAESTHESIA: cardiovascular;

BRAIN: blood flow, autoregulation;

SURGERY: cardiovascular, cardiopulmonary bypass.

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Cerebral autoregulation and CO₂ responsiveness have not been systematically investigated in man during the early post-CPB period. The aim of this study was to evaluate prospectively CBF autoregulation and CO₂ responsiveness at this time.

Methods

Following institutional approval and after obtaining written informed consent, nine patients undergoing elective cardiac surgery were anaesthetized with an air-O₂-narcotic-relaxant technique (sufentanil 7–22 µg⁻¹, or fentanyl 20–49 µg · kg⁻¹ and 50–100 per cent O₂) and supplemental benzodiazepines (diazepam 0.12–0.25 mg · kg⁻¹, lorazepam 0.10 mg · kg⁻¹, or midazolam 0.1 mg · kg⁻¹). All patients had received their chronic anti-anginal medications in addition to a preoperative narcotic sedative (morphine 0.12 mg · kg⁻¹, lorazepam 0.02–0.06 mg · kg⁻¹).

During CPB, nonpulsatile perfusion was conducted at rates of 2.0–2.5 L · m⁻² · min⁻¹ using a membrane oxygenator (Cobe CML) and a 20-micron arterial line filter. Hypothermia (26°–28° C) was induced in eight patients during CPB, one patient remaining normothermic. Mean arterial pressure (MAP) was maintained greater than 50 mmHg and arterial blood gases were regulated according to alpha-stat (temperature uncorrected) pH management.⁵ Of the nine patients, eight underwent coronary artery bypass grafting while the normothermic CPB patient underwent closed-chamber accessory pathway cryoablation.⁶

No patient with autonomic dysfunction, e.g., insulin-dependent diabetes, uncontrolled hypertension (diastolic BP > 100 mmHg), or those with poor left ventricular function were included in the study. Postoperatively, patients were excluded if there was ongoing myocardial ischaemia or haemodynamic instability requiring inotropes or vasodilators. Patients receiving infusions of nitroglycerin of less than 1 µg · kg⁻¹ · min⁻¹ were included provided the dose did not fluctuate during the study period.

Cerebral blood flow was determined from the averaged clearance of ¹³³Xe measured by ten external scintillation detectors, five located over each cerebral hemisphere (Novo Diagnostics 10a Cerebrograph).⁷ Approximately five mCi of ¹³³Xe in 6 ml saline was injected intravenously for each determination. End-tidal respiratory gas sampling was used to correct for recirculation. The resulting ¹³³Xe clearance curves were assessed by non-compartmental height-over-area analysis.⁸ As this represents the mean flow of all tissue under the detector, the curve was integrated to 15 min rather than infinity to reduce the effect of the extracerebral component.⁹ Standard correction factors were used to compensate for

changes in the xenon partition coefficient due to alterations in temperature and haematocrit.¹⁰

All CBF determinations took place in the intensive care unit three to eight hours after termination of CPB. Each CBF measurement required approximately 13 min for completion of data acquisition. The study was divided into two parts, each assessing either cerebral autoregulation or CO₂ responsiveness, each patient being randomly assigned as to which segment was done first.

Cerebral CO₂ responsiveness was assessed by first measuring baseline CBF at PaCO₂ 40 mmHg (CO₂ Base 1), following which PaCO₂ was increased 10 mmHg and CBF remeasured (high CO₂). The PaCO₂ was then returned to 40 mmHg and CBF was again measured (CO₂ base 2).

For assessment of cerebral autoregulation, CBF was measured initially (MAP base 1), blood pressure was then increased to mean arterial pressure (MAP) 110 mmHg and CBF was remeasured (MAP 110), after which MAP was reduced to 70 mmHg and CBF again measured (MAP 70). Following this, MAP was allowed to return to control levels and CBF measurements repeated (MAP base 2).

Arterial PCO₂, rectal temperature, mean arterial pressure and haemoglobin concentration were measured during each CBF determination. For assessment of CO₂ responsiveness, PaCO₂ was monitored using a capnometer (Hewlett Packard 47210A) and was varied by changing minute ventilation while MAP was varied using phenylephrine and trimethaphan infusions for assessment of cerebral autoregulation. In both parts of the study, base 2 represented a post-intervention control measurement.

All data were analysed by repeated measures analysis of variance (ANOVA) and Scheffe's test comparing each measurement against the other. Results that did not attain significance were subjected to power analysis. Alpha of < 0.05 and beta of 0.20 were used as measures of significance.

Results

All patients in the study underwent surgery and CPB which averaged 99 ± 27 min without incident. Due to time constraints, both parts of the study protocol were performed in only seven of the nine patients, with the other two patients each completing one of the autoregulation or CO₂ responsiveness parts (Table). Of the eight patients undergoing the CO₂ responsiveness investigation, a complete set of three satisfactory CBF measurements was collected in only six patients. Base 2 CBF measurements were excluded in two patients due to unsatisfactory ¹³³Xe clearance curves related to high background activity. A CBF response to elevated PaCO₂

FIGURE 1 Cerebral blood flow (CBF) responsiveness to increases in PaCO_2 measured in six patients after cardiopulmonary bypass. A significant increase in PaCO_2 resulted in a concomitant elevation of CBF (high CO_2) that returned to basal levels with the restoration of normal levels of PaCO_2 (CO_2 base 2).

* $P < 0.05$ vs MAP base 1.

was measured in all eight patients and this was used to calculate cerebral CO_2 reactivity.

The patients studied were all males of mean age 56 yr (range 45 to 68 yr). There were no significant complications during the study period, all patients making uneventful recoveries from surgery, though the incidence of CNS dysfunction during the postoperative period was not specifically investigated.

The normothermic CPB patient did not behave differently from the group as a whole in either the CO_2 responsiveness or autoregulation parts of the study and was thus included in the analysis.

CO₂ responsiveness

In the eight patients studied, the increase in CBF in response to increases in PaCO_2 averaged 1.35 ± 0.5

FIGURE 2 Cerebral blood flow (CBF) and mean arterial pressure (MAP) measured in eight patients after cardiopulmonary bypass. There was no significant change in CBF at any point despite significant changes in MAP (MAP 110, MAP 70).

* $P < 0.05$ vs CO_2 base 1.

$\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg PaCO}_2^{-1}$ (range 0.82–2.41 $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg PaCO}_2^{-1}$), demonstrating intact cerebral CO_2 responsiveness. In the six patients in whom CO_2 base 2 CBF measurements were obtained, despite the significant increase in CBF associated with the elevated PaCO_2 , no significant difference in CBF measurements between the CO_2 base 1 and CO_2 base 2 were found (Figure 1).

Autoregulation

The eight patients in whom data were obtained in response to MAP variation showed no significant difference in CBF between the MAP 110 mmHg, MAP 70 mmHg, or the two baseline measurements, despite significant differences in MAP (Figure 2). Intact cerebral autoregulation over the range MAP 70–110 mmHg was thus demonstrated.

TABLE (Mean $\pm$ SD)

	<i>CO₂ Responsiveness</i>			<i>MAP autoregulation</i>			
	<i>CO₂ Base 1</i>	<i>High CO₂</i>	<i>CO₂ Base 2</i>	<i>MAP Base 1</i>	<i>MAP 110</i>	<i>MAP 70</i>	<i>MAP Base 2</i>
<i>n</i> (patients)	6	6	6	8	8	8	8
Hb (g $\cdot$ dl ⁻¹)	10.8 $\pm$ 1.8	10.0 $\pm$ 1.9	9.9 $\pm$ 2.0	10.4 $\pm$ 2.4	10.4 $\pm$ 2.4	10.2 $\pm$ 2.5	10.0 $\pm$ 2.6*
Rectal Temp. ($^{\circ}\text{C}$)	35.7 $\pm$ 0.6	35.8 $\pm$ 0.7	35.9 $\pm$ 0.6*	36.3 $\pm$ 1.0	36.4 $\pm$ 1.0	36.5 $\pm$ 1.0*	36.6 $\pm$ 1.0*,†
MAP (mmHg)	84 $\pm$ 12	81 $\pm$ 7	87 $\pm$ 10	94 $\pm$ 15	111 $\pm$ 2*	71 $\pm$ 1*,†	90 $\pm$ 8†,‡
PaCO_2 (mmHg)	38 $\pm$ 4	52 $\pm$ 3*	39 $\pm$ 4	40 $\pm$ 5	39 $\pm$ 4	39 $\pm$ 4	39 $\pm$ 4
CBF (ml $\cdot$ 100 g ⁻¹ $\cdot$ min)	26.2 $\pm$ 6.9	42.4 $\pm$ 14*	26.9 $\pm$ 6.6§	26.3 $\pm$ 7.2	26.5 $\pm$ 6.3	25.7 $\pm$ 5.4	26.7 $\pm$ 6.8

* $P < 0.05$ vs Base 1; † $P < 0.05$ vs MAP 110; ‡ $P < 0.05$ vs MAP 70; § $P < 0.05$ vs high CO_2 .

Discussion

It is increasingly apparent that subtle neurological dysfunction occurs post-CPB despite the low (1–2 per cent) incidence of severe disability.^{1,3} In 312 patients who underwent CPB, Shaw *et al.*¹ were able to detect new neurological changes in 61 per cent of patients postoperatively. Although these changes were mostly minor and non-disabling, some were of more importance, e.g., development of primitive reflexes (three per cent), ophthalmological abnormalities (25 per cent), stroke (five per cent). At the time of discharge from hospital they had resolved in only four per cent of patients.

Abnormalities in CBF have also been reported after CPB. Henriksen *et al.*⁴ measured CBF preoperatively and on the fourth and eighth postoperative days in 14 patients undergoing CPB. There was a significant decrease in CBF from $55.3 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ preoperatively, to $43.5 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ on the fourth day and $47.8 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ on the eighth day. In the 11 patients investigated, measurements one year later remained slightly lower (one per cent) in the CPB group. There was no significant change in postoperative CBF in a control group of 15 patients undergoing cerebrovascular surgery.

In a study by Smith *et al.*,² 55 patients undergoing CPB and a control group of 20 patients having thoracic or major vascular surgery were investigated. Preoperatively, and at eight days and eight weeks postoperatively, CBF, neuropsychological status, and neurological signs were assessed. The latter were also assessed 24 hr postoperatively. Only at 24 hr postoperatively was the incidence of neurological signs in the CPB group significantly increased relative to controls. The slight decrease observed in postoperative CBF in the CPB group did not achieve statistical significance.

Despite the low incidence of severe disability, evidence is mounting that CPB causes subtle disturbances in the CNS. The early postoperative period may be associated with marked swings in blood pressure or PaCO_2 . If CBF regulation were deranged, such swings could result in large changes in CBF that could contribute to postoperative neurological dysfunction.

We have found CBF to show an appropriate increase in response to changes in PaCO_2 ($1.35 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$). This is consistent with previously published results (range 0.43 – $2.17 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{mmHg} \cdot \text{PaCO}_2^{-1}$).^{11–16} Similarly, CBF autoregulation over the range of MAP 70–110 mmHg appears to be well maintained during the early post-CPB period.

Because of the relatively small number of patients involved in this study, a 38 per cent change in CBF was required in order to demonstrate a statistically significant change in CBF. However, if autoregulation was im-

paired, the observed 57 per cent change in MAP should have been of sufficient magnitude to produce a significant change in CBF since in a previous study, in which pressure passive CBF was detected in patients managed using pH-stat pH management, a 40 per cent change in MAP produced a 45 per cent change in CBF.⁵ The lack of difference in CBF between base 1 and base 2 measurements, despite interim increases in PaCO_2 , MAP, or CBF, demonstrated the stability of these patients during the study period.

The use of trimethaphan as a hypotensive agent was predicated upon its absence of effect on CBF.¹⁷ Trimethaphan has direct peripheral vasodilating properties and may in addition cause histamine release.^{17,18} This could theoretically increase CBF but numerous studies have shown that trimethaphan does not directly increase CBF.^{17,19}

Phenylephrine, by a direct vasoconstricting action, could have masked an increase in CBF at the higher MAP studied, but there is evidence to suggest that this does not usually occur.²⁰ Intravascular catecholamines do not have direct effects on the cerebral vasculature²¹ as they do not cross the blood brain barrier.²² It is agents with beta-agonist activity that have been shown to increase CBF, although this is presumably secondary to an increase in CMRO_2 .²³ The small reduction in CBF occasionally noted with alpha-agonists such as phenylephrine²⁴ presumably reflects cerebral vasoconstriction in response to the marked hypertension produced.¹⁹

All the patients investigated were unconscious postoperatively, thus the relatively low CBF values (approximately $26 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$) presumably reflect residual anaesthesia in the early post-CPB period. These values are similar to those reported by investigators using similar ^{133}Xe clearance techniques in subjects during fentanyl-diazepam anaesthesia.^{5,25}

A potentially important consideration is our use of alpha-stat (temperature uncorrected), as opposed to pH-stat (temperature corrected), blood gas management during CPB. We have previously demonstrated normal CBF autoregulation and intact flow/metabolism coupling during hypothermic CPB managed by alpha-stat pH management.⁵ It was also shown that pH-stat management resulted in loss of CBF autoregulation with CBF becoming pressure passive.⁵ Whether cerebral autoregulation and CO_2 responsiveness are maintained postoperatively if pH-stat management is employed during CPB has not been investigated.

Our results, obtained after CPB using alpha-stat pH management, demonstrate normal cerebral CO_2 responsiveness and intact cerebral autoregulation over MAP 70–110 mmHg in the early post-CPB period. It is thus unlikely that primary postoperative derangements of

cerebral autoregulation are instrumental in the genesis of neurological dysfunction in patients undergoing CPB with alpha-stat pH management.

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