Tissue oxygenation response to mild hypercapnia during cardiopulmonary bypass with constant pump output

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Background. Tissue oxygenation is the primary determinant of wound infection risk. Mild hypercapnia markedly improves cutaneous, subcutaneous (s.c.), and muscular tissue oxygenation in volunteers and patients. However, relative contributions of increased cardiac output and peripheral vasodilation to this response remains unknown. We thus tested the hypothesis that increased cardiac output is the dominant mechanism.

Methods. We recruited 10 ASA III patients, aged 40–65 yr, undergoing cardiopulmonary bypass for this crossover trial. After induction of anaesthesia, a Silastic tonometer was inserted s.c. in the upper arm. S.C. tissue oxygen tension was measured with both polarographic electrode and fluorescence-based systems. Oximeter probes were placed bilaterally on the forehead to monitor cerebral oxygenation. After initiation of cardiopulmonary bypass, in random order patients were exposed to two arterial CO₂ partial pressures for 30 min each: 35 (normocapnia) or 50 mm Hg (hypercapnia). Bypass pump flow was kept constant throughout the measurement periods.

Results. Hypercapnia during bypass had essentially no effect on \( P_{O_2} \), mean arterial pressure, or tissue temperature. \( P_{CO_2} \) and pH differed significantly. S.C. tissue oxygenation was virtually identical during the two \( P_{CO_2} \) periods [139 (50–163) vs 145 (38–158), \( P=0.335 \) [median (range)]. In contrast, cerebral oxygen saturation (our positive control measurement) was significantly less during normocapnia [57 (28–67)%] than hypercapnia [64 (37–89)%, \( P=0.025 \)].

Conclusions. Mild hypercapnia, which normally markedly increases tissue oxygenation, did not do so during cardiopulmonary bypass with fixed pump output. This suggests that hypercapnia normally increases tissue oxygenation by increasing cardiac output rather than direct dilation of peripheral vessels.

Br J Anaesth 2006; 96: 708–14

Keywords: carbon dioxide, hypercapnia; carbon dioxide, hypercarbia; complications, acidosis, respiratory; heart, cardiac output; oxygenation, tissue, cutaneous; oxygenation, tissue, subcutaneous

Accepted for publication: March 15, 2006

Wound infections are among the most common serious complications of anaesthesia and surgery.¹ All wounds become contaminated. Contamination progresses to a clinical infection when host defence fails. This process occurs during a ‘decisive period’ lasting several hours after contamination;² in other words, during the immediate perioperative period. Oxidative killing by neutrophils is the primary determinant of host resistance to bacterial contamination.³ It is thus unsurprising that factors which increase subcutaneous (s.c.) tissue oxygenation reduce infection risk.⁴

Determinants of s.c. oxygen availability include arterial oxygen pressure,⁴ haemoglobin concentration,⁵ cardiac output,⁶ local perfusion,⁷ fraction of fat in s.c. tissue,⁸ hydration status⁹ and autonomic responses to pain.¹⁰ Mild-to-moderate hypercapnia also improves tissue oxygen availability.¹¹ For example, s.c. oxygenation
increased from 63 (14) to 89 (19) mm Hg \( (P=0.01) \) when arterial \( \text{PCO}_2 \) increased from 35 to 50 mm Hg.\(^1\) This 26 mm Hg increase is likely to be clinically important.\(^1\)

There are two mechanisms by which hypercapnia might improve tissue oxygenation. The first is activation of central\(^1\) and peripheral\(^4\) chemoreceptors, which promotes release of catecholamines.\(^1\)\(^6\) Catecholamines, in turn, increase cardiac output,\(^1\)\(^1\) enhance systemic vascular conductance\(^1\)\(^4\)\(^6\) and increase venous return.\(^1\)\(^9\)\(^\cdots\)\(^2\)\(^0\)\(^2\)\(^1\)\(^2\)\(^3\) Interestingly, hypercapnia is not associated with increased blood pressure,\(^1\)\(^1\) at least not during anaesthesia, because baroreflex-mediated parasympathetic activity reduces systemic vascular resistance (SVR) and heart rate.\(^1\)\(^7\)\(^2\)\(^1\)

The second mechanism by which hypercapnia might improve tissue oxygenation is direct, locally mediated peripheral vasodilation that may overwhelm sympathetic vasoconstriction.\(^2\)\(^2\)\(^3\)

The relative contribution of increased cardiac output and direct peripheral vasodilation remains unknown; that is, peripheral capacitance vessels could dilate to absorb increased cardiac output or cardiac output could increase in response to systemic vasodilation. Normally, it would be difficult to separate peripheral vasodilation caused by the local action of \( \text{CO}_2 \) from mechanisms that involve increased cardiac output and central autonomic regulation of the circulation. An exception, though, is during cardiopulmonary bypass when the bypass pump can control systemic perfusion. We, therefore, tested the hypothesis that mild hypercapnia increases peripheral tissue and cerebral oxygenation during cardiopulmonary bypass even when the pump flow (cardiac output) remains constant.

Among the various systems currently used for tissue oxygen monitoring, the Clark-type electrode-based method is considered the gold standard. The disadvantage of this method is that the Clark-type electrode consumes oxygen itself, which can decrease the system’s accuracy, especially at lower tissue oxygen tensions. Ruthenium-based fluorescent oxygen probe (optode) systems do not have this disadvantage, but have not been fully validated for clinical use. We thus took this opportunity to validate a new fluorescence optode oxygen-monitoring system by comparing it with the standard polarographic electrode (Clark-type) method and evaluating practical factors related to its use.

### Methods

With the approval of Human Studies Committee at the University of Louisville and written informed consent of patients, we enrolled 10 ASA physical status III patients aged 40–65 yr, undergoing heart surgery on cardiopulmonary bypass. Patients were excluded if they were morbidly obese (BMI>35), had diabetes or peripheral vascular disease of any type, or were taking \( \alpha_2 \)-agonists or other vasoactive drugs. Patients who smoked were included, but were not permitted to smoke during the 8 h before surgery because smoking reduces tissue oxygenation for 1 h.\(^2\)\(^4\)

Using a crossover study design, we compared s.c. tissue oxygen pressure and cerebral oxygen saturation during normocapnia and mild hypercapnia. Based on previous data,\(^1\) we expected that mild hypercapnia (a 15–20 mm Hg increase in arterial \( \text{PCO}_2 \)) would increase s.c. tissue oxygen pressure by at least 15 mm Hg. Assuming, as in our previous studies, that the \( \text{SD} \) would be 15 mm Hg, we estimated that a sample size of 10 would provide an 80% power to detect a statistically significant effect of hypercapnia at an alpha level of 0.05.

### Protocol

Anaesthesia was induced with etomidate (0.3 mg kg\(^{-1}\)), succinylcholine (\( \approx 1 \) mg kg\(^{-1}\)), and fentanyl (3–4 \( \mu \)g kg\(^{-1}\)), and maintained with pancuronium (0.01 mg kg\(^{-1}\) as needed), fentanyl (\( \approx 10 \) \( \mu \)g kg\(^{-1}\) bolus before sternotomy then 2–3 \( \mu \)g kg\(^{-1}\) as needed) and isoflurane. Hypovolaemia reduces s.c. perfusion;\(^2\)\(^9\) therefore, patients were kept well hydrated, especially during the pre-bypass period, by an infusion of crystalloid at a rate of 6–8 ml kg\(^{-1}\) h\(^{-1}\). Patients were actively warmed to maintain core temperature near 36°C before and after the bypass procedure. Because local warming influences tissue oxygenation, the upper arm tonometer site (described below) was protected from active surface warming.

After initiation of cardiopulmonary bypass, pump flow was set to maintain sufficient perfusion with a constant flow at a target mean arterial pressure of 60 mm Hg. Once set, pump outflow was kept constant until the end of the bypass period. Patients were alternately exposed to a \( P_{\text{aCO}} \), of 35 and 50 mm Hg during bypass, using a crossover design. Each designated \( P_{\text{aCO}} \), tension was maintained for about 30 min. \( \text{CO}_2 \) was added to the oxygenator circuit by the perfusionist, as necessary, to maintain the designated \( P_{\text{aCO}} \).

Treatment order was randomly assigned and based on computer-generated codes that were maintained in sealed, sequentially numbered opaque envelopes until the beginning of the bypass procedure. Intraoperatively (including the bypass period), the inspired oxygen concentration (\( F_{\text{IO}} \)) was kept constant for each patient [average of all patients was 0.85 (0.10)].

### Measurements

Demographic and morphometric characteristics and potential confounding factors, including preoperative haemoglobin, smoking status, type and duration of surgery, total amount of crystalloids given and intraoperative core temperature were recorded. Core temperature was measured from the distal oesophagus (Mallockrodt Anaesthesiology Products, St Louis, MO, USA) and Swan-Ganz catheter. Bladder temperature, which was recorded from the urinary catheter, was used to represent core temperature during the bypass period because the chest cavity was open.

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After induction of anaesthesia, 5–6 cm of a 15 cm-long Silastic tonometer (1 mm outer diameter, 0.8 mm inner diameter) was inserted s.c. on the lateral aspect of one upper arm, which was then gently tucked at the patient’s side. S.C. tissue oxygen tension (\(PSO_2\)) was measured with a polarographic electrode system (Licox Medical Systems, Corp., Greenvale, NY, USA). The polarographic oxygen electrode was calibrated on room air at the beginning of each surgery (154 mm Hg), and then positioned within the Silastic tonometer described above. A thermocouple was inserted into the opposite lumen of the tonometer and positioned approximately 1 cm from the oxygen electrode. The system was filled with hypoxic saline to remove air from the catheter.

Calibration and stabilization of the polarographic system required 20–30 min. In vitro accuracy of the polarographic electrodes (in a water bath at 37°C) is ±3 mm Hg for 0–100 mm Hg \(O_2\) and ±5% for 100–360 mm Hg \(O_2\). Temperature sensitivity is 0.25% per degree centigrade, but temperature-compensation is included in the \(PSO_2\) calculations. Polarographic electrode calibration remains stable (within 8% of baseline value for room air) in vivo for at least 8 h. Consequently, polarographic electrodes measure oxygen tension accurately and reliably over a broad range of s.c. temperatures and \(PO_2\) values. S.C. tissue oxygen tension was also measured from the same silicon tubing with the FOXY fluorescence system (Ocean Optics Inc., Dunedin, FL, USA), a relatively new technology. The FOXY-PI600 oxygen probe was simultaneously inserted into the silicon catheter. The fibre-optic probe conveys excitation light produced by a blue light emitting diode (LED) to a sol–gel thin film coating on the membrane at the probe tip. Fluorescence quenching of this probe is related to the partial pressure of oxygen by the Stern–Volmer equation. Fluorescence generated at the tip is collected by the probe and carried by optical fibre to the detector. We performed a two-point calibration of the optode at 0 and 154 mm Hg (\(F_{IO_2}\): 0 and 0.21) before insertion.

Cerebral oxygen saturation was monitored by a non-invasive near-infrared reflectance spectroscopic oximeter (INVOS 3100, Somanetics, Troy, MI, USA). Cerebral oximetry reflects the balance between regional oxygen supply and demand.

**Data analysis**

The major outcomes of our study were s.c. oxygen tension, as measured by two different systems, and cerebral oxygen saturation.

Intraoperative values were recorded at 5 min intervals. Tissue oxygenation values were monitored continuously and recorded at the end of each 30 min interval. The average values of the tissue oxygen gathered at the end of each 30 min interval were then compared between the periods. Demographic and morphometric factors were recorded.

Outcomes were compared between the groups with paired, two-tailed t-tests. Non-normally distributed results were analysed with Wilcoxon signed-rank tests. Results are presented as means (SDs or 95% confidence intervals), actual values, median (range), or percentages; \(P<0.05\) was considered statistically significant. Additionally, two-period crossover methodology described by Hills and Armitage was used to investigate treatment effects and possible period effects for the three major outcomes.

Linear regression and Bland–Altman analysis were used to compare tissue oxygen tensions obtained from the polarographic electrode (Licox) and fluoroscopic optode (Foxy) systems.

**Results**

The patients were 56 (42–62) yr old and three were women. Three of the ten were obese (BMI between 30 and 35 kg m\(^{-2}\)). The duration of surgery averaged 3.5 h, which included 1–1.5 h of cardiopulmonary bypass. Five patients had coronary artery bypass graft (CABG) surgery, five had valve replacement surgery, and one had both arterial grafting and a valve replacement. All but one of the patients had a history of cigarette smoking. Preoperative haemoglobin and other laboratory values were within normal range (Table 1).

During bypass, measurements of \(F_{IO_2}\), \(PSO_2\), pump outflow, mean arterial pressure, core (bladder) temperature, and s.c. tissue temperature were similar during the normocapnic and hypercapnic periods (Table 2). Arterial \(CO_2\) values were presented as means (range or SDs) or actual values. *SI units [conventional units]

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics and potential confounding factors. Data presented as means (range or SDs) or actual values. *SI units [conventional units]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>56 (42–62)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>3/7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 (12)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84 (21)</td>
</tr>
<tr>
<td>BMI (kg m(^{-2}))</td>
<td>28 (5)</td>
</tr>
<tr>
<td>BMI &gt;30 kg m(^{-2}) (n)</td>
<td>3</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>203 (38)</td>
</tr>
<tr>
<td>Total crystalloids (litre)</td>
<td>3.0 (0.7)</td>
</tr>
<tr>
<td>Type of surgery (n)</td>
<td>4</td>
</tr>
<tr>
<td>CABG</td>
<td>1</td>
</tr>
<tr>
<td>CABG and aortic valve replacement</td>
<td>1</td>
</tr>
<tr>
<td>Mitral and aortic valve replacement</td>
<td>2</td>
</tr>
<tr>
<td>Mitral valve replacement</td>
<td>3</td>
</tr>
<tr>
<td>Smoking status (n)</td>
<td>3</td>
</tr>
<tr>
<td>Never smoked</td>
<td>1</td>
</tr>
<tr>
<td>Quit &gt;12 weeks ago—smoked &gt;20 yr</td>
<td>3</td>
</tr>
<tr>
<td>Quit 3–12 weeks ago—smoked &gt;20 yr</td>
<td>3</td>
</tr>
<tr>
<td>Current smoker—not smoked in the past 24 h</td>
<td>3</td>
</tr>
<tr>
<td>Preoperative laboratory values*</td>
<td>6.1 (1.0) [110 (18)]</td>
</tr>
<tr>
<td>Glucose, mmol litre(^{-1}) [mg dl(^{-1})]</td>
<td>140 (20) [14 (2)]</td>
</tr>
<tr>
<td>Haemoglobin, g litre(^{-1}) [mg dl(^{-1})]</td>
<td>37 (6) [3.7 (0.6)]</td>
</tr>
<tr>
<td>Albumin, g litre(^{-1}) [mg dl(^{-1})]</td>
<td>5 (1) [113 (3)]</td>
</tr>
<tr>
<td>Serum urea nitrogen (BUN), mmol litre(^{-1}) [mg dl(^{-1})]</td>
<td>88 (18) [1.0 (0.2)]</td>
</tr>
</tbody>
</table>

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pressures ($P_aCO_2$) and pH differed significantly, as expected (Table 2). No vasopressor agents were administered before or during bypass.

$P_aO_2$ was virtually identical during each study period. Although the relationship is not known to be linear, s.c. oxygen partial pressure ($P_{sqO_2}$) was approximately one-third that of the $P_aO_2$ ($349 \pm 120 \text{ mm Hg}$ vs $365 \text{ mm Hg}$).

$P_{sqO_2}$ during normocapnia ($P_{CO_2}$ of 35 mm Hg) was similar to that during hypercapnia ($P_{CO_2}$ of 50 mm Hg), whether measured by the Licox or Foxy system (Table 2 and Fig. 1).

On the other hand, hypercapnia caused a clinically important and statistically significant increase in the cerebral oxygen saturation despite constant bypass pump flow and mean arterial pressure ($55 (14)\%$ vs $64 (17)\%$, $P=0.025$, Table 2 and Fig. 2).

Using the two-period crossover methodology, $P_{sqO_2}$, as measured with Licox, had a non-significant treatment effect of 4.9 mm Hg ($P=0.213$, 95% CI $-3.3$ to $13.1$) and a non-significant period effect of 5.1 mm Hg ($P=0.194$, 95% CI $-10.0$ to $19.2$).

### Table 2: Major outcomes with normocapnia and hypercapnia during cardiopulmonary bypass.

<table>
<thead>
<tr>
<th>Target $P_{CO_2}$</th>
<th>35 mm Hg</th>
<th>50 mm Hg</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index—pump outflow (litre $m^{-2}$ min$^{-1}$)</td>
<td>2.5 (0.2)</td>
<td>2.5 (0.1)</td>
<td>0.608</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>65 (6)</td>
<td>66 (6)</td>
<td>0.724</td>
</tr>
<tr>
<td>$P_{O_2}$%</td>
<td>83 (7)</td>
<td>83 (6)</td>
<td>0.979</td>
</tr>
<tr>
<td>$P_aO_2$ (mm Hg)</td>
<td>363 (110)</td>
<td>367 (84)</td>
<td>0.881</td>
</tr>
<tr>
<td>$P_aCO_2$ (mm Hg)</td>
<td>38 (3)</td>
<td>52 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pH</td>
<td>7.42 (0.04)</td>
<td>7.32 (0.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>Core temperature ($^\circ$C)</td>
<td>34.6 (1.1)</td>
<td>34.7 (1.2)</td>
<td>0.850</td>
</tr>
<tr>
<td>S.C. temp—$T_{sc}$ ($^\circ$C)</td>
<td>32.1 (1.7)</td>
<td>32.0 (2.0)</td>
<td>0.193</td>
</tr>
<tr>
<td>Licox $P_{sqO_2}$ (mm Hg)</td>
<td>122 (39)</td>
<td>119 (47)</td>
<td>0.335</td>
</tr>
<tr>
<td>Foxy $P_{sqO_2}$ (mm Hg)</td>
<td>130 (38)</td>
<td>129 (51)</td>
<td>0.322a</td>
</tr>
<tr>
<td>Cerebral oximeter saturation (%)</td>
<td>55 (14)</td>
<td>64 (17)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Fig 1 Mean s.c. tissue oxygen tension values obtained via a polarographic electrode system at the end of the 30 min normocapnia (35 mm Hg $P_{CO_2}$) and hypercapnia (50 mm Hg $P_{CO_2}$) periods. There was no statistically significant difference in s.c. tissue oxygenation between the periods ($P=0.335$).

Fig 2 Mean cerebral oximeter saturation values obtained at the end of 30 min normocapnia (35 mm Hg $P_{CO_2}$) and hypercapnia (50 mm Hg $P_{CO_2}$) periods. Cerebral oxygen saturation was significantly greater during hypercapnia ($P=0.025$).

Fig 3 The correlation between the $P_{sqO_2}$ values obtained with the polarographic electrode (Licox) and fluoroscopic optode (Foxy) systems.
Hypercapnia increases both sympathetic and cardiac vagus nerve activity in anaesthetized dogs. Such co-activation of vagus and sympathetic systems, which can be initiated reflexively or by action on higher centres, has been shown to be of distinct physiological benefit in controlling reactions that relate cardiac function to body need. As the sympathetic and parasympathetic systems are co-activated during systemic hypercapnia, blood pressure and heart rate response depends on the functional balance between these two systems. We were unable to evaluate heart rate during bypass, but have previously shown that both mean arterial blood pressure and heart rate remained essentially unchanged during hypercapnia even though cardiac output increases 25%. 11

Recent evidence indicates that both the sympathetic and parasympathetic nervous systems contribute to regulation of peripheral microcirculation. 34 The presence of parasympathetic-related, high-frequency microvascular oscillations has been recently documented in adrenergically rich peripheral regions—even during nonpulsatile perfusion 34—and has important implications for local flow homeostasis. Interestingly, nonpulsatile flow in the systemic circulation, as during cardiopulmonary bypass, progressively increases sympathetic nerve activity, 35 leading to arterial vasoconstriction and increased SVR. 33 This increase in sympathetic nerve activity is attributable to suppression of baroreflex-mediated inhibition of the vasomotor centre and is associated with local parasympathetic activation 34 in an effort to preserve tissue perfusion. Mild hypercapnia during constant systemic blood flow did not increase tissue oxygenation; however, we cannot exclude the possibility of a differential action of CO2 in regional vascular resistance, 36 which could have diverted systemic perfusion to areas other than s.c. tissues. 37 Our results provided data only from the s.c. tissue. If any perfusion improvements occurred because of a change in vascular resistance, we missed them because of a lack of monitoring. Potential redistribution cannot be excluded either.

In striking contrast to the unchanged s.c. oxygenation during constant systemic blood flow, mild hypercapnia markedly improved cerebral regional oxygen saturation. And the magnitude of the increase was similar to that we have previously observed in patients undergoing elective non-cardiac surgery. 31 This finding is consistent with the fact that sympathetic control of the cerebral vessels is

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**Discussion**

It is well established that mild hypercapnia improves peripheral perfusion and increases tissue PO2. Our main question was whether peripheral vasodilation is a direct effect of the CO2 or a secondary result of increased cardiac output and related central autonomic homeostatic responses. We found that mild hypercapnia did not increase s.c. tissue oxygenation when systemic blood flow and mean arterial pressure remained constant during cardiopulmonary bypass. Increased tissue oxygenation during mild hypercapnia thus most likely results from a hyperdynamic circulatory response and shifting oxyhaemoglobin dissociation curve rather than direct peripheral vasodilation.

Even mild systemic hypercapnia provokes sympathoexcitation15 which increases cardiac output, enhances systemic vascular conductance,18 19 and—because of active vasoconstriction—increases venous return. 19 20 The increase in capacitance vessel tone is mediated via peripheral and central chemoreceptors and does not necessarily parallel changes in overall vascular resistance 18 —and, as our results demonstrate, does not increase s.c. perfusion. Venoconstriction nonetheless increases venous return and is, thus, invariably associated with a sustained increase in cardiac output,14 18 19 31 an effect that dominates a small direct depressant effect of hypercapnic acidosis on the isolated myocardium. 32 33

![Bland–Altman analysis comparing the polarographic electrode (Licox) and fluoroscopic optode (Foxy) systems.](image)

Fig 4 Bland–Altman analysis comparing the polarographic electrode (Licox) and fluoroscopic optode (Foxy) systems. The bias (average difference of Foxy minus Licox method) is plotted on the y-axis and the average of the Foxy and Licox values is plotted on the x-axis. The centre line represents the bias [6.8 (15.0)] whereas the top and bottom lines represent ±2 sds of the bias.

PSO2, as measured with the Foxy system, had similar results with a non-significant treatment effect of 3.8 mm Hg (P=0.562, 95% CI -10.3 to 17.9) and a non-significant period effect of 11.4 mm Hg (P=0.190, 95% CI -2.7 to 25.5). On the contrary, in cerebral oxygen saturation there was a statistically significant treatment effect of 9.5% (P=0.007, 95% CI 4.1–14.9) with a non-significant period effect of 3.4% (P=0.204, 95% CI -2.0 to 8.8).

Tissue oxygenation recorded from the tissue oxygen-monitoring systems correlated well (r=0.92, Fig. 3). The difference between the polarographic and fluoroscopic systems (accuracy, bias) averaged 6.8 (15.0) mm Hg. The precision (2 sds of the difference between the systems) was 30 mm Hg (Fig. 4). The Foxy system proved difficult to use because it was light sensitive, subject to substantial motion artifact, and lacked a small-calibre temperature sensor.
weaker than of other vascular beds, and the contractile state of the cerebrovascular smooth muscle appears to depend mainly on local metabolic factors including the partial pressure of CO₂. Thus, the vasodilator effect of CO₂ is particularly marked in the cerebral circulation where a CO₂ concentration of 7–10% nearly doubles cerebral blood flow (CBF) in humans, while mild hypercapnia (PaCO₂ ~50 mm Hg) impairs autoregulation of CBF and is associated with an overall increase in cerebral oxygenation. A similar cerebrovascular response during cardiopulmonary bypass leads to an increase in CBF that is associated with a reduction in cerebral oxygen consumption. On the other hand, peripheral vasomotor tone that is associated with a reduction in cerebral oxygen consumption. On the other hand, peripheral vasomotor tone that is associated with a reduction in cerebral oxygen consumption.

The mechanism by which CO₂ exerts its direct effects on the cerebral vasculature seems to involve nitric oxide (NO), ATP-sensitive potassium channels, and cyclooxygenase-dependent pathways. The CO₂–NO axis is considered a cardinal pathway for CBF regulation in humans. Thus, although ATP-sensitive and Ca²⁺-activated potassium channels are also major systems that respond to hypercapnic acidosis, their response is incomplete in the absence of NO donors. In both animals and humans, hypercapnic vasodilatation is mediated by inhibition of NO synthase—the enzyme responsible for NO synthesis. It is probable that the vasodilatation to hypercapnic acidosis is mediated either by increased synthesis of NO or increased sensitivity to NO.

A secondary goal of our study was to compare a new fluoroscopic optode based oxygen-monitoring system (Foxy) with the current standard, polarographic electrode system (Licox). The fluorescence optode system is known to be more accurate in lower tissue oxygen environments than the polarographic one, because it does not consume oxygen. However, increased bias and impaired linearity of the relationship between the oxygen-monitoring systems when PsO₂ was above 150 mm Hg indicates reduced accuracy of the fluorescence optode at high tissue oxygenation. Other drawbacks of the fluorescence method include substantial light sensitivity, sensitivity to movement and the lack of a small-calibre temperature probe. These limitations make its use in the clinical setting impractical.

Another potential limitation of our study was that we allowed only a 30 min equilibration period at each designated arterial PCO₂ concentration. (A period of 30 min was chosen because the bypass period sometimes lasted only an hour.) However, 20–30 min is sufficient to obtain stable tissue oxygen values with tonometric systems that accommodate tissue oxygen probes. A further potential limitation of our study was that three of our 10 patients were obese and obesity is known to influence tissue oxygenation. However, because of our crossover design, the effect on tissue oxygenation should have been the same at both concentrations of CO₂. And lastly, we did not provide a positive control by increasing the bypass pump outflow during the study, which would have simulated increased cardiac output. Although we initially thought about putting this in our protocol, because we were working with patients as study subjects, we decided that it would be risky to include it. The clinical importance of the relationship between the bypass pump outflow and weaning the patient off the pump is just too fragile.

In summary, mild hypercapnia—which normally markedly increases s.c. tissue oxygenation—failed to do so during cardiopulmonary bypass when the bypass pump controlled systemic blood flow. In contrast, cerebral oxygen saturation increased as usual. The increase in s.c. oxygen partial pressure that normally accompanies mild hypercapnia thus results largely from increased cardiac output and compensatory autonomic circulatory responses. Potential contribution of shifting of oxyhaemoglobin dissociation curve and decreased oxygen consumption should also be considered.

Acknowledgements

Supported by NIH Grants GM 61655 and DE 14879-01A1 (Bethesda, MD), the Joseph Drown Foundation (Los Angeles, CA, USA), the Oesterreichische Nationalbank Jubiläumsfonds, the Gheens Foundation (Louisville, KY, USA), Ocean Optics Inc. Spectroscopy Educational Grant program, and the Commonwealth of Kentucky Research Challenge Trust Fund (Louisville, KY, USA). O.A. is the recipient of a Research Training Grant from the Foundation for Anesthesia Education and Research. Somanetics, Inc. (Troy, MI USA) donated the INVOS cerebral oximeter probes. Tyco-Mallinckrodt Anesthesiology Products, Inc. (St Louis, MO, USA) donated the thermocouples we used. We thank Gilbert Haugh, MS, for help with the statistical analysis, Nancy Alsip, PhD, for editorial assistance (both from the Outcomes Research Institute, University of Louisville), and Dr Harvey Edmonds for suggestions about cerebral oxygenation and perfusion monitoring (Department of Anesthesiology, University of Louisville).

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