Inspired oxygen fraction after cardiopulmonary bypass: effects on pulmonary function with regard to endothelin-1 concentrations and venous admixture

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Twenty consecutive patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) were allocated at random to group 1 (n=10, high inspired oxygen fraction (FIO2) after CPB), or group 2 (n=10, moderate FIO2 after CPB). The effects of each FIO2 on arterial and mixed venous concentrations of endothelin-1 (ET-1) and its precursor, Big ET-1, were measured. Venous admixture was calculated to assess the efficiency of pulmonary gas exchange. Patients whose lungs had been ventilated with a FIO2 of 1.0 (exposure time 70 min) after weaning from the CPB machine had significantly greater arterial and mixed venous Big ET-1 concentrations and venous admixture than patients whose lungs were ventilated with a FIO2 of 0.35. In contrast, ET-1 concentrations in the two groups were not significantly different. A reduction of FIO2 from 1.0 to 0.6 reduced venous admixture without lowering endothelial peptide concentrations. On the first postoperative day all peptide concentrations were similar in the two groups, whereas venous admixture remained non-significantly higher in group 1. A short period of high FIO2 immediately after CPB increases endothelin concentrations and pulmonary venous admixture.

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Anaesthesia adversely affects pulmonary function by affecting respiratory system mechanics and gas exchange in the lungs. Impaired oxygenation of the blood occurs in most subjects who are anaesthetized.1 2 Cardiac surgery with the use of extracorporeal circulation is frequently associated with impaired ability of the lungs to oxygenate blood.3 4 It has therefore become routine to increase the inspired oxygen fraction (FIO2) in order to prevent hypoxaemia. Hyperoxegenation generates oxygen radicals and consequently may increase reoxygenation injury after cardiopulmonary bypass (CPB). The superoxide anion may be an important factor in this damage.5 Hyperoxegenation can also increase ventilation–perfusion inequalities and alveolar collapse.6 7 After lung collapse, blood flow, and probably blood volume, are reduced because of hypoxic pulmonary vasoconstriction.8 Both local accumulation of oxygen radicals and local hypoxic pulmonary vasoconstriction may influence regional pulmonary integrity. Recent studies suggest that, of the endothelium-derived factors, endothelin-1 (ET-1), a potent vasoconstrictor, may be an important mediator of hypoxic pulmonary vasoconstriction.9 Its precursor, Big ET-1, could be an even more sensitive measure of endothelial dysfunction.10 Hyperoxaemic normothermic CPB can have adverse effects on tissue oxygenation,11 and uncontrolled reoxygenation results in marked production of conjugated diene as a sign of oxidant damage.12 This damage may increase plasma ET-1 concentrations, as the same increase has been found in patients at risk of developing acute lung injury.13 Reoxygenation damage seems to depend on oxygen tension.14 Reducing FIO2 may be less effective than hyperoxegenation in preventing tissue hypoxaemia. On the other hand, partial denitrogenation can reduce tissue damage and prevents or reduces ventilation–perfusion mismatching.6 7 We hypothesized that a short period of increased FIO2 immediately after CPB has a detrimental effect on both endothelium-derived factors and pulmonary gas exchange.

Materials and methods

Study population
The study was approved by the Ethics Committee of the University Hospital of Basel and written informed consent was obtained from each patient. Patients with significant
pulmonary, endocrine, renal, metabolic or neurological disease were excluded from the study. We also excluded emergency patients and patients requiring preoperative intravenous inotropic drugs, intra-aortic balloon support or mechanical ventilation. Sealed envelopes were used to allocate at random 20 consecutive adults undergoing cardiac surgery with CPB to group 1 (n=10, high $F_{I\text{O}_2}$ (1.0)) or group 2 (n=10, moderate $F_{I\text{O}_2}$ (0.35)).

**Anaesthetic technique and surgery**

Premedication consisted of morphine 0.1 mg kg$^{-1}$ and scopolamine 0.004 mg kg$^{-1}$ i.m. before transfer to the operating room. Anaesthesia was induced with fentanyl (10 µg kg$^{-1}$) and midazolam (0.1–0.15 mg kg$^{-1}$) or hypnomidate (0.02 mg kg$^{-1}$). To achieve intubation of the patient’s trachea, muscular paralysis was achieved with pancuronium (0.1 mg kg$^{-1}$). Anaesthesia was maintained with additional doses of fentanyl and midazolam combined with isoflurane (end-tidal concentration 0.2–0.8 vol%) if necessary. When further doses of neuromuscular blocking agents were required, i.v. pancuronium 2 mg was used. Routine cardiac monitoring included leads II and V5 of the electrocardiogram, pulse oximetry, capnography, oesophageal and rectal temperatures, a 20-G radial artery catheter and a three-lumen 7.5 Fr pulmonary artery catheter (Baxter, Irvine, CA, USA) inserted through the right internal jugular vein. Intravascular systemic and pulmonary artery pressures, heart rate and arterial and mixed venous oxygen partial pressures were recorded (PCMS Workstation, 19845–15–03; Spacelabs, Chatsworth, CA, USA). All patients were ventilated mechanically at a rate of 6 breath min$^{-1}$ with air–oxygen mixture ($F_{I\text{O}_2}$=0.5) using a Sulla 808V ventilator with a circle system 8 ISO (Drägerwerke, Lübeck, Germany) and a Ventilog ventilator (Drägerwerke) with zero end-expiratory pressure. Tidal volume was 8–15 ml kg$^{-1}$ to maintain end-tidal $PCO_2$ at 4.5–4.9 kPa. No further changes in ventilation were made before CPB. Operations were performed with standardized CPB (SARNS 9000; Terumo Cardiovascular System, Ann Arbor, MI, USA) including repeated cold-blood cardioplegia, hollow-fibre membrane oxygenator (Affinity Oxygenator; Medtronic Inc, Minneapolis, MN, USA) with a 40-µ filter in the arterial flow and mild systemic hypothermia (above 32°C) maintained during aortic cross-clamping. The methods of cannulation and heart preservation used were at the surgeon’s discretion and did not differ between groups. During surgery, intravascular volume replacement was achieved with lactated Ringer’s solution. Packed red cells were administered to maintain haematocrit above 25% during CPB and above 28% afterwards. The residual volume of the circuit was retransfused. After the patient waswarmed and weaned from the CPB machine, $F_{I\text{O}_2}$ was set to either 1.0 (high, group 1) or 0.35 (moderate, group 2) with a mean exposure time of 70 min (Table 1). Except for the $F_{I\text{O}_2}$, the ventilatory mode did not differ from the pre-bypass settings in order to preserve equal ventilatory conditions between the groups. Anaesthesia was maintained with additional boluses of fentanyl and midazolam. After surgery, patients were transferred to the intensive care unit (ICU) and ventilated mechanically with an $F_{I\text{O}_2}$ of 0.6 in both groups. Intravenous fentanyl and midazolam were used for analgesia and sedation. Postoperative care was standardized for all patients and extubation was accomplished at the earliest clinically appropriate time after the patient had been weaned from pressure-support ventilation. Criteria for extubation included being conscious, normothermia, haemodynamic stability, adequate pulmonary function with a respiratory rate between 10 and 20 breath min$^{-1}$ and satisfactory blood gases, adequate urine output and minimal chest tube output.

**Blood sampling**

Blood samples were obtained from the distal lumen of the pulmonary artery catheter and from the cannula in the radial artery. Peptide concentrations and calculations determining venous admixture (see below) were based on analyses of these blood samples, which were obtained at the following times: (i) during anaesthesia before surgery (baseline); (ii) 20 min after CPB had been discontinued, before sternal closure; (iii) 90 min after arrival in the ICU; (iv) on the first postoperative day in the ICU (Table 1).

**Peptide analyses**

Freshly collected blood was anticoagulated with ethylenediamine tetraacetate and put on ice immediately, and centrifuged within 1 h to separate plasma. The plasma samples were stored at −70°C and mixed well before assaying. For ET-1 and Big ET-1 analyses, a sandwich-type enzyme immunoassay (Biomedica, Vienna, Austria) was used. Direct measurements of the peptides were performed in duplicate according to the manufacturer’s instructions. To provide maximum sensitivity, the kits for ET-1 and Big ET-1 had highly specific immunofinity-purified polyclonal capture antibodies and monoclonal detection antibodies. In the first step, sample and monoclonal detection antibody were added simultaneously to microtitre plate wells precoated with capture antibody. Big ET-1 and ET-1, if present in the sample, bound and formed a sandwich with the detection antibody. After a washing step, which removed non-specifically bound material, a peroxidase-conjugated antibody detected the presence of bound detection antibodies. After removal of unbound conjugate by washing, tetra-

| Table 1 Study plan for blood sampling and measurements obtained. CPB, cardiopulmonary bypass; $F_{I\text{O}_2}$, inspired oxygen fraction; ICU, intensive care unit. |
| --- | --- | --- |
| Time | $F_{I\text{O}_2}$ for group 1 | $F_{I\text{O}_2}$ for group 2 |
| During anaesthesia before CPB | 0.5 | 0.5 |
| 20 min after weaning from CPB machine | 1.0 | 0.35 |
| 90 min after arrival in the ICU | 0.6 | 0.6 |
| After extubation of patient’s trachea (day 1) | 0.4 | 0.4 |
methylbenzidine was added to the wells as a substrate. Big ET-1 and ET-1 were quantified by an enzyme-catalysed colour change detectable using a standard ELISA reader. The amount of colour was directly proportional to the amount of ET-1 and Big ET-1 present in the sample. The concentration range of quality control samples was between 2 and 6 fmol ml⁻¹, with intra- and interassay coefficients of variation of 2.5–5.5 and 3.2–10.9% respectively. The detection limit for Big ET-1 was 0.1 fmol litre⁻¹ and for ET-1 it was 0.2 fmol litre⁻¹.

**Venous admixture**

The amount of venous admixture as a percentage of the total flow (Qs/Qt)×100 was calculated from the standard equation Qs/Qt = (CcO₂ – CaO₂)/(CcO₂ – CvO₂), where CcO₂ = end-pulmonary capillary oxygen content, CaO₂ = arterial oxygen content and CvO₂ = mixed venous oxygen content.15 Arterial and mixed venous blood gas measurements were performed by using a standard technique with the electrodes calibrated for the required partial pressure ranges (ABL 500; Radiometer, Copenhagen, Denmark). The end-pulmonary capillary oxygen content was calculated by using the equation for the alveolar oxygen partial pressure as follows: PAO₂ = [(760 mm Hg - 47 mm Hg)×FAO₂] - (PACO₂×1.25), where PACO₂ is the arterial carbon dioxide partial pressure. Arterial and mixed venous oxygen saturations and haemoglobin were performed by haemoximetry (OSM2, Copenhagen, Denmark). To assess oxygenation when FAO₂ was varied, the oxygenation index (PAO₂/FAO₂ ratio) was also calculated.

**Statistical analyses**

Multiple comparisons were performed by the use of Friedman analysis of variance for repeated measures. Groups were compared by the use of the Wilcoxon rank-sum test. For post hoc comparisons, Tukey’s test was applied if appropriate and probability values were calculated. The Spearman rank correlation coefficient (rₛ) was used to analyse relationships between variables. A P value of less than 0.05 was considered significant. For all calculations, the Statistica® 4.5 software package (StatSoft, Tulsa, OK, USA) was used.

**Results**

Patient details before CPB are presented in Table 2. There was no correlation between patient characteristics and measured clinical data.

**Effects of high FAO₂ immediately after CPB**

Ventilating the patient’s lungs with a FAO₂ of 1.0 after weaning from the CPB machine (group 1) resulted in significantly greater arterial and mixed venous Big ET-1 concentrations (2.6±1.2 and 2.7±1.2 fmol litre⁻¹ respectively) compared with patients who received a moderate FAO₂ of 0.35 (1.4±0.4 fmol litre⁻¹ for both Big ET-1 concentrations) (group 2) (P < 0.05) (Fig. 1). In contrast, ET-1 concentrations in the two groups were not significantly different (Fig. 1). In addition in group 1, arterial and mixed venous ET-1 concentrations were significantly greater during hyperoxygenation than before bypass, whereas group 2 showed no difference in ET-1 concentrations between the bypass and pre-bypass values.

In group 1, venous admixture was significantly greater during hyperoxygenation (20.9±7.5%) than before bypass (8.1±3.8%), whereas group 2, with a moderate FAO₂ of 0.35, showed no significant difference for this variable (Fig. 1). The PAO₂/FAO₂ ratio after CPB was significantly greater in group 1 (310±157 mm Hg) than in group 2 (225±43 mm Hg) (P < 0.05).

Pre-bypass values of pulmonary artery pressures were significantly greater in group 1 (25±5) than in group 2 (19±4), but were similar after CPB (23±6 vs 20±8). Peptide concentrations did not correlate with haemodynamic variables, except for a weak, non-significant correlation in group 1 between arterial ET-1 and pulmonary artery pressure (rₛ=0.60), and between mixed venous ET-1 concentration and right atrial pressure (rₛ=0.60) after CPB. There was no correlation between peptide concentrations and venous admixture.

Changing the FAO₂ from 1.0 (group 1) and 0.35 (group 2) to 0.60 in both groups resulted in no significant changes in peptide concentrations and venous admixture in the ICU. In group 1, however, mixed venous and arterial ET-1 and Big ET-1 values remained significantly increased compared with the pre-bypass values despite reduction of the FAO₂ (Fig. 1). There were no significant differences in peptide values between the groups.

**Prolonged effects of high FAO₂ after CPB**

On the first postoperative day, peptide concentrations were similar in the two groups (Fig. 1). However, venous admixture remained slightly greater in group 1 (6.3±2.6) than in group 2 (4.5±2.4), although the difference was not significant (P = 0.12). Extubation times were similar in the two groups (756±253 min after intubation in group 1 vs 764±243 min in group 2). The PAO₂/FAO₂ ratio, respiratory variables and time of discharge from the ICU did not differ significantly between the two groups.

**Discussion**

We found that a short period of increased FAO₂ immediately after CPB affected endothelial and gas exchange function. Big ET-1 concentrations and venous admixture after hyperoxygenation were significantly greater compared with pre-bypass values and the group with the moderate FAO₂ of 0.35. A reduction of FAO₂ from 1.0 to 0.6 decreased venous admixture without lowering endothelial peptide values.

Big ET-1 concentrations were elevated during exposure of the lungs to pure oxygen. Because Big ET-1 is the precursor of ET-1, pulmonary endothelial integrity may
be altered by hyperoxenation. In our patients, the increase in peptide values was not as great as that seen in patients at risk of developing acute lung injury, where ET-1 values were significantly elevated.\textsuperscript{13,17} None of these studies measured changes in Big ET-1. The physiological significance of Big ET-1 is still not clear, but Big ET-1 may be a more sensitive indicator of endothelial changes when compared with ET-1.\textsuperscript{10} Nonetheless, the present findings call for a re-evaluation of hyperoxenation, a practice that generates oxygen radicals\textsuperscript{18} and could worsen re-oxygenation injuries. The superoxide anion may be a central agent for this damage, especially because re-oxygenation is associated with a burst of superoxide anions\textsuperscript{5} and may generate reactive oxygen intermediates.\textsuperscript{19} Endothelial cells exposed to hyperoxia for 30 min produce free radicals via mitochondrial electron transport mechanisms.\textsuperscript{20} Adverse effects on tissue oxygenation during hyperoxenemic normothermic CPB are known,\textsuperscript{11} and uncontrolled re-oxygenation results in marked production of conjugated dienes as a sign of oxidant damage.\textsuperscript{12} In our patients, no measure of lipid hydroperoxide formation as an indicator of oxidant stress was included,\textsuperscript{12} but oxidant damage may increase plasma ET-1 concentrations.\textsuperscript{13} We do not know if the increased plasma peptide concentrations were caused by increased production, decreased pulmonary extraction or both. The lungs are exposed to virtually all of the cardiac output and thus contain oxygen radicals and released ET-1. Alterations of pulmonary function with increased venous admixture may alter net clearance or production of ET-1 by the lungs. If the adverse effects of oxygen caused by hyperoxia can be more clearly attributed to tissue oxygenation, we suggest that hyperoxia should be avoided and \( F_{\text{IO}_2} \) should be reduced.

In our study, intrapulmonary shunt was assessed by using the oxygen technique, and included regions with low ventilation/perfusion ratios. Thus, the ‘oxygen shunt’ was not a pure shunt and we therefore call it ‘venous admixture’. However, it is known that after CPB, regions with low ventilation/perfusion ratios are relatively small compared with true shunt (5 vs 27% of cardiac output).\textsuperscript{21} We calculated this shunt, as we did for the single measurement after CPB, during pure oxygen breathing, which eliminated any contribution to the shunt value from regions with low ventilation/perfusion ratios. The oxygen content of pulmonary capillary blood was calculated from alveolar oxygen tension. The difference between capillary and arterial content could have been artefactually increased because one of these values was calculated (as a high oxygen partial pressure) and the other variables from the shunt equation were measured. Although the oxygen technique has limitations in the description of intrapulmonary shunt, our calculated venous admixture data varied clearly with different \( F_{\text{IO}_2} \). In addition, for our clinical trial the oxygen technique was less complex and costly compared with other techniques using inert tracer gases.

Arterial plasma ET-1 concentration has a small but significant correlation with pulmonary arterial pressure.\textsuperscript{22} Arterial ET-1 also correlates directly with right atrial pressure, pulmonary vascular resistance to systemic vascular resistance ratio, peak airway pressure and airway resistance.\textsuperscript{22} The non-significant correlation between plasma ET-1 values and pulmonary artery pressure is consistent with other studies in which ventilation of the lung with 100% oxygen had no significant acute effect on vascular resistance in the normal human lung.\textsuperscript{23} Pulmonary arterial pressure values were not equal in the two groups before CPB, indicating the difficulty of getting a good match in this kind of a study. Data obtained during different oxygenation regimes after CPB showed similar pressure values, suggesting no acute effect of post-bypass hyperoxia on vascular resistance. Other possible effects of hyperoxia, such as inhibition of flow in lymphatic vessels that can affect extravascular lung water and thus influence pulmonary integrity, were not analysed in our study and could also change pulmonary function.\textsuperscript{24} Our results suggest that decreasing intraoperative \( F_{\text{IO}_2} \) was sufficient to reduce alveolar collapse and subsequent pulmonary shunt, and suggest caution in using high \( F_{\text{IO}_2} \) after weaning from CPB. Interestingly, a reduction of \( F_{\text{IO}_2} \)

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**Table 2** Clinical characteristics of the patients undergoing CPB. Data are (mean (SD) or range). Statistical analysis revealed no significant difference between the two study groups except for the sex of the groups (preponderence of males in group 1). *Weight height; †baseline (pre-bypass) values.

<table>
<thead>
<tr>
<th>Study conditions</th>
<th>High ( F_{\text{IO}_2} ) (group 1)</th>
<th>Moderate ( F_{\text{IO}_2} ) (group 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>9/1</td>
<td>5/5</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>68 (53–81)</td>
<td>65 (46–80)</td>
</tr>
<tr>
<td>Body mass index* (kg m\textsuperscript{-2})</td>
<td>27.1 (5.5)</td>
<td>25.7 (5.0)</td>
</tr>
<tr>
<td>Body surface area (m\textsuperscript{2})</td>
<td>1.9 (0.2)</td>
<td>1.8 (0.2)</td>
</tr>
<tr>
<td>Systemic arterial pressure mean† (mm Hg)</td>
<td>79 (9)</td>
<td>79 (19)</td>
</tr>
<tr>
<td>Right atrial pressure mean† (mm Hg)</td>
<td>10 (4)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Pulmonary artery pressure mean† (mm Hg)</td>
<td>25 (5)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>(&lt;\text{PaO}_2&gt;÷\text{FiO}_2&lt;sub&gt;1&lt;/sub&gt;) (mm Hg)</td>
<td>331 (119)</td>
<td>363 (75)</td>
</tr>
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<td>Coronary artery surgery</td>
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<tr>
<td>Aortic valve or mitral valve surgery</td>
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<td>6</td>
</tr>
<tr>
<td>Cardiopulmonary bypass times (min)</td>
<td>116 (34)</td>
<td>84 (38)</td>
</tr>
<tr>
<td>Time between completion of CPB and arrival in the ICU (min)</td>
<td>70 (15)</td>
<td>76 (26)</td>
</tr>
</tbody>
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Fig 1 Changes in concentrations of Big ET-1 (A), ET-1 (B) and venous admixture (C) before cardiopulmonary bypass (Pre) ($F_{O_2}$=0.5), after weaning from the CPB machine before sternal closure (+20 min) ($F_{O_2}$=1.0 in group 1 and 0.35 in group 2), 90 min after arrival in the intensive care unit (ICU) ($F_{O_2}$=0.6) and on the first postoperative day (Day 1) ($F_{O_2}$=0.4). Data were skewed and are therefore presented as median and 25–75% interquartile range. Filled circle in the bar denotes different $F_{O_2}$ values for groups 1 and 2 (1.0 and 0.35 respectively). Group 2 had an outlier with high arterial ET-1 values (range 3.6–4.7 fmol litre$^{-1}$) throughout the study. Comparisons with the patient’s data revealed no explanation for this finding. These data were excluded from the statistical analysis in order to simplify statistical interpretation.

from 1.0 to 0.6 reduced venous admixture without lowering endothelial peptide concentrations. It is obvious that lowering $F_{O_2}$ can increase the risk of hypoxaemia. Twenty minutes after CPB, blood gas analysis in five patients ventilated with a $F_{O_2}$ of 0.35 revealed a range of $P_{A\text{O}_2}$ from 7.7 to 10.3 kPa, resulting in arterial oxygen saturation between 90 and 97%. However, acid–base balance was not severely affected, with a pH between 7.28 and 7.52.

Although venous admixture remained slightly greater in group 1 than in group 2 on the first postoperative day, there was no difference in outcomes, such as time to extubation. However, it should be stressed that the time to extubation
is influenced by many factors and cannot be used as an index of equal pulmonary integrity in the two groups in the present study.

In conclusion, a short period of high $F_{O_2}$ immediately after CPB changes endothelial peptide and gas exchange. The considerable increase in venous admixture associated with hyperoxia and its prolonged effect on pulmonary function, which persisted in our patients even on the first postoperative day, contrasts with the expected advantages of controlled cardiac reoxygenation. The relationship between the oxygen-induced increase in peptide plasma concentration and pulmonary gas exchange may not be direct. More complex mechanisms may be involved, which require further investigation for their clarification.

References