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Effects of different inspired oxygen fractions on lipid peroxidation during general anaesthesia for elective Caesarean section†

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Key points

- Lipid peroxidation is increased in both mother and fetus during general anaesthesia for Caesarean section.
- Using $F_{I_{O_2}}$ of 1.0 rather than 0.3 or 0.5 does not cause increased lipid peroxidation.
- An $F_{I_{O_2}}$ of 1.0 increases oxygen transfer from the mother to the fetus.

Background. During general anaesthesia (GA) for Caesarean section (CS), fetal oxygenation is increased by administering an inspired oxygen fraction ($F_{I_{O_2}}$) of 1.0. However, it is unclear whether such high $F_{I_{O_2}}$ will increase oxygen free radical activity.

Methods. We randomized 39 ASA I–II parturients undergoing elective CS under GA to receive 30% (Gp 30), 50% (Gp 50), or 100% (Gp 100) oxygen with nitrous oxide and sevoflurane adjusted to provide equivalent minimum alveolar concentration. Baseline maternal arterial blood before preoxygenation and maternal arterial, umbilical arterial and venous blood at delivery were sampled for assays of the by-product of lipid peroxidation, isoprostane, and for measurement of blood gases and oxygen content.

Results. Maternal and umbilical isoprostane concentrations were similar among the three groups at delivery, despite significantly increased maternal and fetal oxygenation in Gp 100. However, paired comparisons of maternal delivery *vs* baseline concentration of isoprostane showed an increase at delivery for all groups [Gp 30: mean 342 (SD 210) *vs* 154 (65) pg ml^{-1}, P=0.016; Gp 50: 284 (129) *vs* 156 (79) pg ml^{-1}, P=0.009; Gp 100: 332 (126) *vs* 158 (68) pg ml^{-1}, $P<0.001$]. The magnitude of increase was similar in all three groups and independent of the $F_{I_{O_2}}$ or duration after induction.

Conclusions. GA for CS is associated with a marked increase in free radical activity in the mother and baby. The mechanism is unclear but it is independent of the inspired oxygen in the anaesthetic mixture. Therefore, when 100% oxygen is administered with sevoflurane for GA, fetal oxygenation can be increased, without inducing an increase in lipid peroxidation.

Keywords: anaesthesia, general; anaesthesia obstetric; Apgar scores; Caesarean section; fetus; lung, hyperoxia; oxygen, inspired concentration; oxygen, partial pressure, saturation; oxygen, toxicity; surgery

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We have previously reported that during general anaesthesia (GA) for elective Caesarean section (CS), the administration of an inspired oxygen fraction ($F_{I_{O_2}}$) of 1.0 increased fetal oxygenation compared with $F_{I_{O_2}}$ values of 0.3 and 0.5.[1] However, studies during regional anaesthesia for elective CS have shown that the use of high $F_{I_{O_2}}$ can induce a concomitant increase in free radical activity, causing lipid peroxidation in the mother and baby.[2] Lipid peroxidation causes tissue damage and compromises the defence of the fetus against further oxidative stress by depleting the antioxidants in the body.[3–11] Moreover, lipid peroxide end-products of tissue damage can disrupt cellular function by formation of disulphide bridges across nucleotide or amino acid chains[12] and inhibits lymphocytic activity.[13–15] Because it is not known whether using a high $F_{I_{O_2}}$ would have the same effect of increasing free radical activity during GA, we designed this study to investigate the effects of different $F_{I_{O_2}}$ on maternal and umbilical cord plasma concentrations of 8-iso-prostaglandin F2α (isoprostane), a marker of lipid peroxidation in patients having elective CS under GA.

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Methods

This study was approved by the Clinical Research Ethics Committee of The Chinese University of Hong Kong. Thirty-nine ASA physical status I–II, term parturients having elective CS under GA were recruited after giving written informed consent. This study was conducted concurrently with our previously reported study with an overlap of 15 patients.[1]

Patients received premedication with ranitidine 150 mg orally the night before and on the morning of surgery. On arrival to the operating theatre, 30 ml of sodium citrate, 0.3 M, was given and patients were kept in the left-tilted position until delivery. Under local anaesthesia, a wide bore i.v. cannula was inserted in the forearm, and a baseline sample of arterial blood was obtained from the radial artery for analysis of blood gases, oxygen content, and plasma concentrations of isoprostane. Standard monitoring comprising of non-invasive arterial pressure, electrocardiography, and pulse oximetry was attached.

Patients were then randomized by drawing of shuffled, coded, opaque envelopes to be ventilated with either 30% (Gp 30), 50% (Gp 50), or 100% (Gp 100) oxygen after induction of anaesthesia until delivery. Nitrous oxide and end-tidal sevoflurane were adjusted to provide equivalent minimum alveolar concentration (MAC) values: Gp 30 received $F_{I_{N_2O}}$ 0.7 and end-tidal concentration of sevoflurane 0.6%, Gp 50 received $F_{I_{N_2O}}$ 0.5 and end-tidal sevoflurane 1.0%; and Gp 100 received end-tidal sevoflurane 2.0%.

The oxygen analyser on the anaesthesia machine (Narkomed 4, North American Dräger, Telford, PA, USA) was calibrated immediately before each study. After preoxygenation, rapid sequence induction with cricoid pressure was achieved using thiopental 4 mg kg^{-1} and succinylcholine 1.5 mg kg^{-1}. To maintain double blinding, one investigator who was not involved with data collection controlled the delivery of the anaesthetic gases via an anaesthetic machine that was kept at an angle and shielded from other investigators who were blinded to the group allocation. These investigators were responsible for the blood sampling, blood analysis, and patient care. After confirming tracheal intubation, atracurium was given as required and the lungs were ventilated to maintain end-tidal carbon dioxide concentration of 4.3 kPa.

Oxygen and anaesthetic concentrations were measured using the integrated modules of the anaesthetic machine. To rapidly achieve the end-tidal concentration of the anaesthetic mixture, a fresh gas flow of 6 litre min^{-1} with the sevoflurane vaporizer set at 6% was initially given via the circle circuit for the first 60 s. Subsequently, the sevoflurane vaporizer was adjusted as required to provide the allocated end-tidal concentration. All monitoring data were captured on a Macintosh computer using a software developed within our department.

Our contingency plan for patients who developed a pulse oximetry reading of $<95\%$ was to withdraw the patient from the study and to administer a higher $F_{I_{O_2}}$ to restore the oximetry reading to $\geq 95\%$. Such cases would be recorded, but excluded from analysis. Hypotension, defined as a decrease in systolic arterial pressure to <100 mm Hg, would be treated by bolus infusion of Hartmann's solution. If insufficient blood was sampled from the maternal or umbilical vessels, the case would be excluded and a replacement patient recruited for that $F_{I_{O_2}}$ group allocation. Times of commencement of preoxygenation, skin incision, uterine incision, and delivery were recorded.

At delivery, a sample of maternal arterial blood was obtained, and a segment of umbilical cord was isolated using double clamps before the infant's first breath, from which umbilical artery (UA) and umbilical vein (UV) blood samples were obtained for analyses of blood gases, oxygen content, and isoprostane. After oxytocin 10 IU and morphine 0.15 mg kg^{-1} i.v. were given, anaesthesia was maintained using $F_{I_{O_2}}$ 0.3, $F_{I_{N_2O}}$ 0.7, and end-tidal sevoflurane 0.6% in all patients. Apgar scores at 1 and 5 min were assessed by a paediatrician who was blinded to the study. At the end of surgery, residual neuromuscular block was antagonized using neostigmine and atropine, and the trachea was extubated when deemed appropriate by the anaesthetist. Total blood loss was assessed by weighing wet swabs minus dry weight, measuring net blood volume in the suction bottle, and visual estimation of blood on drapes and on the floor.

Laboratory analysis of oxygen indices and lipid peroxides

Oxygen indices in the blood were measured using a blood gas analyser (Corning 278 pH/blood gas analyser, Medfield, MA, USA) and a co-oximeter (IL 682 CO-oximeter, Instrumentation Laboratory, Lexington, MA, USA). A correction for 70% fetal haemoglobin was used in the analysis of oxygen content in the UA and UV blood.

The remaining blood sample was centrifuged and the plasma stored at -70°C, for subsequent batch analysis of 8-iso-prostaglandin F2α (isoprostane). Free radical activity was quantified by the plasma concentration of isoprostane, an end-product of lipid peroxidation. Total plasma isoprostane was determined by gas chromatography–mass spectrometry according to our previously published method.[16] Plasma samples were deproteinized and hydrolysed; free and esterified isoprostanes were extracted by solid-phase extraction columns with citric acid/methanol/cyclohexane and ammonia solution/methanol and then derivatized by bis(trimethylsilyl)trifluoroacetamide and pentafluorobenzyl bromide. Concentrations of total plasma isoprostanes eluted at the retention time of an internal standard of 8-iso-prostaglandin F2a-D4 were quantified using a 30 m$\times$0.25 mm$\times$0.25 μm DB-5MS capillary column on an Agilent 6890 plus series gas chromatograph system, equipped with an Agilent 7683 autosampler and interfaced to an Agilent 5973N mass spectrometer in negative chemical ionization mode (Agilent Technologies Inc., Santa Clara, CA, USA). The absolute recovery was 83 (SD 1.9)%, and analytical accuracy was 99.0 (0.4)% with a linearity of $r^2=0.9985$.

Statistical analysis

From our previous study,[2] the mean (SD) of UA isoprostane was 122 (73) pg ml^{-1} in mothers who were given air to breathe, but