Effects of high inspired oxygen fraction during elective Caesarean section under spinal anaesthesia on maternal and fetal oxygenation and lipid peroxidation†

K. S. Khaw[1*], C. C. Wang[2], W. D. Ngan Kee[1], C. P. Pang[3] and M. S. Rogers[2]

[1]*Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, China.*
[2]*Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong, Hong Kong, China.*
[3]*Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong, China*

**Corresponding author: Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, China*

Background. Oxygen supplementation is given routinely to parturients undergoing Caesarean section under regional anaesthesia. While the aim is to improve fetal oxygenation, inspiring a high oxygen fraction ($F_{I_{O_2}}$) can also increase free radical activity and lipid peroxidation in both the mother and baby. In this prospective, randomized, double-blind study, we investigated the effect of high inspired oxygen fraction ($F_{I_{O_2}}$) on maternal and fetal oxygenation and oxygen free radical activity in parturients having Caesarean section under spinal anaesthesia.

Methods. Forty-four healthy parturients were randomized to breathe either 21% (air group) or 60% oxygen (oxygen group) intraoperatively via a ventimask. Maternal arterial blood was collected at 5-min intervals from baseline until delivery, and umbilical arterial and venous blood was collected at delivery. We measured blood gases and the products of lipid peroxidation (8-isoprostane, malondialdehyde (MDA), hydroperoxide (OHP)) and purine metabolites.

Results. At delivery, the oxygen group had greater maternal arterial P_{O_2} [mean 30.0 (SD 6.3) *vs* 14.2 (1.9) kPa; mean difference 15.8 kPa, 95% confidence interval 12.9–18.7 kPa, $P<0.001$] and greater umbilical venous P_{O_2} [4.8 (1.0) *vs* 4.0 (1.4) kPa; mean difference 0.8 kPa, 95% confidence interval 0.0–1.5 kPa, $P=0.04$] compared with the air group. Maternal and umbilical plasma concentrations of lipid peroxides (8-isoprostane, MDA, OHP) were greater in the oxygen group than in the air group ($P<0.05$).

Conclusions. We conclude that breathing high $F_{I_{O_2}}$modestly increased fetal oxygenation but caused a concomitant increase in oxygen free radical activity in both mother and fetus.

Br J Anaesth 2002; **88**: 18–23

Keywords: anaesthetic techniques, subarachnoid; anaesthesia, obstetric, Caesarean section; oxygen, supplement; oxygen, free radical activity

Accepted for publication: July 27, 2001

During spinal anaesthesia, changes in respiratory function occur[1] and oxygen supplementation is commonly given to prevent maternal oxyhaemoglobin desaturation and to optimize fetal oxygenation. Some studies have shown improvement in the umbilical blood gas and acid–base parameters under general and epidural anaesthesia.[2–5] However, Kelly and colleagues showed that administration of 35% oxygen during spinal anaesthesia did not improve fetal umbilical vein P_{O_2} or pH.[1] Few data are available on the efficacy of administering a greater inspired oxygen fraction ($F_{I_{O_2}}$). Moreover, high $F_{I_{O_2}}$ induces maternal hyperoxia and this may promote the formation of free radicals and lipid peroxidation.

In this randomized, double-blinded study, we investigated the effect of administration of a high $F_{I_{O_2}}$ on maternal and neonatal oxygenation and free radical formation in women having Caesarean section under spinal anaesthesia. The main outcomes we assessed were maternal arterial and

† This article is accompanied by Editorial II.

Table 1 Indications for elective Caesarean delivery

Indication	Oxygen group (n=22)	Air group (n=22)
Cephalopelvic disproportion or previous Caesarean section	13	13
Breech presentation	6	4
Transverse or unstable lie	0	2
Low-lying placenta or antepartum haemorrhage	2	1
Uterine fibroid	1	1
Genital herpes	0	1

umbilical cord blood gases and maternal and neonatal plasma concentrations of markers of oxygen free radical activity.

Materials and methods

This study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. We recruited 44 ASA I–II non-labouring, term parturients scheduled for elective Caesarean section under spinal anaesthesia after informed written consent. Patients were premedicated with ranitidine 150 mg orally the night before and on the morning of surgery. On arrival at the operating theatre, i.v. access was secured, standard monitoring was attached and a radial arterial cannula was inserted in the non-dominant forearm under local anaesthesia. Patients were then randomized, by drawing shuffled coded opaque envelopes, to breathe either 21% (air group) or 60% oxygen (oxygen group) intraoperatively. Air or oxygen was supplied from the anaesthetic machine (Narkomed 4; North American Dräger, Telford, PA, USA) to a high-flow venturi-type facemask (Intersurgical, Wokingham, UK) to provide the assigned $F\mathrm{I}_{\mathrm{O}_2}$. The oxygen analyser of the anaesthesia machine was used to confirm the $F\mathrm{I}_{\mathrm{O}_2}$ from the facemask before each use.

Spinal anaesthesia was then performed. After i.v. preload with lactated Ringer's solution 20 ml kg^{-1}, 0.5% hyperbaric bupivacaine 2.0 ml and fentanyl 15 μg were injected intrathecally with the patient in the right lateral position. The patient was then turned supine with left lateral tilt. Preparation and surgery started after checking that the level of the block was adequate. Our contingency for patients in the air group who developed a pulse oximetry reading of <94% was to increase the $F\mathrm{I}_{\mathrm{O}_2}$to 28%. Hypotension, defined as a decrease in systolic arterial pressure of more than 20% from baseline or to less than 100 mm Hg,[6] was treated with i.v. boluses of ephedrine, as required. Nausea and vomiting were treated with metoclopramide 10 mg i.v. once hypotension had been excluded. The times from starting oxygen supplementation to delivery, skin incision to delivery (I–D) and uterine incision to delivery (U–D) were recorded using a stopwatch. After delivery, a blinded paediatrician assessed Apgar scores.

Maternal arterial (MA) blood samples were taken before the start of anaesthesia, with the patient breathing room air, and at 5-min intervals after applying the facemask until delivery of the baby. The investigator who performed all the blood analyses was blinded to the $F\mathrm{I}_{\mathrm{O}_2}$ and did not participate in patient care. Fetal umbilical arterial (UA) and venous (UV) blood samples were collected from a segment of umbilical cord, double-clamped before the infant's first breath. For each blood sample, blood gas analysis was performed immediately using a Corning 278 pH/blood gas analyser (Medfield, MA, USA). The remainder of the sample was centrifuged and the plasma was stored at –70°C for subsequent batch analysis for 8-isoprostaglandin $F_2\alpha$ (8-isoprostane), malondialdehyde (MDA), organic hydroperoxides (OHP) and metabolites of oxidative purine metabolism.

Plasma concentrations of MDA were estimated as reactive substances by a thiobarbituric acid adduction method as described by Richard and colleagues[7] with partial modification.[8] An enzymatic technique[9] was used to determine OHP. For the measurement of purine and pyrimidine metabolites, the concentrations of cytosine, uracil, cytidine, hypoxanthine, xanthine, uric acid, guanine, uridine, thymine, adenine, inosine, guanosine and adenosine were determined simultaneously by reverse-phase high-performance liquid chromatography modified partially from previously described techniques.[10] Total free and esterified 8-isoprostane was estimated with an enzyme immunoassay kit (Cayman Chemical, Ann Arbor, MI, USA) with a precision of 97.9%.

Statistical analysis

In a previous study, we found that the mean and standard deviation of UA plasma concentrations of MDA and OHP during elective Caesarean section were 0.580 (0.029) and 0.135 (0.058) μmol l^{-1} respectively.[11] Using these data, we calculated that a sample size of 22 patients in each group yielded >80% power to detect a difference of 0.05 μmol l^{-1} of MDA or OHP with a type I error probability of 0.05. Data were tested initially for equality of variances using Levene's test, and the normal probability plot was used subsequently to test for normality. On the basis of these findings, statistical comparison was performed using either Student's t-test or the Mann–Whitney U-test. The χ^2 test was used to compare equality of proportions, and the association between $P\mathrm{a}_{\mathrm{O}_2}$, 8-isoprostane MDA and OHP in maternal and umbilical blood was compared using the Spearman rank correlation. Results are presented as mean and standard deviation or median and range where appropriate. P<0.05 was considered significant.

Results

All patients completed the study. The indications for surgery are summarized in Table 1. Maternal and fetal

Table 2 Maternal characteristics and arterial blood gas (ABG) data. Mean (SD), median (range). n.s. = not significant

	Air group (n=22)	Oxygen group (n=22)	P
Characteristics			
Age (yr)	31.5 (23–38)	32.1 (25–43)	n.s.
Height (cm)	154.7 (4.7)	155.9 (4.7)	n.s.
Weight (kg)	64.2 (6.6)	66.8 (7.7)	n.s.
ABG baseline			
pH	7.42 (0.02)	7.43 (0.02)	n.s.
P_{O_2} (kPa)	14.3 (2.1)	14.8 (9.9)	n.s.
P_{CO_2} (kPa)	4.1 (0.3)	4.0 (0.4)	n.s.
Base excess (mmol litre^{-1})	–2.4 (1.3)	–2.5 (1.4)	n.s.
ABG during surgery			
pH	7.43 (0.04)	7.44 (0.03)	n.s.
P_{O_2} (kPa)	14.3 (2.5)	31.8 (5.9)	<0.001
P_{CO_2} (kPa)	4.3 (2.3)	4.0 (2.4)	n.s.
Base excess (mmol litre^{-1})	–1.8 (1.4)	–2.0 (1.5	n.s.
ABG at birth			
pH	7.41 (0.04)	7.43 (0.03)	n.s.
P_{O_2} (kPa)	14.2 (1.9)	30.0 (6.3)	<0.001
P_{CO_2} (kPa)	4.4 (0.7)	4.1 (0.5)	n.s.
Base excess (mmol litre^{-1})	–2.1 (1.8)	–2.6 (1.9)	n.s.

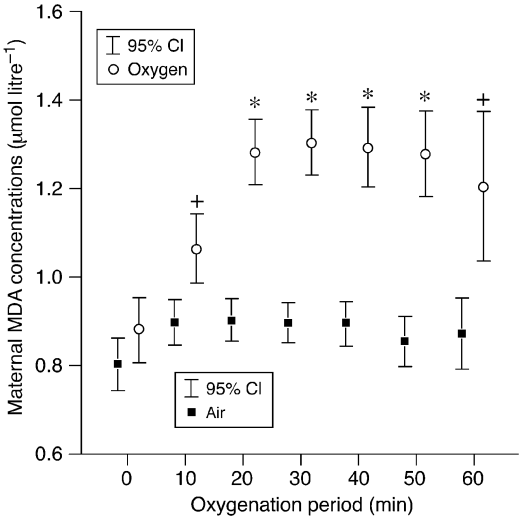

Fig 1 Maternal plasma concentrations of malondialdehyde at 10-min intervals. Data are mean (95% confidence interval) concentration for each interval after commencement of oxygen supplementation ^{+}P<0.05; $^{*}P$<0.001.

characteristics, duration of oxygen exposure, timed intervals to delivery from skin incision (I–D) and uterine incision (U–D) were similar between groups (Tables 2 and 3). No treatment for arterial desaturation was required and the incidence of hypotension was similar in the two groups.

Maternal blood analysis

The MA blood gases data are summarized in Table 2. Baseline parameters while breathing room air were similar. Compared with the air group, the oxygen group had greater arterial Pa_{O_2}intraoperatively [mean 31.8 (SD 5.9) *vs* 14.3 (2.5) kPa, mean difference 17.5 kPa, 95% confidence interval 16.3–18.4 kPa, P<0.001] and at delivery [mean 30.0 (6.3) *vs* 14.2 (1.9) kPa; mean difference 15.8 kPa, 95% confidence interval 12.9–18.7 kPa, P<0.001]. There were no differences in the other parameters (pH, Pa_{CO_2} and base excess). Mean intraoperative plasma concentrations of MDA were greater in the oxygen group than in the air group [1.26 (0.22) *vs* 0.89 (0.16) μmol l^{-1}, P<0.05]. The increase in MDA was significant within 10 min of exposure to the higher FI_{O_2} (Fig. 1) and at birth both isoprostane and MDA were higher in the oxygen than in the air group (Table 4). The concentrations of OHP and purine metabolites were similar between groups.

Apgar scores and umbilical cord blood analysis

Apgar scores were similar between groups, with all scores >7 at 1 min and >9 at 5 min. The umbilical cord blood gases are summarized in Table 3. Umbilical venous Pa_{O_2} was greater in the oxygen than in the air group [4.8 (1.0) *vs* 4.0 (1.4) kPa; mean difference 0.7 kPa, 95% confidence interval 0.0–1.5 kPa, P=0.04]. There was a positive correlation between UV Pa_{O_2} and maternal arterial Pa_{O_2} at delivery (r=0.516, P<0.001) (Fig. 2). Other umbilical venous and arterial blood gas variables were similar between groups.

Plasma concentrations of lipid peroxides were greater in both the UA and UV samples of the oxygen than in the air group (Table 4). In both groups, there was a positive correlation between the MA Pa_{O_2} and the UV concentrations of 8-isoprostane (r=0.87, P<0.001) (Fig. 3), OHP (r=0.61, P<0.001) (Fig. 4) and MDA (r=0.56, P<0.001) (Fig. 5). Paired comparison of plasma concentrations of MDA showed significant increases as early as in the first 10 min after starting oxygen supplementation (Fig. 1). A weak correlation was found between the MA and the UV concentrations of MDA (r=0.38, P<0.05) and OHP (r=0.29, P=0.61), and plasma UA and UV concentrations of purine and pyrimidine metabolites were similar between groups.

Discussion

The rationale for providing supplementary oxygen to the mother during Caesarean section is to optimize neonatal outcome.[2–5] Although several previous studies have shown benefits, such as improved UA Pa_{O_2}, UV Pa_{O_2}, acid–base status and enhanced fetal adaptation, most of these studies were based on general anaesthesia. Therefore, it may not be valid to extrapolate their findings to spinal anaesthesia. Nonetheless, giving oxygen supplementation to patients undergoing Caesarean section under regional anaesthesia is commonly advocated.[12] Ramanathan and colleagues reported that UV Pa_{O_2} was improved when parturients receiving epidural anaesthesia breathed increased FI_{O_2} (47–100% FI_{O_2}).[5] However, in a more recent study, Kelly

Table 3 Fetal characteristics, timed intervals, Apgar scores and umbilical cord blood gas data. Values are mean (SD), median (range) or number (%). I–D = interval from skin incision to delivery. U–D = interval from uterine incision to delivery. n.s. = not significant

	Air group (*n*=22)	Oxygen group (*n*=22)	*P*
Fetal characteristics			
Maturity (wk)	38.1 (37–40.3)	38.1 (37–39.4)	n.s.
Birth weight (kg)	3.08 (2.9–3.7)	3.14 (2.6–3.9)	n.s.
Timed intervals			
I–D (min)	7.2 (6.2–7.6)	7.5 (6.3–8.1)	n.s.
U–D (s)	68 (52–75)	69 (55–85)	n.s.
Duration of O_2 exposure (min)	52.7 (35–70)	53.2 (33–150)	n.s.
Apgar score			
1 min	9 (7–10)	9 (8–10)	n.s.
5 min	10 (9–10)	10 (9–10)	n.s.
<7 at 1 min	0 (0%)	0 (0%)	n.s.
<7 at 5 min	0 (0%)	0 (0%)	n.s.
Umbilical arterial blood gases			
pH	7.25 (0.09)	7.24 (0.09)	n.s.
P_{O_2} (kPa)	2.4 (0.6)	2.4 (0.8)	n.s.
P_{CO_2} (kPa)	7.2 (1.7)	7.5 (1.38)	n.s.
Base excess (mmol litre^{-1})	–4.6 (3.4)	–4.7 (3.8)	n.s.
Umbilical venous blood gases			
pH	7.29 (0.08)	7.30 (0.07)	n.s.
P_{O_2} (kPa)	4.0 (1.4)	4.8 (1.0)	<0.05
P_{CO_2} (kPa)	6.1 (0.9)	6.0 (0.8)	n.s.
Base excess (mmol litre^{-1})	–4.4 (3.7)	–4.2 (3.3)	n.s.

Table 4 Maternal and umbilical lipid peroxide concentrations. Values are mean (SD); units are μmol litre^{-1}. n.s. = not significant; N/A=not available

	Air group (*n*=22)	Oxygen group (*n*=22)	*P*
Maternal arterial (baseline)			
Isoprostane	118.8 (21.3)	127.4 (28.5)	n.s.
Malondialdehyde	0.89 (0.13)	0.93 (0.12)	n.s.
Organic hydroperoxides	0.13 (0.02)	0.14 (0.02)	n.s.
Maternal arterial (during surgery)			
Isoprostane	N/A	N/A	N/A
Malondialdehyde	0.89 (0.16)	1.26 (0.22)	<0.001
Organic hydroperoxides	0.14 (0.02)	0.14 (0.03)	n.s.
Maternal arterial (at birth)			
Isoprostane	121.8 (23.8)	200.6 (54.3)	<0.001
Malondialdehyde	0.89 (0.16)	1.12 (0.32)	<0.05
Organic hydroperoxides	0.14 (0.02)	0.14 (0.02)	n.s.
Umbilical venous			
Isoprostane	135.3 (66.7)	403.0 (100.4)	<0.001
Malondialdehyde	0.47 (0.13)	0.78 (0.16)	<0.05
Organic hydroperoxides	0.15 (0.05)	0.50 (0.17)	<0.001
Umbilical arterial			
Isoprostane	122.1 (73.4)	215.2 (92.7)	<0.001
Malondialdehyde	0.40 (0.06)	0.48 (0.10)	<0.001
Organic hydroperoxides	0.18 (0.09)	0.39 (0.10)	<0.001

and colleagues reported that parturients who received spinal anaesthesia had no maternal oxyhaemoglobin desaturation despite deterioration in respiratory mechanics, and that administration of 35% oxygen did not improve UV Pa_{O_2}.[1] In our study, we found that administration of 60% $F_{I_{O_2}}$ to parturients undergoing spinal anaesthesia resulted in a modest increase in UV Pa_{O_2}. However, because the magnitude of this increase was relatively small and because there was no difference in neonatal outcome, the clinical advantage of administering a high $F_{I_{O_2}}$ compared with air routinely to elective cases is questionable, provided that continuous monitoring with pulse oximetry is available. Moreover, administration of a high $F_{I_{O_2}}$ was associated with increased free radical activity in both the mother and fetus.

Direct detection of free radicals is extremely difficult because of their brief lifespan. Thus, in our study we measured lipid hydroperoxides, the products of attack by free radicals on polyunsaturated fatty acids, as 'footprints' of free radical activity.[13 14] Isoprostanes, formed by non-enzymatic oxygenation of arachidonic acid in membrane phospholipids, are highly specific as markers for *in vivo* oxidative stress.[15] The best-characterized isoprostane is 8-isoprostaglandin $F_2\alpha$ (8-isoprostane), which is abundant in plasma and urine. MDA and OHP concentrations are less specific, and can be influenced by the extent of prostaglandin metabolism as well as by free radical activity.

Pathological generation of free radicals commonly involves one of several possible pathways. We have shown previously an association between increased concentrations of lipid peroxides and prolonged labour, fetal distress, oligohydramnios and tight nuchal cord entanglement.[16–21] In these conditions, free radicals are generated via the pathways involving hypoxic stress and ischaemia–reperfusion injury. During hypoxia, xanthine dehydrogenase is converted into xanthine oxidase. After reperfusion, xanthine oxidase catalyses the formation of hydroxyl free radicals from the breakdown of purine metabolites, xanthine and hypoxanthine.[22] Thus, an accompanying increase in purine metabolites is a co-marker of ischaemia–reperfusion injury. Hyperoxia *per se* generates free radicals via an alternative pathway involving direct mitochondrial electron transfer, with no concurrent formation of purine metabolites. Thus, in our study, because there was no increase in purine metabolites, the most likely mechanism for the generation of free radicals was maternal hyperoxia.[23 24]

Lipid peroxide concentrations were much greater in UV than in UA blood, suggesting that the main site of free radical activity was the placenta, the interface where hyperoxia occurs. Concentrations of 8-isoprostane were greater in umbilical than in maternal blood, implying generation in the fetoplacental unit. Concentrations of MDA were greater in maternal than in umbilical blood, but were unlikely to be the result of placental transfer because of the weak correlation between the maternal and umbilical concentrations.[11] In the maternal blood, the increase in lipid peroxides results from the net effect of lipid peroxidation and free radical scavenging throughout the body, whereas the increase in the umbilical vein reflects the origin more specifically at the placenta. A positive correlation between maternal arterial Pa_{O_2} and the umbilical lipid peroxide concentration suggests a direct relationship

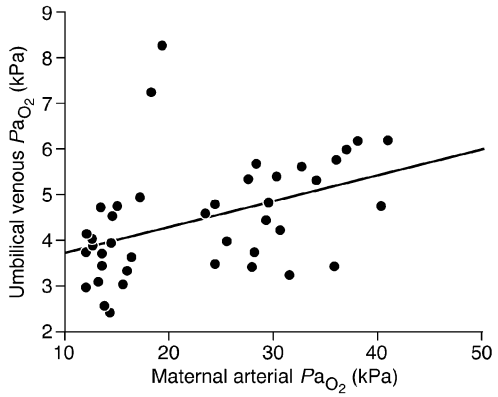

Fig 2 Scatter-plot of maternal arterial Pa_{O_2} at delivery and umbilical venous Pa_{O_2}. Data from air and oxygen groups are presented. r=0.516, P<0.001.

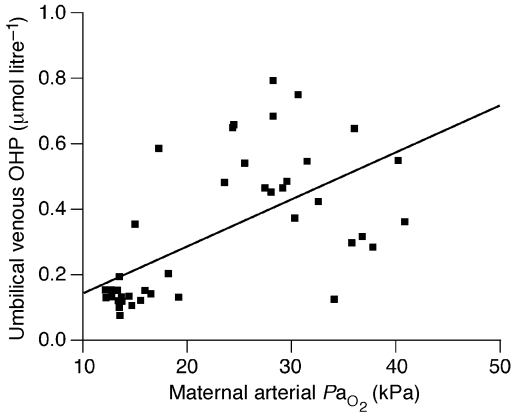

Fig 4 Scatter plot of maternal arterial Pa_{O_2} at delivery and umbilical venous organic hydroperoxides. Data from air and oxygen groups are presented. r=0.611, P<0.001.

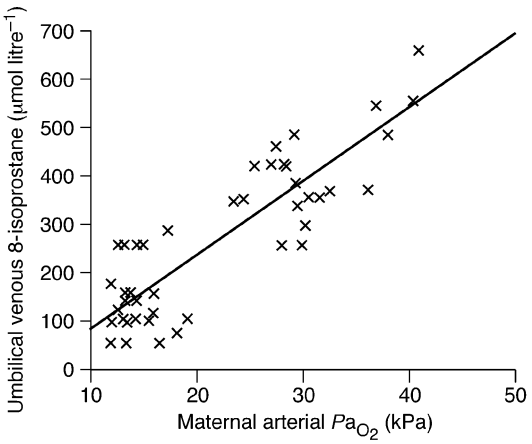

Fig 3 Scatter-plot of maternal arterial Pa_{O_2} at delivery and umbilical venous concentration of 8-isoprostane. Data from air and oxygen groups are presented. r=0.870, P<0.001.

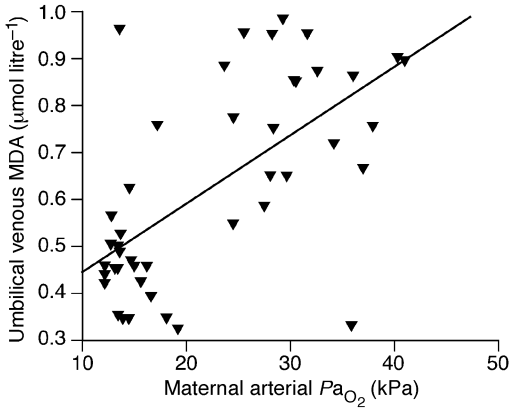

Fig 5 Scatter plot of maternal arterial Pa_{O_2} at delivery and umbilical venous malondialdehyde. Data from air and oxygen groups are presented. r=0.556, P<0.001.

between the oxygen partial pressure and the extent of free radical activity in the fetoplacental unit.

The clinical relevance of the increase in free radical activity we found in the oxygen group is uncertain. Although clinical effects were not apparent in our study, free radicals cause depletion of intrinsic antioxidant systems and could weaken the infant's ability to withstand any subsequent neonatal insult. MDA, a product of lipid peroxidation, is toxic because of its ability to form disulphide bridges across nucleotide or amino acid chains,[25] and also causes immunosuppression by inhibiting lymphocytic activity.[26] Our study was confined to healthy, elective cases with uncomplicated pregnancies. Although we found no difference in neonatal outcome between groups, Apgar scores can only demonstrate very gross changes, and in elective low-risk cases maternal hyperoxygenation would not be expected to have a significant effect on an outcome that is already likely to be favourable.

Conversely, the relative benefit of administration of a high FI_{O_2} where there is fetal compromise is unknown. It has been shown that hyperoxia increases the formation of free radicals, which may exacerbate tissue damage in ischaemia reperfusion injury.[23 24 27 28] Hyperoxia mediates tissue injury in bronchopulmonary dysplasia, retinopathy of prematurity, persistent ductus arteriosus, necrotizing enterocolitis and intracranial haemorrhage.[29–31] Furthermore, when oxygen was compared with air during neonatal resuscitation, a poorer outcome resulted because of the generation of free radicals.[32 33] Therefore, further investigation is required to clarify the relative advantages and disadvantages of high FI_{O_2} in emergency Caesarean section when there is fetal distress, as high FI_{O_2} may increase fetal oxygenation, but may also exacerbate ischaemia–reperfusion injury in the fetus.

Patient comfort is also an issue. This has led to the investigation of different methods of oxygen delivery during Caesarean section.[34] In our experience, parturients

sometimes complain of discomfort from wearing oxygen facemasks, which may be unnecessary given the questionable benefit of supplementary oxygen.

Acknowledgement

We thank Mr Raymond Chung (statistician) for advice and help with analysis.

References

1 Kelly MC, Fitzpatrick KT, Hill DA. Respiratory effects of spinal anaesthesia for Caesarean section. *Anaesthesia* 1996; **51**: 1120–2

2 Baraka A. Correlation between maternal and fetal P_{O_2} and P_{CO_2} during Caesarean section. *Br J Anaesth* 1970; **42**: 434–8

3 Fox GS, Houle GL. Acid–base studies in elective caesarean sections during epidural and general anaesthesia. *Can Anaesth Soc J* 1971; **18**: 60–71

4 James FM, Crawford JS, Hopkinson R, Davies P, Naiem H. A comparison of general anesthesia and lumbar epidural analgesia for elective Cesarean section. *Anesth Analg* 1977; **56**: 228–35

5 Ramanathan S, Gandhi S, Arismendy J, Chalon J, Turndorf H. Oxygen transfer from mother to fetus during Cesarean section under epidural anesthesia. *Anesth Analg* 1982; **61**: 576–81

6 Rout CC, Rocke DA, Levin J, Gouws E, Reddy D. A reevaluation of the role of crystalloid preload in the prevention of hypotension associated with spinal anesthesia for elective Cesarean section. *Anesthesiology* 1993; **79**: 262–9

7 Richard MJ, Portal B, Meo J, Coudray C, Hadjian A, Favier A. Malondialdehyde kit evaluated for determining plasma and lipoprotein fractions that react with thiobarbituric acid. *Clin Chem* 1992; **38**: 704–9

8 Wong SH, Knight JA, Hopfer SM, Zaharia O, Leach CN, Sunderman FW. Lipoperoxides in plasma as measured by liquid-chromatographic separation of malondialdehyde-thiobarbituric acid adduct. *Clin Chem* 1987; **33**: 214–20

9 Heath RL, Tappel AL. A new sensitive assay for the measurement of hydroperoxides. *Anal Biochem* 1976; **76**: 184–91

10 Simmonds HA, Duley JA, Davies PM. Analysis of purines and pyrimidines in blood, urine and other physiological fluid. In: Hommes FA, ed. *Techniques in Diagnostic Human Biochemical Genetics: A Laboratory Manual*. New York: Wiley-Liss, 1991; 397–424

11 Rogers MS, Mongelli M, Tsang KH, Wang CC. Fetal and maternal levels of lipid peroxides in term pregnancies. *Acta Obstet Gynecol Scand* 1999; **78**: 120–4

12 Shnider S, Levinson G. Anesthesia for Cesarean section. In: Shnider S, Levinson G, eds. *Anesthesia for Obstetrics*, 3rd Edn. Williams and Wilkins, Philadelphia, 1993; 217

13 Gutteridge JM, Halliwell B. The measurement and mechanism of lipid peroxidation in biological systems. *Trends Biochem Sci* 1990; **15**: 129–35

14 Halliwell B, Gutteridge JM. Lipid peroxidation, oxygen radicals, cell damage, and antioxidant therapy. *Lancet* 1984; **1**: 1396–7

15 Morrow JD, Hill KE, Burk RF, Nammour TM, Badr KF, Roberts LJ. A series of prostaglandin F2-like compounds are produced in vivo in humans by a non-cyclooxygenase, free radical-catalyzed mechanism. *Proc Natl Acad Sci USA* 1990; **87**: 9383–7

16 Mongelli M, Wang CC, Wang W, Pang CC, Rogers MS. Oxygen free radical activity in the second stage of labor. *Acta Obstet Gynecol Scand* 1997; **76**: 765–8

17 Rogers MS, Wang CC, Mongelli JM, Pang CC, Duley JA, Chang AMZ. Lipid peroxidation in cord blood at birth: a marker of fetal hypoxia during labour. *Gynecol Obstet Invest* 1997; **44**: 229–33

18 Rogers MS, Mongelli JM, Tsang KH, Wang CC, Law KP. Lipid peroxidation in cord blood at birth: the effect of labour. *Br J Obstet Gynaecol* 1998; **105**: 739–44

19 Wang CC, Rogers MS. Lipid peroxidation in cord blood: a randomised sequential pairs study of prophylactic saline amnioinfusion for intrapartum oligohydramnios. *Br J Obstet Gynaecol* 1997; **104**: 1145–51

20 Wang CC, Rogers MS. Lipid peroxidation in cord blood: the effects of umbilical nuchal cord. *Br J Obstet Gynaecol* 1997; **104**: 251–5

21 Wang CC, Rogers MS. Lipid peroxidation in cord blood: the effect of amniotic fluid volume. *Br J Obstet Gynaecol* 1997; **104**: 1140–4

22 Roy RS, McCord JM. Superoxide and ischemia: conversion of xanthine dehydrogenase to xanthine oxidase. In: Greenwald RA, Cohen G, eds. *Oxygen Radicals and their Scavenging Systems: Cellular and Medical Aspects*. Vol. 2. New York: Elsevier Science, 1983; 145–53

23 Turrens JF, Boveris A. Generation of superoxide anion by the NADH dehydrogenase of bovine heart mitochondria. *Biochem J* 1980; **191**: 421–7

24 Turrens JF, Freeman BA, Crapo JD. Hyperoxia increases H_2O_2 release by lung mitochondria and microsomes. *Arch Biochem Biophys* 1982; **217**: 411–21

25 Ward RJ, Peters TJ. Free radicals. In: Marshall WJ, Bangert SK, eds. *Clinical Biochemistry: Metabolic and Clinical Aspects*. New York: Churchill Livingstone, 1995; 765–77

26 Zhang Q, Li T, Huang Y. [Effect of lipid peroxide on lymphocytes and its role in postburn immunosuppression.] *Zhonghua Zheng Xing Shao Shang Wai Ke Za Zhi* 1995; **11**: 205–8

27 Wu S, Tamaki N, Nagashima T, Yamaguchi M. Reactive oxygen species in reoxygenation injury of rat brain capillary endothelial cells. *Neurosurgery* 1998; **43**: 577–83

28 Zweier JL, Duke SS, Kuppusamy P, Sylvester JT, Gabrielson EW. Electron paramagnetic resonance evidence that cellular oxygen toxicity is caused by the generation of superoxide and hydroxyl free radicals. *FEBS Lett* 1989; **252**: 12–6

29 Clyman RI, Saugstad OD, Mauray F. Reactive oxygen metabolites relax the lamb ductus arteriosus by stimulating prostaglandin production. *Circ Res* 1989; **64**: 1–8

30 Northway WH, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med* 1967; **276**: 357–68

31 Campell K. Intensive oxygen therapy as a possible cause of retrolental fibroplasia: a clinical approach. *Med J Aust* 1950; **2**: 48–50

32 Lundstrom KE, Pryds O, Greisen G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1995; **73**: F81–6

33 Saugstad OD, Rootwelt T, Aalen O. Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: the Resair 2 study. *Pediatrics* 1998; **102**: 130–7.

34 Crosby ET, Halpern SH. Supplemental maternal oxygen therapy during caesarean section under epidural anaesthesia: a comparison of nasal prongs and facemask. *Can J Anaesth* 1992; **39**: 313–6