Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants

K E Lundstrøm, O Pryds, G Greisen

Abstract
To determine if the use of oxygen in the delivery room influences subsequent global cerebral blood flow (CBF), 70 infants of gestational age of less than 33 completed weeks were randomly assigned to receive room air (group I) or 80% oxygen (group II) during the initial stabilisation at birth. In group I supplemental oxygen was administered on clinical indications, when required. After being admitted to the neonatal intensive care unit all infants were treated according to our normal practice. At a postnatal age of 2 hours CBF was measured by xenon clearance. Seventy four per cent of the infants in group I were successfully stabilised without the need for supplemental oxygen. CBF was significantly higher in group I than in group II (CBF median (interquartile range): 15-9 (13-6-21-9) v 12-2 (10-7-13-8) ml/100 g/minute). Differences in oxygen exposure seemed to be the only explanation for the differences in CBF. No differences in short term outcome were found between the groups.

(Arch Dis Child 1995; 73: F81-F86)

Keywords: cerebral blood flow, preterm, resuscitation.

Inhalation of 100% oxygen reduces global cerebral blood flow (CBF) in newborn infants.1 2 However, the duration of vasoconstriction following hyperoxaemia in the neonatal period remains unclear. The sensitivity to hyperoxaemia seems to decrease with maturity, and the effect may be prolonged in the immature brain.3 In newborn kittens the large arteries of the retina were severely constricted for several minutes by exposure to 80% oxygen.4 At normalisation of Po2, a similarly long lasting decrease in CBF velocity induced by a threefold increase in Po2 was demonstrated in preterm infants; CBF velocity normalised along with Po2 in term infants.5

Extremely low birthweight infants can be treated appropriately with room air or 30–40% oxygen in the delivery room.6 Routine use of 80–100% oxygen during the initial stabilisation at birth, as often recommended,7 may therefore produce hyperoxaemia in some infants. Greisen8 and Pryds et al9 showed that CBF in newborn preterm infants is low compared with these values in older children and adults. These results have recently been confirmed by other authors.10 The infants described by Greisen and Pryds were treated with 100% oxygen at birth. We therefore hypothesised that low CBF values might be caused by an extremely prolonged cerebral vasoconstriction following a few minutes of hyperoxaemia caused by routine use of oxygen shortly after birth. To test this, we conducted a randomised, controlled trial in which premature infants were assigned to receive room air or 80% oxygen during the initial stabilisation in the delivery room. Two hours after birth we measured CBF, and in an attempt to test for any systemic effect of hyperoxaemia, we also tested cardiac left ventricular output (LVO), mean arterial blood pressure (MABP), and heart rate at the same time.

Method

Enrolment criteria were a gestational age of <33 completed weeks and no known severe malformations. Women with incipient preterm delivery (gestational age of <33 weeks) were informed about the study and random allocation was delayed until immediately before delivery. Patients were not pre-selected, but enrolment in the study was undertaken only with the knowledge of one of the authors present. Infants were randomly assigned to receive initially room air (group I) or 80% oxygen (group II) during stabilisation in the delivery room. A subgroup of 12 infants in each group were monitored by pulse oximetry in the delivery room to test the differences in oxygenation during the treatment. This kind of monitoring is not routine in the department and could not be performed on all infants as no pulse oximeter was continuously available. Ten healthy, term infants not receiving any treatment were monitored by pulse oximetry during the first 10 minutes after birth for comparison with the preterm infants. Infants were excluded before randomisation if severe malformations or hydrops had been diagnosed antenatally. Exclusion criteria after delivery were severe congenital malformations, or need for mechanical ventilation, or death before 2 hours of age. Mechanical ventilation was used as an exclusion criterion because it has a major impact on both systemic and cerebral haemodynamics.

Data on all inborn premature infants from 1 September 1991 to 31 August 1992 fulfilling the inclusion criteria but not enrolled in the study were collected and compared with those of the study population to determine if the latter were representative of our population of inborn preterm infants.

The principal investigator was present at delivery in almost every case. According to routine procedures in our department, all infants were initially ventilated by bag and face mask with high pressures for at least two to four breaths to increase the functional residual
Xenon in 0.9% saline (total volume 1 ml) was described possible to glucose and oxygen status was evaluated by as well as the actual ventilatory injection. pH and was life.11 of TcPo2 was determined. If TcPo2 initially, an intravenous bolus of 60, 30-40% was administered, and an intravenous bolus of aminophylline or caffeine citrate were routinely administered, and vitamins E and K were administered by intramuscular injection. The indications for intubation and mechanical ventilation were FIO2 of >0.60, Pco2 of >9.5 kPa, and pH <7.25 or recurrent apnoea. Using nasal CPAP and these strict guidelines for intubation, it is possible to maintain most preterm infants spontaneously breathing during the first days of life.11

Two hours after birth a capillary blood sample was collected for analysis of blood glucose and haemoglobin concentration, Pco2, and pH. MABP was measured oscillometrically (Dinamap, Criticon, Tampa, USA), and heart rate and transcutaneous values were recorded as well as the actual ventilatory support. The oxygen status was evaluated by TcPco2. CBF and LVO were also measured at the same time.

All CBF measurements were performed with the infant undisturbed in the incubator, as described before.12 One half to 1 mCi/kg xenon in 0.9% saline (total volume 1 ml) was injected into a peripheral vein over 10–15 seconds. The clearance was recorded by scintillation detectors placed over one frontoparietal region and the thorax, respectively. CBF was calculated from the time the activity of xenon in the lung had decreased to 15% of its peak activity, using the Obrist compartment analysis, modified to adjust for increased recirculation of tracer. CBFx is the weighted mean of grey and white matter flow. The blood-brain barrier coefficient was set to 0.8 ml/g and adjusted for blood Hb.13 As the neonatal head is small and the scintillation geometry allows for counting from a volume of 100–200 ml, CBFx is considered to represent global CBF and is expressed as ml/100 g/minute. The test-retest variation of the method is 10–15%.14 Patient radiation was 0.2 mSv. Analyses of xenon data were performed without knowledge of randomisation.

Measurement of the internal diameter (D) of the ascending aorta (trailing edge to leading edge) just above the aortic valve was performed in late systole using combined B- and M-mode echocardiography from a parasternal short axis view (Aloka SSD 800 with a 5 MHz probe). The space and time average mean velocity (V) was measured at the same site using pulsed Doppler ultrasound velocimetry with a specially designed 5 MHz probe positioned at the suprasternal notch (Alfred Vingmed). LVO is derived by the formula:

\[ LVO = \frac{\pi \times D^2 \times V \times 60}{4 \times \text{Birthweight}} \text{ml/kg/minute} \]

This method correlates well with cardiac output measured with thermodilution in infants.15 16

DATA ANALYSIS
A power test with α=0.05 and β=0.10 revealed that 35+35 patients were required to detect a 10% difference in CBF between the two groups.

To adjust for positive skewing, CBF values were transformed logarithmically to obtain homogeneity of variance in the analyses.

Statistical analyses were done using the Mann-Whitney U test for unpaired data and the \( \chi^2 \) test for categorical data. Stepwise linear regression analysis was used to determine whether the effect of randomisation on CBF could be indirect through differences in other variables.

The computer program SPSSpc+ (Chicago, USA) was used for statistical evaluation. Parental consent was obtained for all infants before randomisation. The protocol was approved by the research ethics committee for the counties of Copenhagen and Frederiksberg. The study was carried out in the period 1 November 1990 to 15 April 1993.

Results
Mean SaO2 increased in the 12 infants in each of the randomisation groups during stabilisation as well as in the healthy term infants.
Oxygen at birth and prolonged cerebral vasocostriction in preterm infants

Figure 1  Median, upper, and lower quartile values of pulse oximetry readings in group I (SaO₂, 21% oxygen), group II (SaO₂, 80% oxygen) and in 10 healthy term infants (Δ, normal). For exact values and P values of differences, see table 1.

Table 1  Data of pulse oximetry readings (% oxygen saturation) in 12 infants treated with 21% oxygen at birth (group I), 12 treated with 80% oxygen at birth (group II), and 10 normal term infants (term, no treatment).

<table>
<thead>
<tr>
<th>Time after birth</th>
<th>Term, no treatment (n=10)</th>
<th>Group I (n=12)</th>
<th>Group II (n=12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Minutes</td>
<td>66 (56-75)%</td>
<td>70 (65-74)%</td>
<td>83 (74-93)%</td>
<td>0.009</td>
</tr>
<tr>
<td>5 Minutes</td>
<td>80 (55-85)%</td>
<td>75 (65-87)%</td>
<td>92 (90-97)%</td>
<td>0.0001</td>
</tr>
<tr>
<td>7 Minutes</td>
<td>83 (68-85)%</td>
<td>80 (70-87)%</td>
<td>94 (90-95)%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are median (IQR). P values are derived by Kruskall-Waliss ANOVA, normal term infants and group I being different from group II.

(fig 1). There was, however, a persistent difference between the infants receiving 80% oxygen and the two other groups, the infants receiving 80% oxygen having a much higher SaO₂ (table 1).

In the study group one infant was excluded after randomisation as he required intubation before 2 hours of age; all the remaining 69 infants were alive and breathing spontaneously, 65 of them on nasal CPAP, at 2 hours of life.

The perinatal characteristics were similar in the two groups and differed from the reference population only in terms of birthweight and temperature on admission to intensive care (table 2).

All infants were transported to intensive care within 10 minutes of delivery. This means that the duration of the planned different strategies for oxygen administration was less than 10 minutes. As transport time is on average 30 seconds, neither CPAP, ventilation, nor oxygen were administered during the transport.

Fourteen infants received caffeine citrate and 54 received aminophylline shortly after birth. The infants were equally distributed between the two groups.

The infants in group I received less oxygen at the time of measurements than the infants in group II (median Fio₂ 0.21 v 0.30, P=0.004, Mann-Whitney U test), while no significant difference was found in TcPO₂ between the groups.

Two hours after birth, CBF was significantly higher in group I than in group II (median (interquartile range): 15-9 (13-6-21.9) ml/100 g/minute v 12.3 (10.7-13.8) ml/100 g/minute; P<0.0001, Mann-Whitney U test). LVO showed no significant difference between the groups (median (interquartile range): 235 (209-282) ml/kg/minute v 202 (178-253) ml/kg/minute; P=0.10, Mann-Whitney U test). Heart rate was significantly higher in group I than in group II whereas other parameters were similar (table 3). The distribution of CBF between the groups is shown in fig 2.

Stepwise multiple regression analysis revealed that randomisation was the strongest explanatory variable on CBF at 2 hours of age (P<0.0001). TcPCO₂ (β=0.22, P=0.04) and TcPO₂ (β=0.23, P=0.04) were positively related to CBF; MABP, haemoglobin concentration, and gestational age did not reach significance. Neither LVO nor any other variable were significantly related to the different CBF values either in univariate analysis or in multiple regression analysis in combination with randomisation.

Nine (26.5%) infants in group I required supplemental oxygen during the first 10 minutes of life, maximal Fio₂ was 0.35 in four infants and 0.50 in five. Significantly more of these nine infants still required supplemental oxygen at the age of 2 hours compared with the rest of group I (6/9 v 5/25, P=0.03, χ² test). No differences in perinatal data, CBF (median (interquartile range): group I 10 (6-20-24) ml/100 g/minute v 15.7 (13-6-20.8) ml/100 g/minute; P=0.78, Mann-Whitney U test), or other variables at 2 hours of age were found between these two subgroups of infants, which is why they were not separated in the analysis.

All those infants not receiving supplemental oxygen at 2 hours of age (group I, n=23, group II, n=12) had been without supplemental oxygen for at least 90 minutes before CBF was measured. Analysis of this subgroup revealed a significant difference in CBF between the randomisation groups (median (interquartile range): group I 16.1 (13.6-22.6) ml/100 g/minute, group II 12.6 (10.1-14.6) ml/100 g/minute; P=0.006, Mann-Whitney U test).

Short term outcome (table 4) was similar between the two study groups and between the total study group and the reference population. Cystic periventricular leucomalacia was not diagnosed in any infant included in the study.

Table 2  Perinatal data for two randomisation groups and background population (values are median (range) or absolute numbers (%)).

<table>
<thead>
<tr>
<th>Group I (21% oxygen, n=34)</th>
<th>Group II (80% oxygen, n=36)</th>
<th>Background population (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g)</td>
<td>1043 (610-2590)</td>
<td>1113 (550-1870)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>29 (25-32)</td>
<td>29 (25-32)</td>
</tr>
<tr>
<td>Umbilical cord pH</td>
<td>7.32 (7.21-7.44)</td>
<td>7.32 (7.02-7.44)</td>
</tr>
<tr>
<td>Apgar score 1 minute</td>
<td>8 (10)</td>
<td>8 (3-10)</td>
</tr>
<tr>
<td>Apgar score 5 minutes</td>
<td>10 (8-10)</td>
<td>10 (6-10)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.0 (35.5-38.0)</td>
<td>36.9 (35.6-37.5)</td>
</tr>
<tr>
<td>Caesarean section (No (%))</td>
<td>23 (67-6)</td>
<td>29 (80-6)</td>
</tr>
<tr>
<td>Antenatal steroid (No (%))</td>
<td>None</td>
<td>4 (11.8)</td>
</tr>
<tr>
<td>One dose</td>
<td>6 (17-6)</td>
<td>6 (16-7)</td>
</tr>
<tr>
<td>Two doses</td>
<td>24 (70-6)</td>
<td>25 (69-4)</td>
</tr>
<tr>
<td>No information</td>
<td>0</td>
<td>3 (8-3)</td>
</tr>
</tbody>
</table>

*P<0.01, background population compared with study group; Mann-Whitney U test.
Table 3: Median (interquartile range) data for two randomisation groups at time of measurement (±postnatal age)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (21% oxygen)</th>
<th>Group II (80% oxygen)</th>
<th>P</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF (ml/100 g/minute)</td>
<td>15.9 (13.6–21.9)</td>
<td>12.3 (10.7–13.8)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>LVO (ml/kg/minute)</td>
<td>235 (209–282)</td>
<td>202 (178–253)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>0.21 (0.21–0.30)</td>
<td>0.30 (0.21–0.38)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>PaCO2 (kPa)</td>
<td>11.0 (9.3–12.5)</td>
<td>11.8 (10.8–13.1)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>6.1 (5.3–6.5)</td>
<td>6.1 (5.3–6.5)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>36.5 (33.8–40.0)</td>
<td>36.0 (32.0–42.0)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>158 (150–165)</td>
<td>150 (140–163)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (mmol/l)</td>
<td>11.8 (10.7–12.7)</td>
<td>12.0 (11.0–12.9)</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Blood glucose (mmol/l)</td>
<td>3.3 (2.2–4.7)</td>
<td>3.3 (2.2–3.9)</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Postnatal age (minutes)</td>
<td>133 (120–150)</td>
<td>145 (130–150)</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>

*Mann-Whitney U test.

Discussion

The hypothesis of our randomised trial, that routine administration of 80% oxygen at birth to newborn preterms influences CBF at 2 hours of age, was confirmed. This is a clinical study, however, and some weaknesses of design have to be considered.

The assignment to treatment group was known to the physician providing initial treatment. The knowledge of a difference in oxygen administration might have influenced other aspects of care, such as the use of CPAP or ventilation. There is no obvious mechanism, however, linking such differences to a difference in CBF two hours later. The CBF measurement in itself is objective and cannot be influenced by the investigator. Randomisation was not known to nurses and physicians caring for the infant in the intensive care unit.

The direct effect of the intervention, 80% vs 21% oxygen, was only documented in part. In the subgroups of 12+12 infants pulse oximetry from three to seven minutes after delivery demonstrated a significant difference in oxygen saturation, the recordings from infants treated with 21% oxygen being similar to those from 10 healthy term infants and at the same level as previously published values.17-19 Pulse oximetry, however, is a non-invasive technique and only estimates arterial oxygen saturation. We did not document that the infants receiving 80% oxygen were indeed hyperoxic; the median pulse oximetry readings at five and seven minutes being 92% and 94%, respectively.

No prospective collection of data regarding oxygen administration or transcutaneous values in the interval between admittance to intensive care and the time of CBF measurement was performed. Chart review indicated that the differences in oxygen exposure may have exceeded the initial 10 minutes. However, retrospective analysis of the subgroup of infants certainly not receiving supplemental oxygen for at least 90 minutes before the measurement of CBF still revealed a significant difference in CBF between the groups. Therefore, though the exact difference in duration of oxygen exposure between the two groups is unclear, this analysis suggests that the effect on CBF may persist considerably beyond the exposure.

More oxygen was administered at 2 hours of age to the infants treated with 80% oxygen at birth but there was no difference in TcPO2 between the groups. Arterial blood samples were not collected at the time of CBF measurement. The reason for the high levels of TcPO2 in both groups may be that a probe temperature of 44°C for transcutaneous measurements produces an overreading of PO2 in patients with a thin epidermis when compared with arterial measurements.20 An overreading of more than 2 kPa, however, is unusual and few infants could have been significantly hypoxaemic – that is, PaO2 below 7 kPa at the time of CBF measurement. Multiple linear regression showed that group assignment remained the strongest explanatory variable on CBF, but, surprisingly, regression also showed that CBF was slightly positively associated with the current TcPO2 level. The correlation between TcPO2 and CBF may have been confounded by intermediate factors (indicating the possibility of bias in transcutaneous measurement of oxygen tension), or may simply be random.

The need for more oxygen in group II could possibly be explained by toxic oxygen metabolites which are known to produce bronchoconstriction and pulmonary vasconstriction.21 However, the pulmonary effects of oxygen exposure were not directly examined in this study.

In summary, although our data are imperfect, we found no other likely explanation for the difference in CBF at 2 hours of age than the difference in oxygen exposure preceding the measurement. This suggests a prolonged effect of hyperoxaemia, possibly mediated through toxic oxygen metabolites on cerebral vessels of the newborn premature infant. The effect seemed to be more pronounced for cerebral vessels than for systemic circulation, as cardiac left ventricular output was not significantly lower in the infants treated with 80% oxygen. The statistical power of the
Table 4. Short term clinical outcome

<table>
<thead>
<tr>
<th></th>
<th>Group I (21% oxygen)</th>
<th>Group II (80% oxygen)</th>
<th>Background population (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>(n = 34)</td>
<td>(n = 35)</td>
<td></td>
</tr>
<tr>
<td>Retinopathy of prematurity (grade 3–5)</td>
<td>2 (5-9)</td>
<td>6 (17-1)</td>
<td>7 (6-1)</td>
</tr>
<tr>
<td>Necrotising enterocolitis</td>
<td>1 (2-9)</td>
<td>2 (5-7)</td>
<td>2 (1-7)</td>
</tr>
<tr>
<td>Intraventricular haemorrhage (grades III–IV)</td>
<td>2 (5-9)</td>
<td>3 (6-6)</td>
<td>3 (2-6)</td>
</tr>
<tr>
<td>Oxygen therapy day 28</td>
<td>5 (14-2)</td>
<td>7 (20-9)</td>
<td>9 (7-8)</td>
</tr>
<tr>
<td>Persistent ductus arteriosus</td>
<td>9 (11-8)</td>
<td>11 (14-8)</td>
<td>17 (14-8)</td>
</tr>
<tr>
<td>RDS (surfactant treatment)</td>
<td>3 (8-6)</td>
<td>6 (17-1)</td>
<td>16 (13-9)</td>
</tr>
</tbody>
</table>

The figures are absolute numbers (% of group).

No significant difference is present between the two randomisation groups or between the study group and the background population.

study, however, was not sufficient to rule out an effect on LVO. The small but significant difference in heart rate between the groups may be random, and no correlation was present between CBF and heart rate.

Stuart et al.22 demonstrated that short term (20 minutes) in vitro exposure of umbilical vessels to a 95% oxygen–5% carbon dioxide gas mixture caused a 30% inhibition in the ability to produce prostacyclin, an important vasodilator and antithrombotic metabolite of arachidonic acid. In another study of 4 to 6 day old kittens a 33% reduction in retinal 6-keto-prostaglandin F1α (the end product of prostacyclin) was observed after 48 hours of treatment with 80% oxygen, and these changes were still present after 24 hours of recovery in room air.23 A reduction in total retinal prostanooids which paralleled the changes observed in prostacyclin was also found, suggesting that the biochemical effect of hyperoxia on retinal vascular arachidonic acid metabolism occurred at the level of cyclooxygenase. Hyperoxia could exert a similar effect on the prostacyclin production of endothelial cells of cerebral vessels of preterm infants. Continued presence of cyclooxygenase inhibitors like free oxygen radicals following the hyperoxic insult or a slow turnover rate of cyclo-oxygenase in preterm cerebral endothelium might explain the prolonged effect.

Adenosine is believed to have an important role in the regulation of cerebrovascular resistance.24 However, 68 of the infants included in this study received either aminophylline or caffeine citrate. Both drugs are antagonists to adenosine25 and an effect of hyperoxemia mediated through adenosine receptors therefore seems unlikely.

Prolonged cerebral vasocstriction may make the brain more susceptible to hyperoxemia episodes or ischaemia. Hyperoxemia or normoxemia in the recovery period from oxygen induced retinopathy worsened the pathological findings in kittens while treatment with 28% oxygen in the same period ameliorated the retinopathy compared with recovery in room air.26 27 In contrast, hyperoxemia did not influence the brain damage in newborn piglets resuscitated from profound hypoxia with either 21% or 100% oxygen.28 Our data show that most preterm infants (25/34, or 74%) can be stabilised at birth without supplemental oxygen. The results are in agreement with a study of asphyxiated, mainly term, newborn infants in India randomised to receive 100% oxygen or room air during the resuscitation.29 Obviously, most of our infants were in a good condition as judged by umbilical cord pH and Apgar scores. No infant in our study required intubation in the delivery room and only nine infants developed respiratory distress requiring surfactant replacement therapy (indication for surfactant was a A–O2–P of <0.22 and radiological respiratory distress syndrome). This may be due to the good overall social conditions in Denmark, including effective antenatal care with extensive use of steroids and proactive management of delivery. Thus the success of atmospheric air in our study may not be reproducible in other populations of preterm infants.

In conclusion, our study suggests that routine administration of high oxygen concentration just after birth produces a persistent cerebral vasocostriction in premature neonates. While supplemental oxygen administered on clinical indication did not influence CBF. This may be specific for preterm neonates in the period immediately after birth. The potential biological and clinical implications are important. The prevention and treatment of hypoxia must remain the highest priority during resuscitation. However, a vasocostriction and in particular a reduced vasodilating capacity of the cerebral vessels may increase the risk of cerebral damage in the newborn period. Our results need to be confirmed in a different clinical setting.

2 Rahilly PM, Effects of 2% carbon dioxide, 0.5% carbon dioxide and 100% oxygen on cranial blood flow of the human neonate. Pediatrics 1980; 66: 685-9.
16 Alversen DC. Pulsed Doppler assessment of ascending aorta flow velocity in newborns and infants: clinical


Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants.

K. E. Lundstrøm, O. Pryds and G. Greisen

Arch Dis Child Fetal Neonatal Ed 1995 73: F81-F86
doi: 10.1136/fn.73.2.F81

Email alerting service

These include:
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/