ABSTRACT. Objective. Birth asphyxia represents a serious problem worldwide, resulting in ~1 million deaths and an equal number of serious sequelae annually. It is therefore important to develop new and better ways to treat asphyxia. Resuscitation after birth asphyxia traditionally has been carried out with 100% oxygen, and most guidelines and textbooks recommend this; however, the scientific background for this has never been established. On the contrary, theoretic considerations indicate that resuscitation with high oxygen concentrations could have detrimental effects. We have performed a series of animal studies as well as one pilot study indicating that resuscitation can be performed with room air just as efficiently as with 100% oxygen. To test this more thoroughly, we organized a multicenter study and hypothesized that room air is superior to 100% oxygen when asphyxiated newborn infants are resuscitated.

Methodology. In a prospective, international, controlled multicenter study including 11 centers from six countries, asphyxiated newborn infants with birth weight >999 g were allocated to resuscitation with either room air or 100% oxygen. The study was not blinded, and the patients were allocated to one of the two treatment groups according to date of birth. Those born on even dates were resuscitated with room air and those born on odd dates with 100% oxygen. Informed consent was not obtained until after the initial resuscitation, an arrangement in agreement with the new proposal of the US Food and Drug Administration’s rules governing investigational drugs and medical devices to permit clinical research on emergency care without the consent of subjects. The protocol was approved by the ethical committees at each participating center. Entry criterion was apnea or gasping with heart rate <80 beats per minute at birth necessitating resuscitation. Exclusion criteria were birth weight <1000 g, lethal anomalies, hydrops, cyanotic congenital heart defects, and stillbirths. Primary outcome measures were death within 1 week and/or presence of hypoxic-ischemic encephalopathy, grade II or III, according to a modification of Sarnat and Sarnat. Secondary outcome measures were Apgar score at 5 minutes, heart rate at 90 seconds, time to first breath, time to first cry, duration of resuscitation, arterial blood gases and acid base status at 10 and 30 minutes of age, and abnormal neurologic examination at 4 weeks.

The existing routines for resuscitation in each participating unit were followed, and the ventilation techniques described by the American Heart Association were used as guidelines aiming at a frequency of manual ventilation of 40 to 60 breaths per minute.

Results. Forms for 703 enrolled infants from 11 centers were received by the steering committee. All 94 patients from one of the centers were excluded because of violation of the inclusion criteria in 86 of these. Therefore, the final number of infants enrolled in the study was 609 (from 10 centers), with 288 in the room air group and 321 in the oxygen group.

Median (5 to 95 percentile) gestational ages were 38 (32.0 to 42.0) and 38 (31.1 to 41.5) weeks (NS), and birth weights were 2600 (1320 to 4078) g and 2560 (1303 to 3900) g (NS) in the room air and oxygen groups, respectively. There were 46% girls in the room air and 41% in the oxygen group (NS). Mortality in the first 7 days of life was 12.2% and 15.0% in the room air and oxygen groups, respectively; adjusted odds ratio (OR) = 0.82 with 95% confidence intervals (CI) = 0.50–1.35. Neonatal mortality was 13.9% and 19.0%; adjusted OR = 0.72 with 95% CI = 0.45–1.15. Death within 7 days of life and/or moderate or severe hypoxic–ischemic encephalopathy (primary outcome measure) was seen in 21.2% in the room air group and in 23.7% in the oxygen group; OR = 0.94 with 95% CI = 0.63–1.40.

Heart rates did not differ between the two groups at any time point and were (mean ± SD) 90 ± 31 versus 93 ± 33 beats per minute at 1 minute and 110 ± 27 versus 113 ± 30 beats per minute at 90 seconds in the room air and oxygen groups, respectively.

Apgar scores at 1 minute (median and 5 to 95 percentiles) were significantly higher in the room air group (5 [to 6.7]) than in the oxygen group (4 [1 to 7]); however, at 5 minutes there were no significant differences, with 8 (4 to 9) versus 7 (3 to 9). There were significantly more infants with very low 1-minute Apgar scores (<4) in the oxygen group (44.4%) than in the room air group (32.3%).
There also were significantly more infants with 5-minute Apgar score <7 in the oxygen group (31.8%) than in the room air group (24.8%). There were no differences in acid base status or Sao, during the observation period between the two groups. Mean (SD) PaO, was 31 (17) versus 30 (22) mm Hg in cord blood in the room air and oxygen groups, respectively (NS). At 10 minutes PaO, was 76 (32) versus 87 (49) mm Hg (NS), and at 30 minutes, the values were 74 (29) versus 89 (42) mm Hg in the room air and oxygen groups, respectively.

Median (95% CI) time to first breath was 1.1 (1.0–1.2) minutes in the room air group versus 1.5 (1.4 to 1.6) minutes in the oxygen group. Time to the first cry also was in mean 0.4 minute shorter in the room air group compared with the oxygen group. In the room air group, there were 25.7% so-called resuscitation failures (bradycardia and/or central cyanosis after 90 seconds) that were switched to 100% oxygen after 90 seconds. The percentage of resuscitation failures in the oxygen group was 29.8%.

Conclusions. This study with patients enrolled primarily from developing countries indicates that asphyxiated newborn infants can be resuscitated with room air as efficiently as with pure oxygen. In fact, time to first breath and first cry was significantly shorter in room air versus oxygen-resuscitated infants. Resuscitation with 100% oxygen may depress ventilation and therefore delay the first breath. More studies are needed confirming these results before resuscitation guidelines are changed.

Pediatrics 1998;102(1). URL: http://www.pediatrics.org/cgi/content/full/102/1/e1; asphyxia, newborn infant, room air, resuscitation, oxygen.

ABBREVIATIONS. HIE, hypoxic–ischemic encephalopathy; CI, confidence interval; ANOVA, analysis of variance; OR, odds ratio.

Birth asphyxia continues to represent a major clinical problem, and worldwide ~4 million newborn infants are affected annually. It has been estimated that of these, 1 million die, and an approximately equal number develop sequelae such as cerebral palsy, mental retardation, and epilepsy. Although birth asphyxia is a more serious problem in developing countries, still ~6/1000 newborn infants in developed countries develop hypoxic–ischemic encephalopathy (HIE) after birth asphyxia, and ~25% of the moderate and 75% to 100% of the severe cases later have major neurodevelopmental sequelae. Therefore it is important to develop new and more effective ways to prevent and treat asphyxia.

Traditionally, newborn infants have been resuscitated with 100% oxygen. In fact, most textbooks and guidelines in the field recommend the use of 80% to 100% O₂.45 Although neonatal resuscitation is frequently performed, we have not been able to find any scientific basis for this recommendation. The only related experimental study took place in the 1960s, and this study indicates that the outcome in newborn rabbits resuscitated with room air is comparable with the outcome with 100% O₂.

To investigate whether newborn infants can be resuscitated with room air, we performed a series of animal experiments before we carried out a clinical pilot study in which we resuscitated 42 asphyxiated newborn infants with room air and 42 with 100% O₂. We were able to demonstrate that room air was as efficient as 100% O₂ for resuscitation with regard to normalization of heart rate, time to first breath, and acid base status during the first 30 minutes of life. Apgar scores at 5 minutes were significantly higher in the room air group. There were no significant differences between the groups for neurologic symptoms or survival during the first week of life. The small number of infants in that study precluded more extensive statistical analyses. Therefore, to test our hypothesis further, a larger sample size was needed. Accordingly, a multicenter study was initiated; the results are reported in this article.

METHODS

The protocol was approved by the ethical committee for human investigation at each participating center. For practical reasons, informed consent could not be obtained before enrollment. After resuscitation, informed consent for continued inclusion in the planned follow-up study was obtained from the parents. This arrangement was approved by the ethical committees and is in agreement with the consensus statement from the coalition conference of acute resuscitation and critical care researchers, and the new proposal of the US Food and Drug Administration’s rules governing investigational drugs and medical devices to permit clinical research on emergency care without the consent of the subjects.69

Hypothesis and Study Organization

The hypothesis of the study was that room air is superior to 100% oxygen when asphyxiated newborn infants are resuscitated. The study was organized as an international multicenter trial with 11 participating centers from six countries. The steering committee was located in Oslo, Norway. There were one or two contact persons responsible for the organization at each participating center. None of the participants had any conflicts of interest.

Based on the sample size calculation and the approximate incidences of birth asphyxia at the participating centers, the necessary period for recruiting patients was estimated to be 18 months. However, it was decided before the study started that the enrollment period should not exceed 2 years. Patients were enrolled from June 1, 1994, to May 31, 1996; some of the centers joined the study after it had started.

Criteria for Inclusion and Exclusion

The entry criterion for enrollment in the study was apnea or gasping with heart rate <80 beats per minute at birth necessitating resuscitation. Exclusion criteria were birth weight <1000 g, lethal anomalies, hydrops, cyanotic congenital heart defects, and stillbirths. A stillbirth was diagnosed when a heart rate was never established.

Treatment Allocation and Guidelines for Management

For practical reasons, the study was not blinded. In addition, after thorough considerations it was decided that formal randomization was not feasible in this study. Because resuscitation is a medical emergency requiring immediate treatment, we were concerned that a formal randomization (with, for instance, sealed envelopes) could have resulted in a delay in treatment. Such a delay also may have resulted in a reduced number of enrolled infants, especially the most depressed infants, possibly giving a nonrepresentative sample. As in the pilot study, the infants were therefore placed in one of the two treatment groups according to date of birth. Those born on even dates were resuscitated with room air (room air group), and those born on odd dates were resuscitated with 100% oxygen (oxygen group).

The existing routines for resuscitation in each participating unit were followed. A face mask and bag were used, and the infants were intubated endotracheally when necessary. The ventilation techniques described by the American Heart Association were used as guidelines aiming at a frequency of manual ventilation of 40 to 60 breaths per minute. At each center, at least two trained people involved in the study took part in the resuscitation of all.
infants in the study. Resuscitation started immediately after delivery of the infant when a stop watch was started by one of the members of the resuscitation team.

To reduce any incremental risk of this study to a minimum as in the pilot study, if an infant treated with room air did not respond adequately to resuscitation within 90 seconds after delivery, the infant was switched to 100% oxygen. This was designated treatment failure. Criteria for treatment failure were heart rate <80 beats per minute and/or central cyanosis at 90 seconds after delivery, and they were recorded for both groups. Treatment failures in the room air group, although switched to 100% oxygen after 90 seconds, were analyzed in the room air group.

The duration of resuscitation was measured from delivery until the infant had spontaneous breathing with a heart rate >100 beats per minute, as suggested by the American Heart Association. Resuscitation was withdrawn after 30 to 45 minutes if spontaneous breathing had not been established.

Outcome Measures

The primary outcome measures were death within 1 week and/or presence of HIE, grade II or III, according to a modification of Sarnat and Sarnat. According to this classification, HIE grade I (mild) includes irritability, hyperalertness, mild hypotonia, and poor sucking; grade II (moderate) includes lethargy, seizures, marked abnormalities of tone, and requirement of tube feeding; and grade III (severe) includes coma, prolonged seizures, severe hypotonia, and failure to maintain spontaneous respiration. We also registered survival after 28 days of life.

Secondary outcome measures were Apgar scores at 5 minutes, heart rate at 90 seconds, time to first breath, time to first cry, duration of resuscitation, arterial blood gases and acid base status at 10 and 30 minutes of age, and abnormal neurologic examination after 4 weeks. In addition, arterial oxygen saturation was recorded in some infants by pulse oximetry at 1, 3, 5, and 10 minutes of life. Time to reach arterial oxygen saturation of 75% also was recorded if possible. Umbilical cord blood was sampled in eight centers (time 0), and four obtained arterial blood (three obtained blood by needle stick and one by catheterization) and four obtained venous cord blood.

Sample Size and Statistical Analysis

Based on the findings in the pilot study, to demonstrate a significant reduction in mortality and/or moderate to severe HIE from 15% to 9%, we needed to enroll 920 infants. A reduction from 15% to 8% would, however, require 648 enrolled infants (significance level 0.05; power 80%).

All calculations were performed with SPSS for Windows 6.1.2 (SPSS Inc, Chicago, IL), and graphs produced by Microsoft Power Point Version 4.0 (Seattle, WA), GraphPad Prism (San Diego, CA), or SPSS. Mean and SD units are given, and parametric tests (two-tailed t tests) were used when the variables were approximately normally distributed. Median and 95% confidence intervals (CIs) or 5 and 95 percentiles are given, and nonparametric tests (two-tailed Mann–Whitney U test) were used when the distribution of the variable was not normal. Repeated-measures analysis of variance (ANOVA) and \( \chi^2 \) tests were used when appropriate. Logistic or Cox regression analysis was used when the comparison between the two groups was adjusted for gender, gestational age, and birth weight.

Interim analyses were performed after 150 and 300 enrolled infants. Because there were no significant differences between the two groups with regard to primary outcome measure or mortality in the first week or within 28 days of life, the study continued.

RESULTS

Patients

Forms for 703 enrolled infants from 11 centers were received by the steering committee. Eighty-six of 94 infants from one center had been included without meeting the inclusion criteria for resuscitation, and all 94 infants from that center were excluded by the steering committee. Of the remaining infants, 16 had been allocated to the wrong group (10 born on even dates given oxygen and 6 born on odd dates given room air) because of a mistake concerning the date in 15 infants, in one case, oxygen was not available and the infant was resuscitated with room air instead. These 16 infants were included in the data analysis in the group in which they had been treated. In addition, four enrolled infants who died were included, although they had potentially lethal congenital conditions that were not recognized until resuscitation had been attempted. Two of these infants had diaphragmatic herniae, one had esophageal atresia with tracheoesophageal fistula, and one had congenital syphilis; all belonged to the room air group. Therefore, a total of 609 infants were eligible for analysis (Fig 1).

Table 1 shows the distribution of these 609 infants in the 10 remaining centers. A total of 107 infants eligible for enrollment in the recruitment period at each participating center were not included in the study, for varying reasons. In some cases, the study team arrived after the resuscitation was started, and in others, the obstetricians did not want to have the infant enrolled. The outcome of these 107 infants was not recorded.

Nineteen (6.6%) and 17 (5.3%) parents in the room air and oxygen groups, respectively, did not give informed consent. These patients consequently were not enrolled in the follow-up study, which is underway.

Baseline Characteristics

Of the 609 infants enrolled, 288 (47.3%) were resuscitated with room air and 321 (52.7%) with oxygen. This should be related to the fact that there were 49.0% even dates and 51.0% odd dates in the enrollment period. Table 2 shows some important pre- and perinatal factors. No significant differences between the two groups were found.

There were 133 females in both the room air group (46.2%) and the oxygen group (41.4%) (NS). Gestational ages ranged from 27 to 44 weeks in both groups. Median gestational age (5 to 95 percentile) was 38.0 (32.0 to 42.0) weeks in the room air group and 38.0 (31.1 to 41.5) weeks in the oxygen group (NS). Birth weights ranged between 1000 and 5550 g in the room air group and between 1000 and 5270 g in the oxygen group. Median birth weights (5 to 95 percentile) were 3100 (2500 to 3700) g in the room air group and 3000 (2600 to 3500) g in the oxygen group (NS).

**TRIAL PROFILE**

Fig 1. Trial profile of the 609 infants meeting inclusion criteria.
TABLE 1. Eligible and Included Infants According to City

<table>
<thead>
<tr>
<th>Center</th>
<th>Eligible</th>
<th>Included</th>
<th>RA/O2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delhi</td>
<td>158</td>
<td>158</td>
<td>64/94</td>
</tr>
<tr>
<td>Bombay</td>
<td>132</td>
<td>123</td>
<td>52/71</td>
</tr>
<tr>
<td>Madras</td>
<td>100</td>
<td>100</td>
<td>54/46</td>
</tr>
<tr>
<td>Cairo</td>
<td>87</td>
<td>87</td>
<td>47/40</td>
</tr>
<tr>
<td>Chandigarh</td>
<td>47</td>
<td>47</td>
<td>19/28</td>
</tr>
<tr>
<td>Mansoura</td>
<td>34</td>
<td>34</td>
<td>21/13</td>
</tr>
<tr>
<td>Manila</td>
<td>110</td>
<td>26</td>
<td>16/10</td>
</tr>
<tr>
<td>Tärtu</td>
<td>30</td>
<td>26</td>
<td>10/16</td>
</tr>
<tr>
<td>Valencia</td>
<td>13</td>
<td>6</td>
<td>4/2</td>
</tr>
<tr>
<td>Tønsberg</td>
<td>6</td>
<td>2</td>
<td>1/1</td>
</tr>
<tr>
<td>Total</td>
<td>716</td>
<td>609</td>
<td>288/321</td>
</tr>
</tbody>
</table>

Abbreviations: RA, room air; O2, oxygen.

TABLE 2. Maternal and Fetal Variables

<table>
<thead>
<tr>
<th>Maternal or Fetal Variable</th>
<th>Room Air</th>
<th>Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous pregnancies mean (SD)</td>
<td>2.2 (1.5)</td>
<td>2.3 (1.6)</td>
</tr>
<tr>
<td>Previous deliveries, mean (SD)</td>
<td>1.8 (1.3)</td>
<td>1.8 (1.2)</td>
</tr>
<tr>
<td>Maternal anemia, n (%)</td>
<td>58/265 (21.9)</td>
<td>66/300 (22.0)</td>
</tr>
<tr>
<td>Preeclampsia, n (%)</td>
<td>52/280 (18.6)</td>
<td>61/312 (19.6)</td>
</tr>
<tr>
<td>Vaginal delivery, n (%)</td>
<td>169/286 (59.1)</td>
<td>202/320 (63.1)</td>
</tr>
<tr>
<td>Sedation, n (%)</td>
<td>41/272 (16.8)</td>
<td>43/312 (13.8)</td>
</tr>
<tr>
<td>Pain relief, n (%)</td>
<td>119/270 (44.1)</td>
<td>132/305 (43.3)</td>
</tr>
<tr>
<td>Fetal bradycardia, n (%)</td>
<td>104/273 (38.1)</td>
<td>118/301 (39.2)</td>
</tr>
<tr>
<td>Premature, n (%)</td>
<td>75/286 (26.0)</td>
<td>72/321 (22.4)</td>
</tr>
<tr>
<td>BW &lt;2500 g, n (%)</td>
<td>115/288 (39.9)</td>
<td>137/321 (42.7)</td>
</tr>
<tr>
<td>Meconium, n (%)</td>
<td>119/280 (42.5)</td>
<td>140/316 (44.3)</td>
</tr>
<tr>
<td>Intubated, n (%)</td>
<td>73/288 (25.3)</td>
<td>82/321 (25.5)</td>
</tr>
</tbody>
</table>

No significant differences between the groups were found.
Maternal anemia: hemoglobin <10 g/L.
Preeclampsia: systolic blood pressure >140–160 mm Hg and proteinuria (>0.3 g/24 h, or positive urinary findings for protein) after 20 weeks of pregnancy.
Breech position: *5.6%, **8.1%.
Prematurity: <37 weeks gestational age.
Meconium indicates meconium-stained amniotic fluid.

percentile) were 2600 (1320 to 4078) g and 2560 (1303 to 3900) g (NS) in the room air and oxygen groups, respectively.

Primary Outcome Measure, Mortality, and HIE

None of the 33 infants recruited from the three European centers died. Mortality among the other centers did not vary significantly. Death within 7 days (or before discharge if discharged before 7 days), death within 28 days, and death within 7 days and/or HIE, grade II or III (primary outcome measure) are shown for all centers combined in Table 3. Mortality before 28 days was borderline significantly lower in the room air group, with odds ratio (OR) = 0.69. However, with a logistic regression multivariate analysis correcting for gender, birth weight, and gestational age, this difference was not significant. HIE grade II or III was not different between the two groups.

Heart Rate and Apgar Scores

Heart rates (Fig 2) in the room air and oxygen groups at 1 minute were (mean ± SD) 90 ± 31 versus 93 ± 33 and at 90 seconds were 110 ± 27 versus 113 ± 30. There were no significant differences between the two groups in heart rate over the first 30 minutes of life (repeated-measures ANOVA). The number of infants with heart rates <60, 80, or 100 beats per minute did not differ between the two groups at any time.

Median (5 to 95 percentile) Apgar scores in the room air and oxygen groups, respectively, were 5 (1 to 6.7) and 4 (1 to 7.5) (P = .004) at 1 minute, 8 (4 to 9) and 7 (3 to 9) (P = .12) at 5 minutes, and 8 (5 to 10) and 7 (3.5 to 9) (P = .29) at 10 minutes (Table 3). There were significantly more infants with very low 1-minute Apgar scores (<4) in the oxygen group (n = 142/320; 44.4%) than in the room air group (n = 92/286; 32.3%) (P = .001). However, at 5 and 10 minutes of age, this difference between the groups did not reach significance. There were significantly more infants with 5-minute Apgar scores <7 in the oxygen group (n = 102/321; 31.8%) than in the room air group (n = 71/286; 24.8%) (P = .03); however, at 10 minutes, no such difference between the groups was found.

Blood Gases, Oxygen Saturation, and Acid Base Status

Blood gases and acid base status are given in Table 4. In umbilical cord blood and at 10 minutes of life, no differences in PaO2 between the groups were found; however, at 30 minutes, PaO2 was significantly higher in the oxygen group than in the room air group [89 (42) mm Hg; n = 156 vs 74 (29) mm Hg; n = 115; P = .002]. Paco2 was not significantly different between the groups in umbilical cord blood, at 10 minutes, or at 30 minutes of life. Base deficit and pH did not differ between the groups either in umbilical venous or arterial cord blood or in arterial or capillary blood at 10 or 30 minutes of life. There was no difference in base deficit at any time point between survivors and nonsurvivors.

TABLE 3. Total Number of Registered Infants With Adverse Outcome

<table>
<thead>
<tr>
<th>Event</th>
<th>RA</th>
<th>Oxygen</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death within 7 days</td>
<td>35/288 (12.2%)</td>
<td>48/321 (15.0%)</td>
<td>0.79</td>
<td>0.49–1.26</td>
</tr>
<tr>
<td>Death within 28 days</td>
<td>40/288 (13.9%)</td>
<td>61/321 (19.0%)</td>
<td>0.69</td>
<td>0.44–1.06</td>
</tr>
<tr>
<td>Death within 28 days</td>
<td>40/267 (15.0%)</td>
<td>61/294 (20.7%)</td>
<td>0.67</td>
<td>0.43–1.04</td>
</tr>
<tr>
<td>Death within 7 days or HIE grade II or III</td>
<td>61/288 (21.2%)</td>
<td>76/321 (23.7%)</td>
<td>0.87</td>
<td>0.59–1.27</td>
</tr>
<tr>
<td>HIE grade II or III</td>
<td>47/288 (16.3%)</td>
<td>55/321 (17.1%)</td>
<td>0.94</td>
<td>0.62–1.45</td>
</tr>
</tbody>
</table>

a N = 609 (univariate) and N = 589 (multivariate). Death number (percent) in room air (RA) and oxygen (O2) groups and OR for various adverse events when comparing the room air group versus the oxygen group. The multivariate analysis is adjusted for gender, gestational age, and birth weight. The 73 infants in the room air group that had been switched to oxygen after 90 seconds because of so-called resuscitation failure (see text) were analyzed in the room air group.

b Compared with children followed for 28 days. N = 561 (univariate) and N = 543 (multivariate). At 28 days, 21 infants were lost to follow-up in the room air group and 27 infants in the oxygen group.
Versus 91 (7)%

Ent at 0.21 (0.21 to 1.00) in both groups.

30 minutes, the values were not significantly different.

Duration of Resuscitation, Treatment Failure

Fig 2. Heart rates between 1 and 30 minutes after birth in infants resuscitated with room air or 100% oxygen. Mean and SD are given. Open bars indicate room air group; hatched bars, oxygen group. No significant differences between the two groups were found.

Fig 3. Apgar scores at 1, 5, and 10 minutes after birth in infants resuscitated with room air or 100% oxygen. Median values and 5 to 95 percentiles are given. Open bars indicate room air group; hatched bars, oxygen group. *P = .004.

Arterial oxygen saturation was measured with pulse oximetry in all centers at 1, 3, 5, and 10 minutes of age, however, in only a limited number of patients, and it did not differ significantly between the two groups (repeated-measures ANOVA). Mean (SD) SaO₂ was in the room air and oxygen group, respectively, at 1 minute [65 (11)% n = 75 versus 61 (14)% n = 67]; 3 minutes [82 (13)% n = 87 versus 81 (11)% n = 91]; 5 minutes [86 (10)% n = 102 versus 88 (10)% n = 103]; and 10 minutes [90 (6)% n = 112 versus 91 (7)% n = 120].

Median (5 to 95 percentile) Fio₂ at 10 minutes was 0.21 (0.21 to 1.00) in the room air group and 0.23 (0.21 to 1.00) in the oxygen group (P < .0001). However, at 30 minutes, the values were not significantly different at 0.21 (0.21 to 1.00) in both groups.

Time to First Breath, First Cry, and SaO₂ of 75%,

Duration of Resuscitation, Treatment Failure

Median (95% CI) time to first breath was 1.1 (1.0 to 1.2) minutes and 1.5 (1.4 to 1.6) minutes in the room and oxygen groups, respectively (P = .004), and time to first cry was 1.6 (1.5 to 1.7) minutes in the room air group and 2.0 (1.8 to 2.2) minutes in the oxygen group (P = .006). Median (95% CI) duration of resuscitation was 2.0 minutes in both groups (P = .09); at 30 minutes, 38 infants were on artificial ventilation. Median (95% CI) time to reach SaO₂ of 75% was 1.5 (1.4 to 1.6) minutes in the room air group (n = 103) versus 2.5 (1.9 to 3.1) minutes in the oxygen group (n = 109) (P = .27). At each time point, more room air infants had taken their first breath than O₂ infants (Fig 4). All P values are adjusted for gender, gestational age, and birth weight by Cox regression analysis.

In the room air group, there were 73/284 (25.7%) so-called treatment failures who were switched to oxygen 90 seconds after delivery. However, if the same criteria (bradycardia and/or central cyanosis after 90 seconds) were applied to the oxygen group, the number was 88/295 (29.8%), not significantly different from that for the room air group. These infants had a high mortality both at 7 days (33% vs 28%; NS) and at 28 days of life (41% vs 35%; NS) in the room air and oxygen groups, respectively.

**DISCUSSION**

In this prospective, international multicenter study, we have not been able to verify the hypothesis that room air is superior to 100% oxygen for resuscitation of newborn infants. However, the study indicates that asphyxiated newborn infants can be resuscitated just as well with ambient air as with 100% oxygen. In fact, uncorrected neonatal mortality tended to be lower in the room air group compared with the oxygen group (OR = 0.69; 95 CI = 0.44–1.06). However, when correcting for gender, gestational age, and birth weight, this reduction in mortality was not significant.

The Apgar scores at 1 minute were significantly lower, and the time to first cry and first breath were significantly longer in the oxygen group, compared with the room air-resuscitated group. There also were more infants with low Apgar scores at 1 and 5 minutes of age in the oxygen group, indicating some possible unknown adverse effects by using 100% oxygen for resuscitation.

The theoretic background for this study was based on our findings from the mid-1970s when we demonstrated that the purine metabolite hypoxanthine accumulates in body fluids and tissues during hypoxia. Because hypoxanthine is a potential oxygen radical generator, we suggested that the injury often noted in the posthypoxic reoxygenation period could be caused by an explosive generation of oxygen radicals by the hypoxanthine–xanthine oxidase system. This hypothesis could explain the well known oxygen paradox, a phenomenon describing that injury related to hypoxia occurs, to a large extent, in the reoxygenation period. Because it had been shown in vitro that the amount of oxygen radicals produced by the hypoxanthine–xanthine oxidase system increases with the oxygen concentration as well as with the hypoxanthine concentration, we, therefore, suggested that resuscitation should be performed with...
as low a concentration of supplemental oxygen as possible.12

In a series of experiments in young and newborn pigs that we have performed in recent years to test whether resuscitation can be carried out with room air, we were able to demonstrate that room air resuscitation normalizes blood pressure, acid-base variables, hypoxanthine in plasma and brain microdialysate, cerebral blood flow, and somatosensory evoked potentials as efficiently as resuscitation with 100% O2.14–20 In addition, brain morphologic changes 4 days after the hypoxic insult were similar in both groups of piglets.17

The present study showed a delay in the onset of hypoxic breathing in infants resuscitated with 100% oxygen compared with room air. This could be one explanation for the lower 1-minute Apgar scores found in the oxygen group. Resuscitation with 100% oxygen perhaps may induce lung atelectasis or depress ventilation or other vital functions of the infants. In newborn hypopneic lambs ventilated with 100% oxygen, the minute ventilation already was reduced after 45 seconds compared with room air-ventilated animals;21 thus, it is possible that resuscitation with oxygen depresses ventilation quickly.

It is known from animal and clinical studies in adults that 100% O2 in some circumstances reduces oxygen consumption,22,23 and there are indications that the energy metabolism of the brain might be affected.20,24,25 In premature animals and human infants, an opposite effect has been found because hyperoxia has been shown to increase oxygen consumption.26 In full-term newborn infants at 1 to 2 days of life, it was found that after a few minutes of hyperoxia (100% O2), the work of breathing and the metabolic rate were increased. Immediately after the onset of hyperoxic breathing, there was a decrease in minute ventilation. This response was, however, short-lasting and quickly reversed into an increase in ventilation.26

In one study on adult dogs, a decreased neurologic survival was found when 100% oxygen versus room air was given after cerebral ischemia.27 Furthermore, a reduced cerebral blood flow was detected at 2 hours of age in preterm infants supplemented with 80% oxygen versus room air immediately after birth.28 The brain of the newborn infant may respond differently to 100% oxygen than the brain of adult animals, and whether resuscitation with 100% oxygen might be harmful obviously needs further investigation.

In this study, we found it necessary to use a quasirandomized method of allocating infants to the two treatment groups, namely according to odd or even dates of birth. This was necessary to simplify enrollment in the different centers because delay in resuscitation could be detrimental to the infants. From a statistical point of view, this form of systematic assignment should, however, represent a satisfactory procedure. The use of odd and even dates and related types of allocation has been used previously in a number of other works, many of them studies of emergency procedures.29–33

Nonetheless, because the study was not strictly randomized, an important question when evaluating the significance of the present results is whether the two groups were similar, or if there was evidence of bias. The resuscitation teams at each participating center did its utmost to avoid any bias in the recruitment. For instance, the number of infants included in each group corresponds closely with the number of even and odd dates in the enrollment period. A completely balanced randomization would have resulted in 288 and 321 who were actually enrolled into each group. Also, the similarity in birth weight, gestational age, and severity of as-

### TABLE 4. Blood Gases and Acid Base Status

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Room Air</th>
<th>Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pO2 mm Hg</td>
<td>31 (17)</td>
<td>30 (22)</td>
</tr>
<tr>
<td>pCO2 mm Hg</td>
<td>50 (15)</td>
<td>50 (19)</td>
</tr>
<tr>
<td>pH</td>
<td>7.11 (0.14)</td>
<td>7.12 (0.18)</td>
</tr>
<tr>
<td>BD mmol/L</td>
<td>14.7 (6.1)</td>
<td>14.2 (6.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10 Min</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>pO2 mm Hg</td>
<td>76 (32)</td>
<td>87 (49)</td>
</tr>
<tr>
<td>pCO2 mm Hg</td>
<td>39 (14)</td>
<td>38 (13)</td>
</tr>
<tr>
<td>pH</td>
<td>7.17 (0.11)</td>
<td>7.15 (0.13)</td>
</tr>
<tr>
<td>BD mmol/L</td>
<td>14.0 (5.0)</td>
<td>14.5 (5.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>30 Min</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>pO2 mm Hg</td>
<td>74 (29)</td>
<td>89 (42)</td>
</tr>
<tr>
<td>pCO2 mm Hg</td>
<td>32 (13)</td>
<td>30 (11)</td>
</tr>
<tr>
<td>pH</td>
<td>7.25 (0.10)</td>
<td>7.26 (0.12)</td>
</tr>
<tr>
<td>BD mmol/L</td>
<td>11.2 (5.2)</td>
<td>12.1 (5.8)</td>
</tr>
</tbody>
</table>

*p = .002 compared with room air value.

![Fig 4. Kaplan–Meier plot showing the proportion that had not taken the first breath in room air- and oxygen-resuscitated newborn infants. Time to first breath was significantly longer in the oxygen-resuscitated group compared with the room air-resuscitated group.](image)
phyxia evaluated by acid-base variables in umbilical cord blood of the two groups indicates that there has been no or only minor selection bias. Furthermore, because the study was not blinded, a bias in treatment is possible. For instance, we did not record the ventilation pressure used or the postresuscitation care, thus, differences in handling of the infants in the two groups cannot be ruled out.

The centers from developed countries participating in this study enrolled few patients because of a low number of births and a low incidence of birth asphyxia. Because the mortality in the three European centers was zero in this study, the high mortality in our study therefore reflects the present situation in many developing countries. Therefore, the results of this investigation cannot be extrapolated directly to units with a low mortality. However, we still believe the data also may have important implications for developed countries.

Whether there are differences in long-term neurologic outcome cannot be answered in the present study, but a follow-up investigation of the enrolled infants between 18 and 24 months of age is underway.

In conclusion, this study has not demonstrated significantly improved survival by using room air instead of 100% O2 for newborn resuscitation. However, it indicates that resuscitation of asphyxiated newborn infants can be performed with room air just as efficiently as with 100% O2. Room air-resuscitated newborn infants can be performed with room air just as efficiently as with 100% O2. Room air-resuscitated newborn infants also seem to recover more quickly than do infants resuscitated with 100% oxygen, as assessed by Apgar scores, time to first breath, and time to first cry. Although the present study has some limitations, it represents a first step in the evaluation of newborn resuscitation routines. This study does not justify changes of the present routines in itself; these should not be changed until studies in both developed and developing countries confirm the present results. Nevertheless, this investigation shows that optimal resuscitation routines should be assessed more carefully, perhaps also in developed countries.

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