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ARTICLE

Achievement of Targeted Saturation Values in Extremely Low Gestational Age Neonates Resuscitated With Low or High Oxygen Concentrations: A Prospective, Randomized Trial

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What's Known on This Subject

Research on extremely premature resuscitation has addressed optimal means of ventilation and/or prophylactic use of surfactant. However, the use of different F_{IO_2} levels to initiate resuscitation has been reported only once to date.

What This Study Adds

Resuscitating extremely premature neonates with an initial F_{IO_2} of 30% is as effective as 90% in attaining Sp_{O_2} values of 85%. Oxygen load is reduced and significantly more infants can be ventilated with room air after clinical stabilization.

ABSTRACT

OBJECTIVE. Extremely low gestational age neonates have very low oxygen saturation in utero and an immature antioxidant defense system. Abrupt increases in oxygen saturation after birth may cause oxidative stress. We compared achievement of a targeted oxygen saturation of 85% at 10 minutes of life when resuscitation was initiated with low or high fractions of inspired oxygen and levels were adjusted according to preductal pulse oxygen saturation values.

METHODS. A prospective, randomized, clinical trial was performed in 2 level III neonatal referral units. Patients of ≤28 weeks of gestation who required active resuscitation were randomly assigned to the low-oxygen group (fraction of inspired oxygen: 30%) or the high-oxygen group (fraction of inspired oxygen: 90%). Every 60 to 90 seconds, the fraction of inspired oxygen was increased in 10% steps if bradycardia occurred (<100 beats per minute) or was decreased in similar steps if pulse oxygen saturation reached values of >85%. Preductal pulse oxygen saturation was continuously monitored.

RESULTS. The fraction of inspired oxygen in the low-oxygen group was increased stepwise to 45% and that in the high-oxygen group was reduced to 45% to reach a stable pulse oxygen saturation of ~85% at 5 to 7 minutes in both groups. No differences in oxygen saturation in minute-to-minute registers were found independent of the initial fraction of inspired oxygen used 4 minutes after cord clamping. No differences in mortality rates in the early neonatal period were detected.

CONCLUSIONS. Resuscitation can be safely initiated for extremely low gestational age neonates with a low fraction of inspired oxygen (~30%), which then should be adjusted to the infant's needs, reducing the oxygen load to the neonate.

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00494702).

Key Words
oxygen, resuscitation, pulse oximeter, extremely low gestational age neonate, fetal to neonatal transition

Abbreviations
Sp_{O_2}—arterial oxygen by pulse oximetry
HR—heart rate
CPAP—continuous positive airway pressure
F_{IO_2}—fraction of inspired oxygen

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FETAL PULSE OXYGEN saturation (Sp_{O_2}), as measured with reflectance pulse oximetry, is ~43%,[1] and levels increase in the first minutes after birth to 80% to 90%.[2–4] Transition to the extrauterine environment causes oxidative stress, as shown in both experimental and clinical settings.[5–7] A moderate prooxidant tendency associated with birth is beneficial to the newborn infant, because it contributes to the activation of a number of metabolic pathways.[7,8] During perinatal asphyxia and after resuscitation, however, a burst of reactive oxygen and nitrogen species is generated, overwhelming newborn antioxidant capacity and causing damage to cell structures, enzymes, RNA, and DNA.[9,10] The use of high oxygen concentrations during resuscitation (reperfusion) enhances oxidative stress,[11,12] increases damage to organs,[13] and even increases mortality rates.[14–16] Previous studies showed that the antioxidant defense system matures late in gestation.[17,18] Although prenatal corticosteroid treatment substantially enhances the activity of antioxidant enzymes and glutathione redox cycle enzymes, it seems that corticosteroids are not capable of completely eliminating oxidative stress, especially in extremely low birth weight infants.[19,20] Moreover, it has been

shown that hyperoxia, even for short periods, contributes to the development of oxygen-related diseases such as retinopathy of prematurity and bronchopulmonary dysplasia.[21,22]

Our aim was to demonstrate that it was possible to achieve a target Spo_2 of 85% at 10 minutes after birth as effectively by using a low fraction of inspired oxygen (Fio_2) (30%) as by using a high Fio_2 (90%). In addition, with this approach we could reduce the oxygen load administered in the first and potentially decisive minutes of postnatal life to these infants, who are especially prone to develop oxygen toxicity.

METHODS

Patients

This was a prospective, randomized, clinical trial performed as part of a more-comprehensive study on oxygen toxicity in extremely low gestational age neonates (≤28 weeks of gestation) in 2 level III referral centers, La Fe University Hospital (Valencia, Spain) and University Clinical Hospital San Carlos (Madrid, Spain), during an 18-month period (September 2005 through February 2007). The study protocol was approved by the scientific and ethics committees of both hospitals, and parents signed informed consent forms for each enrolled case. Inclusion criteria were gestational age of ≤28 weeks, inborn in 1 of the 2 maternity hospitals, and in need of active resuscitation in the delivery room. Infants at birth were bradycardic (heart rate [HR]: ≤80 beats per minute), hypotonic or hyporeactive, and unable to sustain active and/or effective respiration. Exclusion criteria were uncertainty about gestational age, severe congenital malformations, and chromosomal abnormalities. As soon as the mothers were admitted to the hospital, informed consent was obtained; immediately before delivery, infants were randomly assigned to the high- or low-oxygen group by using sealed envelopes with random numbers provided by an automatic computer program. Oxygen blenders were set to deliver Fio_2 of 90% for the infants in the high-oxygen group and Fio_2 of 30% for those in the low-oxygen group. We noted previously that initial use of room air frequently (~60%) failed to stabilize adequately extremely premature, low birth weight infants with gestational ages between 24 and 26 weeks. Therefore, we chose to initiate ventilation in the low-oxygen group with 30% Fio_2. Twin deliveries were considered as a unit for the purpose of randomization.

Procedures

Infants were resuscitated by an attending neonatologist, a pediatric resident, and a nurse in most deliveries. The attending neonatologist led the resuscitation procedure and took care of the respiratory airway. The resident followed his or her instructions, evaluated clinical responses, and changed the oxygen blender as requested. The nurse was responsible for Spo_2 monitoring and continuous registration of incidents. Resuscitation procedures followed the standards recommended by the Spanish Neonatal Association but included modifications in the management of Fio_2, as described below.[23,24] All infants were resuscitated in a resuscitation unit equipped with a T-piece resuscitator (Neopuff; Fisher & Paykel, Auckland, New Zealand), which provided the possibility of continuous positive airway pressure (CPAP) or intermittent positive pressure ventilation with end expiratory pressure. Other means of ventilation, such as a self-inflating bag or anesthesia bag, were rarely used.

Immediately after birth, the patient was placed under a radiant heater and underwent brief suctioning while a preductal probe for measuring Spo_2 (Radical pulse oximeter; Masimo, Irvine, CA) was applied to the right wrist by the attending nurse and connected to the pulse oximeter.[25] HR was initially assessed through auscultation; once reliable Spo_2 readings were obtained through pulse oximetry, auscultation was interrupted except during intubation procedures, for assessment of correct endotracheal tube position and adequate cardiac response, or when loss of the pulse oximeter signal was evident. Spo_2 readings were considered reliable when HR findings determined through direct auscultation and given by the pulse oximeter were coincident. To achieve maximal sensitivity, HiFi sensors (Masimo, Irvine, CA) were used with 2-second averaging, as recommended in previous studies.[25] Infants who demonstrated increased work of breathing or respiratory difficulties despite CPAP therapy (initially 4 cm H_2O) were intubated to avoid further deterioration. The decision to intubate was not standardized and was made by the attending staff neonatologist after evaluation of the infant's responses to resuscitation maneuvers. This potential for bias was introduced at the request of the staff neonatologist, because of the difficulty of standardization for any given clinical situation. Spo_2, HR, and temperature were recorded, and incidents such as intubation or drug administration were documented.

The initial Fio_2 in both groups was adjusted (increased or reduced) by 10% every 60 to 90 seconds according to the infant's HR and Spo_2. HR was considered the principal clinical parameter reflecting the effectiveness of resuscitation maneuvers. If HR decreased below 100 beats per minute, then Fio_2 was immediately increased by 10%. Additional changes were performed according to the responses obtained. If HR was within normal values (≥100 beats per minute), however, then we adopted an expectant attitude and did not modify Fio_2 on the basis of Spo_2 alone On the contrary, with HR persistently at ≥100 beats per minute, we relied on Spo_2 values to reduce Fio_2 in a stepwise manner, attempting to keep Spo_2 at 85%. Only in severe situations (persistent bradycardia of ≤60 beats per minute for >30 seconds) was the oxygen blender switched directly to 100% oxygen. When Spo_2 values increased very rapidly to >90%, however, Fio_2 was cautiously reduced every 90 seconds in 10% steps, to avoid acute changes in pulmonary vascular tone. Blood gas samples were taken from cord blood at birth and at the time of admission to the NICU.

TABLE 1 **Characteristics of Low Gestational Age Neonates (≤28 Weeks of Gestation) Resuscitated Initially With Low (30%) or High (90%) FIO_2 in the Delivery Room**

	Low-Oxygen Group ($n = 19$)	High-Oxygen Group ($n = 23$)
Gestational age, mean ± SD, wk	26.4 ± 1.9	26.1 ± 1.5
Birth weight, mean ± SD, g	785 ± 165	824 ± 138
Gender, *n*		
Female	9	10
Male	10	13
Prenatal corticosteroid therapy (full schedule), *n*	16	20
Delivery, *n*		
Vaginal	11	12
Cesarean section	8	11
Cord blood pH at birth, mean ± SD	7.09 ± 1.3	7.12 ± 1.02
Apgar score, median (interquartile range)		
1 min	3 (2–7)	3 (2–7)
5 min	5 (3–7)	6 (3–8)

Statistical Analyses

Descriptive statistics were calculated for all parameters in the study. Statistical analysis was performed in 2 steps. One-way analysis of variance was performed first. When the overall comparison of groups was significant, differences between individual groups were investigated with Tukey's method. Differences were considered to be significant at $P < .05$.

Nonparametric statistics were used to compare nonnormally distributed variables. Therefore, the Mann-Whitney *U* test was used for comparisons of nonpaired samples and the Kruskal-Wallis test was used for paired comparisons. Data obtained across time (proportion of infants receiving room air) were compared by using the log-rank test, which allowed us to obtain a *P* value at each time point and to assess differences between groups.[26] Statistical analyses were performed by using SPSS 11 (SPSS, Chicago, IL).

RESULTS

Characteristics of the Population

Table 1 demonstrates some clinical characteristics of the low-oxygen and high-oxygen groups. Patients recruited represented homogeneous populations. Therefore, no differences in relation to gestational age, birth weight, gender, prenatal corticosteroid therapy, type of delivery, cord pH, or Apgar scores at 1 or 5 minutes were found between the groups.

Ventilatory Support in the Delivery Room

Four infants (21.0%) in the low-oxygen group and 5 (30.4%) in the high-oxygen group required immediate endotracheal intubation to achieve adequate ventilation (Fig 1). In addition, 9 infants in the low-oxygen group and 13 in the high-oxygen group, after initial mask CPAP treatment, were switched to intermittent positive pressure ventilation plus mask. Of those, 5 infants in the low-oxygen group and 7 infants in the high-oxygen group required intubation and mechanical ventilation. Therefore, of a total of 19 infants in the low-oxygen group, 6 (31.5%) were admitted to the NICU with mask CPAP ventilation, 4 (21.0%) with intermittent positive pressure ventilation plus mask, and 9 (47.4%) with intubation and mechanical ventilation. In the high-oxygen group, 5 (21.8%) were admitted to the NICU with mask CPAP ventilation, 6 (26.0%) with intermittent positive pressure ventilation plus mask, and 12 (52.2%) with intubation and mechanical ventilation. No differences were found between the low-oxygen and high-oxygen groups in relation to the type of ventilation administered at delivery and at admission to the NICU. No chest compression, surfactant, or medication was adminis-

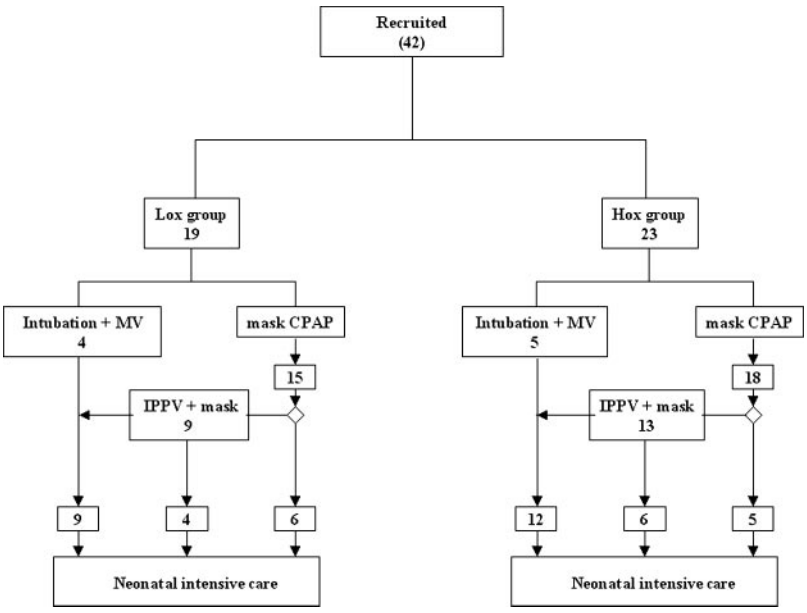

FIGURE 1
Flowchart showing the type of ventilatory support used for extremely low gestational age neonates resuscitated initially with a FIO_2 of 30% (low-oxygen [Lox] group) or 90% (high-oxygen [Hox] group). MV indicates mechanical ventilation; IPPV, intermittent positive pressure ventilation.

TABLE 2 **HR and F_{IO_2} Used to Attain a Target S_{PO_2} of 85% at 10 Minutes After Cord Clamping in Extremely Low Gestational Age Neonates Who Were Resuscitated Initially With Low (30%) or High (90%) F_{IO_2}**

Time	Low-Oxygen Group ($n = 19$)		High-Oxygen Group ($n = 23$)	
	F_{IO_2}	HR, Beats per min	F_{IO_2}	HR, Beats per min
Initial	0.3	85 ± 15	0.9	77 ± 10
2 min	0.38 ± 0.15	119 ± 21	0.86 ± 0.15[a]	106 ± 22
3 min	0.44 ± 0.21	133 ± 14	0.75 ± 0.20[a]	143 ± 15
4 min	0.52 ± 0.16	178 ± 18	0.61 ± 0.18[b]	188 ± 25
5 min	0.55 ± 0.20	163 ± 13	0.52 ± 0.13	168 ± 19
6 min	0.38 ± 0.14	155 ± 22	0.42 ± 0.14	172 ± 27
7 min	0.40 ± 0.18	169 ± 18	0.38 ± 0.07	169 ± 34
8 min	0.36 ± 0.12	171 ± 25	0.34 ± 0.10	158 ± 18
9 min	0.31 ± 0.09	147 ± 15	0.38 ± 0.12	163 ± 12
10 min	0.34 ± 0.11	155 ± 12	0.30 ± 0.08	171 ± 23
15 min	0.32 ± 0.08	161 ± 16	0.34 ± 0.05	167 ± 16

Data are expressed as mean ± SD.
[a] High F_{IO_2} versus low F_{IO_2}, $P < .01$.
[b] High F_{IO_2} versus low F_{IO_2}, $P < .05$.

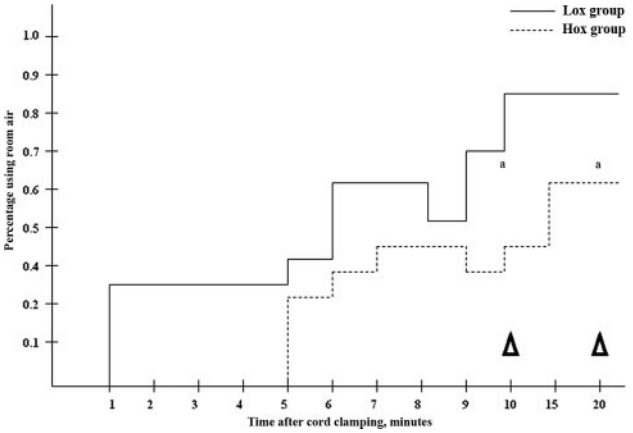

FIGURE 2
Proportions of newborn infants who were ventilated with room air at each time point after delivery in the low-oxygen (Lox) group (initial F_{IO_2}: 30%) and the high-oxygen (Hox) group (initial F_{IO_2}: 90%). The probability of being ventilated with room air (log-rank test) was significantly higher at 10 and 20 minutes (Δ) after birth in the low-oxygen group ([a] $P < .05$).

tered to any infant in the delivery room. In addition, there were no significant differences regarding time to attain clinical stabilization (low-oxygen group: 16.5 ± 0.4 minutes; high-oxygen group: 18.2 ± 0.7 minutes) or body temperature when admitted in the NICU (low-oxygen group: 36.3 ± 0.7°C; high-oxygen group: 36.5 ± 0.4°C).

F_{IO_2} Values

Table 2 shows the timing of F_{IO_2} administered to the 2 groups after cord clamping. In the first 3 minutes after birth, F_{IO_2} in the high-oxygen group was significantly higher than that in the low-oxygen group ($P < .01$). At 4 minutes after birth, differences in F_{IO_2} between the groups were still statistically significant. Thereafter, F_{IO_2} values were not significantly different between the groups for the rest of the trial. No differences regarding HR were found between the groups at any time point. On 3 occasions for the low-oxygen group and on 4 occasions for the high-oxygen group, the oxygen blender was switched directly to 100% oxygen because of persistent bradycardia. Considering an average respiratory rate of 60 breaths per minute and a mean tidal volume of 4 mL/kg, infants in the high-oxygen group received a total of 864.0 mL/kg pure oxygen and those in the low-oxygen group received 465.6 mL/kg pure oxygen. Therefore, the former group received 398.4 mL/kg more oxygen at the end of the resuscitation/stabilization period than did the latter.

Proportions of Infants Ventilated With Room Air

Figure 2 shows the proportions of infants at each time point (minutes after birth) breathing room air in the 2 groups. As shown in Fig 2, the proportion of infants in the low-oxygen group breathing room air was always greater than the proportion in the high-oxygen group. Infants in the low-oxygen group breathing room air represented 42.0% of the total at 5 minutes, 73.7% at 10 minutes, and 84.2% at 15 minutes. In the high-oxygen group, however, room air exposure represented 26.0% at 5 minutes, 43.5% at 10 minutes, and 61.0% at 15 minutes. Comparison of the 2 groups by using the log-rank test showed increased probability of being ventilated with room air at 10 and 20 minutes after birth ($P < .05$) in the low-oxygen group (Fig 2).

S_{PO_2} Values

The times needed to obtain reliable readings from the pulse oximeter were not statistically different between the groups (low-oxygen group: 85.6 ± 28.4 seconds; high-oxygen group: 88.2 ± 30.5 seconds; not significant). Figure 3 shows the evolution of S_{PO_2} values in the 2 groups. Initial S_{PO_2} values in the 2 groups were very similar (low-oxygen group: 45.7 ± 13.5%; high-oxygen group: 48.6 ± 4.7%; not significant). Thereafter, S_{PO_2}

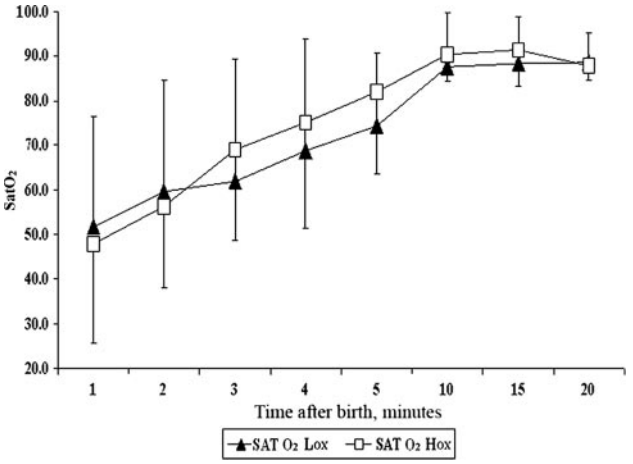

FIGURE 3
S_{PO_2} values in the first 20 minutes after birth in extremely low gestational age neonates randomly assigned to the low-oxygen (Lox) group (initial F_{IO_2} after birth: 30%) or the high-oxygen (Hox) group (initial F_{IO_2} after birth: 90%).

increased in both groups, reaching values of 85.8 ± 5.9% at 5.5 ± 0.7 minutes in the high-oxygen group and 86.2 ± 8.4% at 6.5 ± 1.1 minutes in the low-oxygen group. At 10 minutes after cord clamping, the 2 groups reached similar Spo_2 values (low-oxygen group: 86.9 ± 2.5%; high-oxygen group: 88.7 ± 2.5%; not significant). Moreover, no significant differences were found for Spo_2 between the groups at 20 minutes after birth.

Safety of the Procedure

Although the low-oxygen group attained clinical stabilization (defined as HR of >100 beats per minute, Spo_2 of ≥85%, and good response to stimuli) in the delivery room earlier than the high-oxygen group, differences found were not statistically significant (low-oxygen group: 16.5 ± 0.4 minutes; high-oxygen group: 18.2 ± 0.7 minutes). In addition, no significant differences in body temperature (low-oxygen group: 36.3 ± 0.7°C; high-oxygen group: 36.5 ± 0.4°C) and blood pH (low-oxygen group: 7.18 ± 1.1; high-oxygen group: 7.14 ± 0.9) were found between the groups at admission to the NICU.

Death and Long-Term Complications

No deaths occurred in either group in the neonatal period (<28 days). However, 4 infants in the low-oxygen group and 3 in the high-oxygen group died as a result of respiratory or neurologic complications (intracranial hemorrhage) during hospitalization. Although with the sample size of the present study no significant differences between the groups in the incidence of acute (persistent ductus arteriosus, necrotizing enterocolitis, apneic-bradycardic syndrome, or intraventricular/periventricular hemorrhage) and/or long-term (bronchopulmonary dysplasia, retinopathy of prematurity, or neurosensorial dysfunction) complications were detected at discharge among survivors, there was a tendency toward increased incidence of bronchopulmonary dysplasia ($P < .065$) and retinopathy of prematurity ($P < .069$) in the high-oxygen group at discharge.

DISCUSSION

More than 130 million infants are born every year throughout the world, and it is estimated that, in developing and industrialized countries, asphyxia accounts for 25% of early neonatal deaths.[27] Technologic development, regionalization, and increased competence of intensive care support have been able to reduce early and global neonatal mortality rates.[28] However, it has not been until the past 10 to 15 years that neonatologists have shown interest in critically reviewing non–evidence-based resuscitation procedures that have been used for years.[16,29–36] In addition, we now are aware that interventions for extremely premature infants in the first minutes of life can contribute not only to survival but also to later development.[31,37–39]

In this regard, oxygen administration in the delivery room has become a matter of discussion in the past decade. Different prospective clinical trials have shown that resuscitation can be safely accomplished starting with room air under most circumstances and that the use of pure oxygen may have deleterious effects and increase mortality rates.[10–16] Reactive oxygen species generated through hypoxic reoxygenation are, under normal clinical circumstances, almost totally neutralized by the antioxidant defense system. However, antioxidant enzyme maturation occurs late in gestation, and therefore premature infants are prone to oxidative stress.[20] For resuscitation of infants of extremely low gestational age, it is well known, although little evidence regarding oxygen administration has been published in the literature, that oxygen can be severely damaging to newborn infants and that only a few minutes of hyperoxia can cause protracted oxidative stress.[11] In addition, the use of higher oxygen concentrations, even for short periods, may contribute to the development of bronchopulmonary dysplasia or retinopathy of prematurity.[21,22] The International Liaison Committee on Resuscitation[40] has stated that, although there is insufficient evidence for changing the present practice of using 100% oxygen, special consideration should be used when resuscitating premature infants, because "excessive tissue oxygen may cause oxidant injury and should be avoided, especially in the premature infant." Therefore, we hypothesized that using lower Fio_2 for the resuscitation of extremely low birth weight infants could be effective and contribute to reducing the possible negative consequences of an excess of oxygen. SpO_2 after birth has been studied recently,[2–4] and safe oxygen levels in premature infants have been established at ~85% to 90%.[22,41] Therefore, our aim was to reach a Spo_2 of 85% at 10 minutes after birth while avoiding hyperoxemia, which has been associated with the use of high oxygen concentrations during neonatal resuscitation.[7,12] Although the International Liaison Committee on Resuscitation does not advocate the use of pulse oximetry as a reliable tool for adjusting Fio_2 needs,[40] in previous studies we showed that Spo_2 values are highly predictive of effective neonatal resuscitation, especially if combined with an adequate HR response.[41] In our study, there were no differences between infants resuscitated with low or high oxygen concentrations regarding the time needed to attain the targeted Spo_2. As shown in Fig 2, however, there was a significantly greater probability ($P < .05$) for infants resuscitated with low oxygen levels to be ventilated with room air to maintain adequate Spo_2 once clinical stabilization was achieved. Moreover, infants initially ventilated with 90% Fio_2 received an average of 398.4 mL/kg pure oxygen more in the first 5 minutes of life, compared with those who received 30% Fio_2 as the initial gas admixture. Increasing the number of infants in each group might have made this difference significant. It is important to underscore that little reliable information on "normal" saturation values for very preterm infants is currently available. Most of these infants are immediately ventilated after birth, generally with Fio_2 of >21%; therefore, saturation values do not reflect a physiologic situation. Preductal saturation values of 50% in the first 2 to 3 minutes of life and of 70% at 5 minutes after birth are considered normal.[2–4] Moreover, some premature infants have shown saturation

values of ~30% to 40% with adequate HR during the first 10 minutes of life.[31,34,41–43] Our infants, independent of the F_{IO_2} used, exhibited Spo_2 values within this range and reached targeted Spo_2 value ~10 minutes after cord clamping. We intervened only in cases in which low Spo_2 values were accompanied by marked hypotonia, absence of respiratory effort, and especially persistent bradycardia. Before starting this trial, we were tempted to initiate ventilation in the low-oxygen group with room air. However, it has been shown[42] that initial resuscitation of extremely low gestational age infants (especially with gestational ages between 24 and 26 weeks) with room air leads frequently to failure to achieve clinical stabilization (adequate HR and oxygenation) These results are in agreement with our own previous unpublished experience. It generally has been thought that ventilation with high oxygen concentrations causes pulmonary vasodilation and improvement of myocardial function; however, recent studies have shown that there is no such improvement and even that hyperoxemia may be detrimental and alter pulmonary vasculature responsivity to NO or acetylcholine.[44–47] In our study, we did not see any clinical advantages to the use of higher oxygen concentrations to initiate resuscitation. Both groups maintained adequate Spo_2 values, HRs, and clinical status. Moreover, the needs for additional respiratory therapies were similar in the 2 groups. In future studies, we should monitor preductal and postductal Spo_2 to evaluate shunting in these infants. However, infants who were initially ventilated with higher oxygen concentrations received much more oxygen in total and presumably were at risk for greater oxygen-induced free radical damage, although no differences in early neonatal mortality or neonatal mortality rates were detected.

This study has several limitations. First, the number of infants recruited did not allow us to perform a cohort study with sufficient statistical power. Second, we could have designed this study to reach the targeted Spo_2 of 85% at 15 or 20 minutes after cord clamping, especially for the most premature infants, and this may represent an acceptable end point. Finally, the use of devices to detect exhaled CO_2 (Pedicap; Nellcor Puritan Bennett, Pleasanton, CA), the use of optimal techniques for mask ventilation, and the strict monitoring and limitation of positive pressure are important for future studies. Nonetheless, we conclude that extremely low birth weight infants can be safely resuscitated with an initial F_{IO_2} of 30%. Thereafter, F_{IO_2} should be individually adjusted according to Spo_2 and HR values until stabilization.

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REFERENCES

1. Stiller R, von Mering R, König V, Huch A, Huch R. How well does reflectance pulse oximetry reflect intrapartum fetal acidosis? *Am J Obstet Gynecol.* 2002;186(6):1351–1357
2. Kamlin COF, O'Donnell CPF, Davis PG, Morley CJ. Oxygen saturation in healthy infants immediately after birth. *J Pediatr.* 2006;148(5):585–589
3. Rabi Y, Yee W, Chen SY, Singhal N. Oxygen saturation trends immediately after birth. *J Pediatr.* 2006;148(5):590–594
4. Mariani G, Dik PB, Ezquer A, et al. Pre-ductal and post-ductal O_2 saturation in healthy term neonates after birth. *J Pediatr.* 2007;150(4):418–421
5. Pallardo FV, Sastre J, Asensi M, Rodrigo F, Estrela JM, Viña J. Physiological changes in glutathione metabolism in foetal and newborn rat liver. *Biochem J.* 1991;274(3):891–893
6. Sastre J, Asensi M, Rodrigo F, Pallardó FV, Vento M, Viña J. Antioxidant administration to the mother prevents oxidative stress associated with birth in the neonatal rat. *Life Sci.* 1994; 54(26):2055–2059
7. Vento M, Asensi M, Sastre J, et al. Hyperoxemia caused by resuscitation with pure oxygen may alter intracellular redox status by increasing oxidized glutathione in asphyxiated newly born infants. *Semin Perinatol.* 2002;26(6):406–410
8. Vento M, Sastre J, Martín JA, Lloret A, Miñana JB, Viña J. Cysteine may be an essential amino acid in the premature infant from a functional point of view [in Italian]. *It J Pediatr.* 2002;28(5):352–358
9. Saugstad OD. Hypoxanthine as an indicator of hypoxia: its role in health and disease through free radical production. *Pediatr Res.* 1988;23(2):143–150
10. Saugstad OD. Resuscitation with room air or oxygen supplementation. *Clin Perinatol.* 1998;25(3):741–756
11. Vento M, Asensi M, Sastre J, García-Sala F, Pallardó FV, Viña J. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. *Pediatrics.* 2001;107(4):642–647
12. Vento M, Asensi M, Sastre J, Lloret A, García-Sala F, Viña J. Oxidative stress in asphyxiated term infants resuscitated with 100% oxygen. *J Pediatr.* 2003;142(3):240–246
13. Vento M, Sastre J, Asensi MA, Viña J. Room-air resuscitation causes less damage to heart and kidney than 100% oxygen. *Am J Respir Crit Care Med.* 2005;172(11):1393–1398
14. Saugstad OD, Ramji S, Vento M. Resuscitation of depressed newborn infants with ambient air or pure oxygen: a meta-analysis. *Biol Neonate.* 2005;87(1):27–34
15. Davis PG, Tan A, O'Donnell CPF, Schulze A. Resuscitation of newborn infants with 100% oxygen or air: a systematic review and meta-analysis. *Lancet.* 2004;364(9442):1329–1333
16. Rabi Y, Rabi D, Yee W. Room air resuscitation of the depressed newborn: a systematic review and meta-analysis. *Resuscitation.* 2007;72(3):353–363
17. Chen Y, Whitney PL, Frank L. Comparative responses of premature versus full-term newborn rats to prolonged hyperoxia. *Pediatr Res.* 1994;35(2):233–237
18. Viña J, Vento M, García-Sala F, et al. L-Cysteine and glutathione metabolism are impaired in premature infants due to cystathionase deficiency. *Am J Clin Nutr.* 1995;61(5): 1067–1069
19. Chen Y, Martinez MA, Frank L. Prenatal dexamethasone administration to premature rats exposed to prolonged hyperoxia: a new rat model of pulmonary fibrosis (bronchopulmonary dysplasia). *J Pediatr.* 1997;130(3):409–416
20. Vento M, Escrig R, Sáenz P, et al. Prenatal corticosteroids enhance the antioxidant defense system in extremely premature infants. Presented at the 2006 Pediatric Academic Societies' annual meeting; April 29 to May 2, 2006; San Francisco, CA

21. Saugstad OD. Oxidative stress in the newborn: a 30-year perspective. *Biol Neonate.* 2005;88(3):228–236
22. Deulofeut R, Critz A, Adams-Chapman I, Sola A. Avoiding hyperoxia in infants of <1250 g is associated with improved short- and long-term outcomes. *J Perinatol.* 2006;26(11):700–705
23. Spanish Society for Neonatology, Neonatal Resuscitation Group. *Manual de Reanimación Neonatal [Manual of Neonatal Resuscitation*; in Spanish]. Madrid, Spain: Ergón Editores; 2006
24. Martín-Ancel A, Iriondo Sanz M, Thió Lluch M. Advanced cardiopulmonary resuscitation in the newborn: are there data to justify adopting different protocols for the extremely premature neonate [in Spanish]? *An Pediatr (Barc).* 2007;66(1):1–3
25. O'Donnell CPF, Kamlin COF, Davis PG, Morley CJ. Obtaining pulse oximetry data in neonates: a randomised crossover study of sensor application techniques. *Arch Dis Child Fetal Neonatal Ed.* 2005;90(1):F84–F85
26. Bland JM, Altman DG. The log-rank test. *BMJ.* 2004;328(7447):1073
27. World Health Organization. *Neonatal and Perinatal Mortality: Country, Regional and Global Estimates*. Geneva, Switzerland: World Health Organization; 2006
28. Phibbs CS, Baker LC, Caughey AB, Danielsen B, Schmitt SK, Phibbs RH. Level and volume of neonatal intensive care and mortality in very-low-birth-weight infants. *N Engl J Med.* 2007;356(21):2165–2175
29. O'Donnell CPF, Gibson TA, Davis PG. Pinching, electrocution, ravens' beaks, and positive pressure ventilation: a brief story of neonatal resuscitation. *Arch Dis Child Fetal Neonatal Ed.* 2006;91(5):F369–F373
30. Leone TA, Finer NN. Neonatal resuscitation beyond the basics. *NeoReviews.* 2005;6(4):e177–e183
31. Vanpée M, Walfridsson-Schultz U, Katz-Salomon M, Zupancic JAF, Pursley D. Resuscitation and ventilation strategies for extremely preterm infants: a comparison study between two neonatal centers in Boston and Stockholm. *Acta Paediatr.* 2007;96(1):10–16
32. Aly H, Massaro AN, Patel K, El-Mohandes AAE. Is it safer to intubate premature infants in the delivery room? *Pediatrics.* 2005;115(6):1160–1165
33. Saugstad OD. New guidelines for newborn resuscitation. *Acta Paediatr.* 2007;96(3):333–337
34. Lindner W, Pohlandt F. Oxygenation and ventilation of spontaneously breathing very preterm infants with nasopharyngeal CPAP in the delivery room. *Acta Paediatr.* 2007;96(1):17–22
35. Dawson JA, Davis PG, O'Donnell CP, Kamlin OF, Morley CJ. Free-flow oxygen delivery to newly born infants. *Arch Dis Child Fetal Neonatal Ed.* 2007;92(2):F132–F134
36. Barber CA, Wyckoff MH. Use and efficiency of endotracheal versus intravenous epinephrine during neonatal cardiopulmonary resuscitation in the delivery room. *Pediatrics.* 2006;118(3):1028–1034
37. Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? *Pediatrics.* 2000;105(6):1194–1201
38. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 2001;163(7):1723–1729
39. Markus T, Hansson S, Aner-Wahlin I, et al. Cerebral inflammatory response after fetal asphyxia and hyperoxic resuscitation in newborn sheep. *Pediatr Res.* 2007;62(1):71–77
40. International Liaison Committee on Resuscitation. 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations, part 7: neonatal resuscitation. *Resuscitation.* 2005;67(2–3):293–303
41. Shiao SY, Ou CN. Validation of oxygen saturation monitoring in neonates. *Am J Crit Care.* 2007;16(2):168–178
42. Saugstad OD, Ramji S, Rootwelt T, Vento M. Response to resuscitation of the newborn: early prognostic variables. *Acta Paediatr.* 2005;94(7):890–895
43. Wang CL, Leone TA, Rich W, Finer NN. Room air or oxygen for resuscitation of preterm, very low birthweight (VLBW) neonates. Presented at the 2007 Pediatric Academic Societies' annual meeting; May 5–8, 2007; Toronto, Canada
44. Escrig R, Arruza L, Izquierdo I, et al. Achievement of target saturation in extremely low gestational neonates resuscitated with different oxygen concentrations: a prospective randomized clinical trial. Presented at the 2007 Pediatric Academic Societies' annual meeting; May 5–8, 2007; Toronto, Canada
45. Fugelseth D, Børke WB, Lenes K, Matthews I, Saugstad OD, Thaulow E. Restoration of cardiopulmonary function with 21% versus 100% oxygen after hypoxaemia in newborn pigs. *Arch Dis Child Fetal Neonatal Ed.* 2005;90(3):F229–F234
46. Haase E, Bigam DL, Nakonechny QB, Rayner D, Korbutt G, Cheung PY. Cardiac function, myocardial glutathione, and matrix metalloproteinase-2 levels in hypoxic newborn pigs reoxygenated by 21%, 50% or 100% oxygen. *Shock.* 2005;23(4):383–389
47. Lakshminrusimha R, Rusell JA, Steinhorn RH, et al. Pulmonary arterial contractility in neonatal lambs increases with 100% oxygen resuscitation. *Pediatr Res.* 2006;59(1):137–141
48. Lakshminrusimha R, Rusell JA, Steinhorn RH, et al. Pulmonary hemodynamics in neonatal lambs resuscitated with 21%, 50%, and 100% oxygen. *Pediatr Res.* 2007;62(3):313–318

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