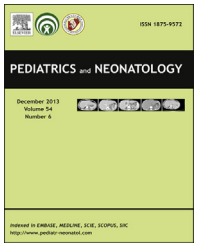
Pediatrics and Neonatology (2013) 54, 373–379

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.pediatr-neonatol.com



ORIGINAL ARTICLE

Efficacy of FiO_2 Increase During the Initial Resuscitation of Premature Infants < 29 Weeks: An Observational Study

Tereza Lamberska [a], **Jana Vaňkova** [b], **Richard Plavka** [a,*]

[a] *Division of Neonatology, Department of Obstetrics and Gynecology, General Faculty Hospital and First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic*
[b] *Department of Bio-Statistics, General Faculty Hospital and First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic*

Received Apr 1, 2013; received in revised form Jun 6, 2013; accepted Jun 29, 2013

Key Words
delivery room;
extremely premature infants;
FiO_2 titration;
ventilatory support

Objective: To evaluate the heart rate (HR) and oxygen saturation (SpO_2) at 15-second intervals within 60 seconds after incremental increases of fractional inspired oxygen (FiO_2) during resuscitation of infants younger than 29 weeks requiring two different forms of ventilatory support.
Study design: Retrospective observational study.
Methods: Forty-three infants were stabilized, 14 by continuous positive airway pressure exclusively (CPAP group), and 29 by positive pressure ventilation (PPV group). Both groups received ventilatory support in a special bed with two cameras enabling the evaluation of all interventions including HR, SpO_2, FiO_2, positive inflation pressure, and positive end-expiratory pressure values. FiO_2 was commenced at 0.30 and titrated in 0.1–0.2 increments every 30–60 seconds. The relationships between the incremental increases of FiO_2 and related SpO_2 and HR changes were evaluated.
Results: Although there was an inverse correlation between initial FiO_2 and SpO_2 in both groups, a significant positive correlation between the incremental increase of FiO_2 and SpO_2 changes after 30 seconds was found only in the CPAP group. Only higher initial levels of FiO_2 had a positive effect on the improvement in SpO_2 in the PPV group.
Conclusion: The efficacy of FiO_2 titration in 0.1–0.2 increments may be attenuated and delayed in extremely preterm infants required PPV during the first 6 minutes of life.

* Corresponding author. Division of Neonatology, Department of Obstetrics and Gynecology, General Faculty, Hospital and First Faculty of Medicine, Charles University in Prague, 18 Apolinarska Street, 128 00 Prague 2, Czech Republic.
E-mail address: richard.plavka@vfn.cz (R. Plavka).

1875-9572/$36
http://dx.doi.org/10.1016/j.pedneo.2013.06.006

1. Introduction

The latest recommendations of the International Liaison Committee on Resuscitation (ILCOR) were expanded to include the use of pulse oximetry during neonatal resuscitation.[1] However, evidence as to the precise management of supplemental oxygen in premature newborns is currently lacking.

Several small, prospective randomized trials confirmed that resuscitation of extremely premature infants (EPI) may be initiated with lower levels of fractional inspired oxygen (FiO_2) between 0.21 and 0.40. [2–4] However, except for one small study reporting a decrease in the incidence of bronchopulmonary dysplasia (BPD) in their low FiO_2 group, there is no evidence favoring these lower FiO_2 values in terms of reduction of adverse long-term outcomes.[5]

Wang et al,[2] Escrig et al,[3] and Rabi et al[4] have shown in randomized trials that it is possible to titrate administration of supplemental oxygen to oxygen saturation measurements in newly born preterm infants. More than 80% of infants initially receiving room air subsequently received supplemental oxygen titrated to attain targeted SpO_2 values.[2,3,6] These cohorts included premature infants stabilized on continuous positive airway pressure (CPAP) as well as those who required positive pressure ventilation (PPV) or intubation in the delivery room.

Oxygen treatment in a newborn will not be effective if the infant's lungs are not aerated, so the primary step is not oxygen treatment but rather the establishment of functional residual capacity. The strategy of oxygen tailoring, as a secondary step to appropriate gradual oxygenation, is based on evidence from small randomized controlled trials[2–4,6] and has been recommended as appropriate by experts in the field of delivery room resuscitation.[7,8] The FiO_2 incremental step of 0.1 every 30–60 seconds being practiced now in ongoing prospective comparative studies such as the premature infants resuscitated with oxygen or air (PRESOX) study and the targeted oxygenation in the resuscitation of premature infants and their developmental outcome (TO2RPIDO) trial. Another study, the room-air versus oxygen administration for resuscitation of preterm infants (ROAR) study, used bigger and quicker FiO_2 increment of 0.2 every 15 seconds to reach a target saturation range.[4] Spontaneously breathing very preterm infants immediately after delivery prolong their expiration by a breath hold to defend lung volume.[9] However, the PPV using the frequencies of 40–60/minute recommended by ILCOR does not allow expiratory braking.[1] This pattern of artificial breathing together with the occurrence of leaks and obstructions may delay uniform lung aeration and establishment of lung volume/alveolar aeration, which may adversely influence the efficacy of supplemental oxygen.[10] There are no clear clinical data that evaluate the efficacy of incremental increases of FiO_2 on the rise of HR and SpO_2, specifically when comparing two very different EPI groups, namely (1) spontaneously breathing on CPAP exclusively, and (2) not spontaneously breathing and requiring PPV. The two different groups would presumably undergo different mechanisms and dynamics in order to establish their functional residual capacity. We undertook this retrospective analysis to test the hypothesis that infants who are not breathing spontaneously and require PPV will respond less well to incremental increases in FiO_2 than those who have established a better FRC by their spontaneous respiratory effort.

2. Objectives

The objectives of this study were to evaluate the HR and SpO_2 changes after incremental increases of FiO_2 in newly born extremely preterm infants receiving CPAP versus infants receiving PPV during the first 6 minutes of life.

3. Patients and methods

This observational study was conducted at the tertiary perinatal center of General Faculty Hospital in Prague, where approximately 4500 infants are delivered and approximately 140 infants <1500 g are admitted into the neonatal intensive care unit annually. In the period from January 2010 to February 2011, delivery room interventions, heart rate, and SpO_2 values were systematically collected from all inborn EPI < 29 weeks to evaluate an internal standardized protocol for resuscitation of EPI. This protocol had been created on a background of current knowledge and evidence. In addition, these prospectively collected data allowed us to analyze our strategy of FiO_2 tailoring retrospectively. All the EPI were placed immediately after delivery onto a specially modified mobile resuscitation warmer bed (ALFAMEDIC sro, Lisov, Czech Republic) with two cameras attached to the frame. One camera recorded all interventions that the patient was receiving on the resuscitaire, whereas the second camera recorded the actual time, pulse oximetry (PO) values, FiO_2, positive inflation pressure (PIP), and positive end-expiratory pressure (PEEP). Using TRAL software sequence analysis made it possible to concurrently evaluate both of the recorded sequences on one screen.[11] All infants were resuscitated according to a standard protocol and algorithm, and were attended by a team of two doctors and two nurses, one of each having a minimum 10 years of neonatal clinical experience.

3.1. Resuscitation procedure

A PO sensor was placed on the right wrist as soon as possible and connected to a PO with a preset 2-second interval (Radical, Masimo, California, USA). Primary settings for the T-piece were as follows: gas flow of 8 L/min, PIP of 26 cmH_2O, and PEEP of 5 cmH_2O. The frequency of PPV in the range of 40–60/minutes was suggested and sustained inflation was not routinely used with the initiation of PPV. CPAP provided by a facemask was given for all infants and PPV via facemask was only initiated if: (1) bradycardia occurred after more than 90 seconds after cord clamping, or (2) spontaneous breathing activity was not sufficient to achieve a target range of SpO_2 after 5 minutes of life. Intubation followed by surfactant administration was indicated when PPV with PEEP was required for more than 6 minutes. FiO_2 was commenced at 0.30 and was subsequently titrated in 0.1–0.20 increments every 30–60 seconds if (1) the preductal SpO_2

value was outside of a defined time-related range (an increasing trend between 60-85% at 2−6 minutes, then between 80−93%), or (2) HR <100/minute persisted for more than 1 minute after the initiation of PPV. If bradycardia <60/minute lasted for more than 30 seconds, a switch to the use of FiO_2 ≥0.80 was suggested.

3.2. Data collection and statistical analysis

All FiO_2 settings, HR and SpO_2 values, and all interventions were assessed and tabulated in 15-second intervals from the collected video recordings of each patient by a single unbiased independent physician who was not involved in the actual resuscitations. All individual incremental increases of FiO_2, performed during the 6 minutes after cord clamping, and the related changes of HR and SpO_2 during the subsequent four 15-second intervals were identified and statistically evaluated in all patients. These data were then compared between the two EPI groups; all infants were divided according to the extent of ventilatory support required: the CPAP group only received CPAP and the PPV group received CPAP and positive pressure inflations. Because the data were collected in 15-second intervals, each incremental increase of FiO_2 (ΔFiO_2^{0-15}) could occur at any time during the 15-second interval (Figure 1). The correlation of the response between the initial HR and SpO_2 values (HR^0 and SpO_2^0) and the resuscitator's adjustment of FiO_2 (FiO_2^{15}) was determined by the Spearman rank correlation and furthermore by the Kruskal-Wallis test. Multiple linear regression and the nonparametric Spearman rank correlation tested the relationship between the ΔFiO_2^{0-15} and HR as well as SpO_2 changes over the next 60 seconds in 15-second intervals ($\Delta HR^{0-15,\ 0-30,\ 0-45,\ 0-60}$; $\Delta SpO_2^{0-15,\ 0-30,\ 0-45,\ 0-60}$) in all infants and in the two groups separately. The nonparametric Mann-Whitney U and Wilcoxon tests were used to compare related changes between the two groups of infants. The Pearson Chi-square test and the Fisher exact test were used for categorical variables. In *post hoc* analysis we used Kruskal-Wallis analysis to test the effect of the extent of ΔFiO_2^{0-15} as well as the initial FiO_2 levels (FiO_2^0) on related changes of $\Delta HR^{0-15,\ 0-30,\ 0-45,\ 0-60}$ and $\Delta SpO_2^{0-15,\ 0-30,\ 0-45,\ 0-60}$.

4. Results

Of the 65 EPIs <29 weeks live-born during the investigational period, 43 EPIs could be enrolled in this study because of different technical difficulties with the extraction of the recorded data: 14 of these were supported by facemask CPAP exclusively, followed by nasal CPAP, and the remaining 29 required PPV (with PEEP) during the first 6 minutes of life. The basic clinical characteristics and delivery room interventions are summarized in Tables 1 and 2. Only 3 of 14 infants (21%) were initially bradycardic <100/minute in the CPAP group, although spontaneous breathing activity was present. In infants requiring PPV, bradycardia <100/minute and/or poor spontaneous breathing activity was the reason for initiation of PPV at the median time (IQR) of 114 seconds (72−150 seconds). In 18 of 29 infants (62%), bradycardia was present in the first clear PO measurement. Within the first 6 minutes of life, 731 measurements of HR as well as SpO_2 in 15-second intervals could be analyzed, 493 in the PPV group and 238 in the CPAP group. Together we found 336 of 731 hypoxemic measurements (46%; below the 10th percentile),[12] 42 of 336 (12%) in the CPAP group and 294/336 (88%) in the PPV group ($p < 0.001$). Only 40 of 731 hyperoxemic measurements (5%; $SpO_2 > 93\%$) were found in all infants, 34 of 40 (85%) in the CPAP group and 6 of 40 (15%) in PPV group ($p < 0.001$).

Seventy-seven incremental increases of FiO_2 were required in 37 of the infants (86%): 26 (34%) were required in 10 infants (71%) in the CPAP group, whereas 27 infants (93%) in the PPV group required 51 incremental increases in FiO_2 (68%). Only seven episodes of a direct switching of FiO_2 to ≥0.80 were identified, all of which were in the PPV group. The characteristics of all incremental increases of FiO_2 and those related to each group are shown in Table 2.

4.1. Interaction between initial HR and SpO_2 values (HR^0, SpO_2^0) and FiO_2 adjustment (FiO_2^{15})

We found a significant negative correlation between SpO_2^0 and FiO_2^{15} values but not between HR^0 and FiO_2^{15} levels in both groups ($r = -0.214$, $p < 0.001$; $r = -0.572$, $p < 0.001$).

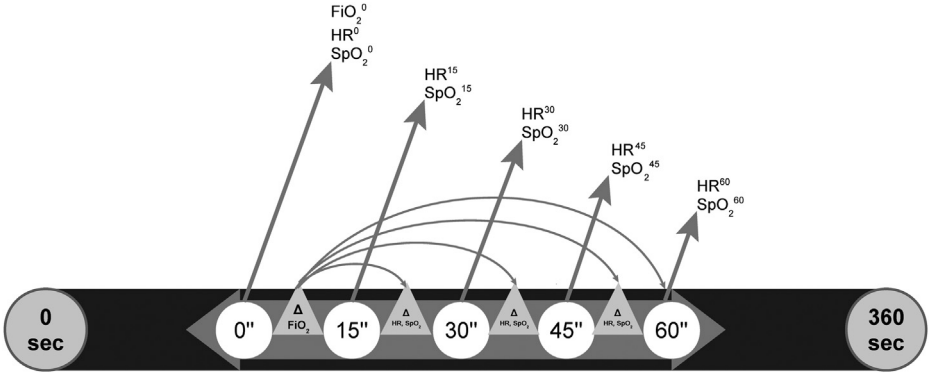


Figure 1 The time labels of HR and SpO_2 values and changes after incremental increases of FiO_2. All incremental increases of FiO_2 were performed at any time during 360 seconds after the cord clamping. Because the data were collected in 15-second intervals, each incremental increase in FiO_2 (ΔFiO_2) could be done at any time during the first 15-second interval. The assigned labels for related values of HR and SpO_2 expressed the real time interval from the time 0 and changes (Δ) in HR and SpO_2 are labeled by time intervals between were calculated. FiO_2 = fractional inspired oxygen; HR = heart rate; SpO_2 = oxygen saturation.

Table 1 Characteristics of infants.

	All infants ($n = 43$)	CPAP group ($n = 14$)	PPV group ($n = 29$)
Gestational age, mean (SD), wk	26.6 (1.8)	27.5 (0.7)[a]	26.1 (1.9)*
Birthweight, mean (SD), g	815 (240)	863 (236)	793 (238)
Male	14 (33)	4 (29)	10 (34)
Full course of antenatal steroids	22 (51)	10 (71)	12 (41)**
Cesarean section	36 (84)	13 (93)	23 (79)
General anesthesia	20 (47)	5 (36)	15 (52)
Placental transfusion (milking)	19 (44)	5 (36)	14 (48)
Multiple birth	12 (28)	2 (14)	10 (34)
Died before discharge	5 (12)	0	5 (17)
Apgar score at 1 min	5 (4–6)	7 (6–8)	4 (2–6)*
Apgar score at 5 min	6 (5–8)	9 (8–9)	6 (5–7)*
HR at 5 min, bpm	135 (122–152)	147 (135–156)	132 (103–149)*
SpO_2 at 5 min, %	75 (49–85)	87 (78–92)	57 (41–77)*
Time of HR $\geq$ 120 bpm achievement, sec	150 (97–277)	105 (90–142)	225 (120–315)*
Time of $SpO_2 \geq 80\%$ achivement, sec	390 (247–555)	225 (165–277)	420 (330–660)*

Data are presented as *n* (%) or median (IQR), unless otherwise indicated.
*$p < 0.01$, Mann-Whitney U test.
**$p = 0.064, \chi^2$ test.
Bpm = beats per minute; HR = heart rate; IQR = interquartile range; SD = standard deviation; SpO_2 = saturation of oxygen.

Furthermore, the Kruskal-Wallis analysis confirmed that the lower the SpO_2^0 values, the higher the FiO_2^{15} level *s* used in both groups ($p < 0.001$). This was not true for the different values of HR^0 and related levels of FiO_2^{15}.

4.2. Correlation between the incremental increases in FiO_2 (ΔFiO_2^{0-15}) and the subsequent HR and SpO_2 changes in 15-second intervals ($\Delta HR^{0-15,\ 0-30,\ 0-45,\ 0-60}$ and $\Delta SpO_2^{0-15,\ 0-30,\ 0-45,\ 0-60}$)

No significant correlation was found between all ΔFiO_2^{0-15} and the subsequent $\Delta HR^{0-15,\ 0-30,\ 0-45,\ 0-60}$ and $\Delta SpO_2^{0-15,\ 0-30,\ 0-45,\ 0-60}$ in all infants by Spearman rank correlation test. When the relationships were correlated for each group separately, a significant correlation between the ΔFiO_2^{0-15} and ΔSpO_2^{0-45} as well as ΔSpO_2^{0-60} was found only in the CPAP group ($r = 0.41$ and $r = 0.51$, respectively, $p < 0.05$).

4.3. FiO_2 levels prior to and after incremental increases of FiO_2 ($FiO_2^{0,\ 15,\ 30,\ 45,\ 60}$) and related values of heart rate and saturation of oxygen in 15-second intervals ($HR^{0,\ 15,\ 30,\ 45,\ 60}$; $SpO_2^{0,\ 15,\ 30,\ 45,\ 60}$)

Significantly higher $FiO_2^{0,\ 15,\ 30,\ 45,\ 60}$ levels were administered in the PPV group and lower related values of $HR^{0,\ 15,\ 30,\ 45,\ 60}$ and $SpO_2^{0,\ 15,\ 30,\ 45,\ 60}$ were found at each time point ($p < 0.01$). The mean [Standard Deviation (SD)] FiO_2^{15} level was significantly higher than mean (SD) FiO_2^0 in both groups [0.31 (0.11) vs. 0.42 (0.15), $p < 0.01$; 0.40 (0.15) vs. 0.55 (0.18), $p < 0.001$]; however, only average (SD) SpO_2^{45} and SpO_2^{60} values in the CPAP group were significantly higher in comparison with SpO_2^0 [56% (18) vs. SpO_2^{45} 68% (17), and SpO_2^{60} 72% (16), $p < 0.01$; Figure 2. The significance of differences between the CPAP and the PPV groups in extent of incremental increases of FiO_2 and related changes of HR and SpO_2 are summarized in Table 3.

4.4. *Post hoc* analysis in PPV group

Despite the nonsignificant correlation between the ΔFiO_2^{0-15} and related $\Delta HR^{0-15,\ 0-30,\ 0-45,\ 0-60}$ and $\Delta SpO_2^{0-15,\ 0-30,\ 0-45,\ 0-60}$ that was found in the group of infants supported by PPV, further Kruskal-Wallis analysis was completed to test if any independent variables such as the extent of ΔFiO_2^{0-15} and the initial levels of FiO_2^0, HR^0, or SpO_2^0 may have had a positive effect on the $\Delta HR^{0-15,\ 0-30,\ 0-45,\ 0-60}$ and $\Delta SpO_2^{0-15,\ 0-30,\ 0-45,\ 0-60}$ as the dependent variables. The significances between those relations are introduced in Table 3. The lower HR^0 and SpO_2^0 values increased significantly ($p = 0.007$ and $p = 0.002$) more than values closer to normal, but without any relation to the FiO_2^0 level or to the extent of the incremental increase of FiO_2. Higher FiO_2^0 level tested from mean (SD) level from 0.30 (0.00) to 0.62 (0.08) had a significant positive effect on SpO_2 rise ($p = 0.002$) and this initial dose-dependent effect was also positively time-related ($p = 0.010$). Larger ΔFiO_2^{0-15} tested from mean (SD) level of 0.05 (0.08) up to 0.37 (0.08) had a borderline significance on a positive rise of SpO_2 ($p = 0.049$).

5. Discussion

During the transition from placental to lung breathing the establishment and the maintenance of alveolar expansion is the first step to oxygenation. This is a dynamic process following delivery and may be influenced by intrinsic variables such as lung maturation, prenatal infection, and the level of spontaneous breathing activity, as well as by extrinsic variables such as the level of the resuscitator's skill, iatrogenic airway obstruction, and mask leak.

This observational study shows the different efficacy of incremental increases in FiO_2 in the two groups of extremely preterm infants with different levels of

Table 2 Delivery room interventions.

	All infants (n = 43)	CPAP group (n = 14)	PPV group (n = 29)	p
Time to first PO data	87 (70–110)	85 (74–101)	95 (70–162)	0.218
CPAP start sec postpartum	72 (50–98)	94 (64–120)	65 (47–90)	0.157
PPV start sec postpartum	114 (72–150)	0	114 (72–150)	
PPV end sec postpartum	339 (250–414)	0	339 (250–414)	
Sustained inflation maneuver	5 (12)	0	5 (17)	0.272
Intubation in DR	15 (35)	0	15 (52)	0.003
Intubation start sec postpartum, sec	378 (348–389)	0	378 (348–389)	
Intubation end sec postpartum	450 (444–759)	0	450 (444–759)	
Surfactant administered in DR	15 (35)	0	15 (35)	0.003
Time of surfactant administration, sec	713 (523–881)	0	713 (523–881)	
Infants with FiO_2 1.0	4 (9)	0	4 (14)	0.319
Infants with incremental increases of FiO_2	37(86)	10 (71)	27 (93)	0.074
Incremental increases of FiO_2, n	77	26	51	0.185
FiO_2 level before incremental increase, mean (SD)	0.37 (0.16)	0.31 (0.11)	0.40 (0.15)	0.009
FiO_2 level after incremental increase, mean (SD)	0.51 (0.20)	0.42 (0.15)	0.55 (0.18)	0.006
Time of FiO_2 incremental increases, sec	195 (145–259)	165 (120–255)	195 (150–270)	0.001

Data are presented as n (%) or median (IQR), unless otherwise indicated.
CPAP = continuous positive airway pressure; DR = delivery room; FiO_2 = fractional inspiratory oxygen; IQR = interquartile range; p = Mann-Whitney U test; PO = pulse dosimeter; PPV = positive pressure ventilation.

spontaneous breathing activity requiring a different extent of ventilatory support to establish their functional residual capacity during the first 6 minutes of life.

We found that the incremental increases of FiO_2 had a significant effect on the improvement in SpO_2 within 45 seconds when the infants were breathing spontaneously on facemask CPAP only. In this group of infants, 18% (42 of 238) of the 15-second interval measurements of SpO_2 were below the 10th percentile and 14% (34 of 238) of measurements had $SpO_2 > 93\%$. Nearly 70% of the measurements of SpO_2 were within target range (the 25th–75th percentile of SpO_2 nomogram) during the first 6 minutes of life.[12] Interestingly, in this small CPAP group of extremely premature infants, the medians and IQRs of HR and SpO_2 at 5 minutes correspond very closely to the reference ranges according to Dawson et al[12] [147 beats per minute (bpm); (135–156) vs. 156 (142–171); 87% (78–92) vs. 86% (80–92)], where 468 neonates with gestational ages from 25 weeks to 42 weeks (only 24% of preterm infants <32 weeks) without any DR interventions were recruited. In a recently published study, Vento et al[13] showed that well-adapted spontaneously breathing very preterm infants can be managed with CPAP via facemask with air and achieve the SpO_2 reference ranges of Dawson et al's[12] nomograms even earlier. Spontaneously breathing very preterm infants prolong their expiration by braking their expiratory flow against a closed or narrowed glottis and thus increase intrapulmonary pressure above atmospheric pressure. This biological force facilitates the clearing of fluid from the lung, resulting in better distribution of gas and opening of the alveoli.[9] This finding is consistent with the good SpO_2 response after incremental FiO_2 increases in our CPAP group. Despite the small sample size of our CPAP group, we think that a certain proportion of extremely premature infants with some spontaneous breathing effort can also be safely managed by CPAP via mask during the first minutes of life with effective gentle tailoring of FiO_2 and achieve the same reference ranges of oxygen saturation as the more mature infants.

The incremental increases of FiO_2 did not, however, increase either SpO_2 or HR values significantly in the infants who had poor spontaneous breathing activity requiring PPV despite the higher mean level of FiO_2 prior to incremental increase to an even larger extent. These differences in FiO_2 tailoring could be explained by mostly larger incremental increases of FiO_2 performed by specialists in the recommended range of 0.1–0.2 (14% of them were identified as the direct switches to $FiO_2 \geq 0.8$). The longer median time of mean FiO_2 incremental increases in PPV group corresponds well with the chronological order of our interventions described in resuscitation procedure. First, CPAP via mask was switched to PPV and then the first incremental increase of FiO_2 followed if bradycardia persisted. In this group of infants, 60% (294 of 493) of the SpO_2 measurements were below the 10^{th} percentile during the first 6 minutes of life.[12] These infants did not respond well to facemask PPV managed by our specialists and finally 41% of them required intubation at the median time (IQR) of 378 (348–389) seconds after delivery. They were significantly more immature, had a lower rate of full antenatal steroid treatment, and had lower Apgar scores at the 1st minute and 5th minute.

In a *post hoc* analysis the larger extent of the incremental increases of FiO_2 was found effective in improving oxygenation with a borderline significance, but when higher initial levels of FiO_2 were used the significantly larger SpO_2 changes were found. This dose-related effect of the initial level of FiO_2 is also time-related and the synergic effect of a higher dose of oxygen and advanced lung aeration may play a role in better oxygenation. These findings correspond well with the significantly longer time needed to achieve stable HR and SpO_2 in this group of EPI. The PPV using

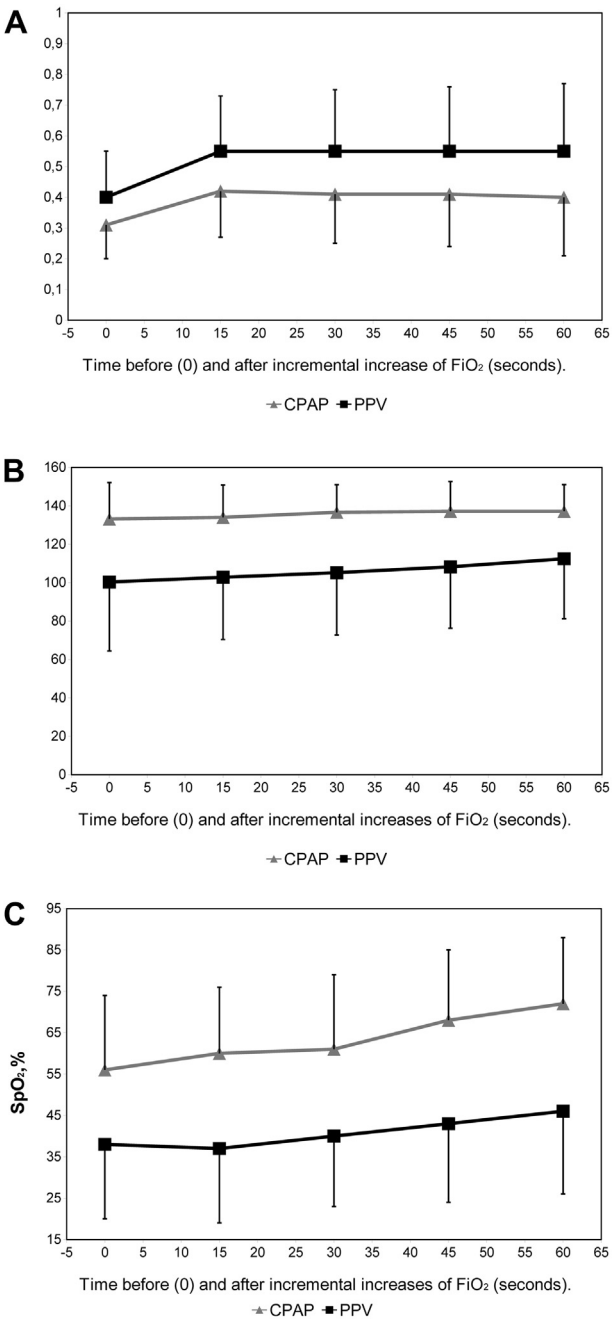


Figure 2 Initial FiO_2 levels prior to and after incremental increases of FiO_2 and related HR and SpO_2 values at each time point within 1 minute in both groups. **(A)** Values of $FiO_2^{0,\ 15,\ 30,\ 45,\ 60}$ in the CPAP group (triangles) and in the PPV group (squares); **(B)** related $HR^{0,\ 15,\ 30,\ 45,\ 60}$ and **(C)** $SpO_2^{0,\ 15,\ 30,\ 45,\ 60}$ values. Mann-Whitney U testing found significant differences between the two groups in independent and both dependent variables at each time point of investigation ($p < 0.01$). The values are mean with standard deviations. CPAP = continuous positive airway pressure; FiO_2 = fractional inspired oxygen; HR = heart rate; PPV = positive pressure ventilation; SpO_2 = oxygen saturation.

Table 3 Significance of differences between continuous positive airway pressure and positive pressure ventilation groups in extents (Δ) of incremental increases of fractional inspired oxygen and related changes (Δ) of heart rate and saturation of oxygen during investigational period (Mann-Whitney U test).*

	15″	30″	45″	60″	0—60″
ΔFiO_2	**0.019**	0.455	0.280	0.195	**0.007**
ΔHR, bpm	0.233	0.120	**0.021**	0.095	0.140
ΔSpO_2, %	0.175	0.490	**0.010**	0.499	**0.011**

Bpm = beats per minute; FiO_2 = fractional inspired oxygen; HR = heart rate; SpO_2 = oxygen saturation.

* Although significantly higher incremental increases in FiO_2 were performed in the positive pressure ventilation (PPV) group, the significantly higher changes in SpO_2 were found in the continuous positive airway pressure group, which was mainly recognized between 30-second and 45-second intervals after FiO_2 increase. In the same time interval, the HR changes were significantly higher in the PPV group but it was not confirmed during the entire investigational period.

frequencies of 40—60/minute recommended by ILCOR does not allow expiratory braking as spontaneous breathing.[1] Manual inflations were performed mostly with a short inflation time, sometimes interrupted by repositioning of the facemask, thereby losing PEEP. The T-piece device was used without changes in the preset pressure and a crossover to self-inflating bag ventilation was not practiced during the first 6 minutes of life. This pattern of artificial breathing together with the common occurrence of leaks and obstructions may delay uniform lung aeration and the establishment of lung volume, which may adversely influence the efficacy of supplemental oxygen.[10] Fuchs et al[14] have shown that a sustained inflation can increase HR rapidly and SpO_2 with slight delay in apneic infants. However, infants in our study did not routinely receive a sustained inflation. Three of five patients increased their HR within 1 minute after one unrepeated 10-second inflation of 25 cmH_2O.

There are several limitations to this study. The infants in the PPV group were more immature, smaller, and sicker and their lungs might have been less developed than those in the CPAP group and required more ventilatory support with poor response to the incremental increases of FiO_2.

The observational retrospective design of this study does not allow identification of the precise time of incremental increases in FiO_2 performed during the 15-second interval. That means that each incremental increase of FiO_2 could have occurred anytime during this 15-second interval and the subsequent HR and SpO_2 changes are related to this 15-second interval and not to the actual time of the FiO_2 increase. We think that the 45—60-second interval should be long enough for the final evaluation of the effect of oxygen changes. Vento et al[5] and Dawson et al[6] considered an interval of at least 30 seconds to be adequate for the evaluation of the potential effect of oxygen changes. It corresponds well with the 30—45-second time interval during which the first significant related changes of SpO_2 were found in our infants who responded well in our CPAP group.

Furthermore, because obstruction and leak episodes were not measured in our study, we cannot comment on

whether the attenuated effect of the oxygen increases was caused primarily by the delayed aeration of the lungs in the poorly spontaneously breathing infants or due to the effects of such obstructions and/or leaks.

Another limitation is that PPV was only initiated if bradycardia was present after 90 seconds or target saturations were not reached by 5 minutes. It is possible that earlier initiation of PPV in infants with marginal respiratory effort might be more effective in establishing functional residual capacity and might lead to a better response to incremental increase of FiO_2.

In conclusion, spontaneous breathing, supported by continuous distending pressure, appears to be the best condition for adequate lung aeration resulting in gradual improvement of oxygenation. These infants can be managed effectively by "gentle" tailoring of FiO_2 in increments of 0.1—0.2 in 30—45-second intervals.

However, when PPV was required in more immature infants who were not initially spontaneously breathing, a much higher incremental increase in FiO_2 was required to improve oxygenation.

Establishment of adequate functional residual capacity should be the primary aim during the first minutes of life in extremely premature infants. The technique of facemask positive pressure ventilation used in this study, which is based on the last ILCOR recommendation, did not achieve adequate lung volume recruitment. Further studies are required in order to determine best ways of lung volume recruitment in infants lacking spontaneous respiratory effort and to accurately guide the administration of FiO_2 during the resuscitation of extremely preterm infants based on the degree of spontaneous respiratory activity.

References

1. Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, et al. Neonatal Resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Pediatrics* 2010;**126**:e1319—44.
2. Wang CL, Anderson C, Leone TA, Rich W, Govindaswami B, Finer NN. Resuscitation of preterm neonates by using room air or 100% oxygen. *Pediatrics* 2008;**121**:1083—9.
3. Escrig R, Arruza L, Izquierdo I, Villar G, Sáenz P, Gimeno A, et al. Achievement of targeted saturation values in extremely low gestational age neonates resuscitated with low or high oxygen concentrations: a prospective, randomized trial. *Pediatrics* 2008;**121**:875—81.
4. Rabi Y, Singhal N, Nettel-Aguirre A. Room-air versus oxygen administration for resuscitation of preterm infants: the ROAR study. *Pediatrics* 2011;**128**:e374—81.
5. Vento M, Moro M, Escrig R, Arruza L, Villar G, Izquierdo I, et al. Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. *Pediatrics* 2009;**124**:e439—49.
6. Dawson JA, Kamlin CO, Wong C, te Pas AB, O'Donnell CP, Donath SM, et al. Oxygen saturation and heart rate during delivery room resuscitation of infants <30 weeks' gestation with air or 100% oxygen. *Arch Dis Child Fetal Neonatal Ed* 2009;**94**:F87—91.
7. Finer N, Saugstad O, Vento M, Barrington K, Davis P, Duara S, et al. Use of oxygen for resuscitation of the extremely low birth weight infant. *Pediatrics* 2010;**125**:389—91.
8. Vento M. Tailoring oxygen needs of extremely low birth weight infants in the delivery room. *Neonatology* 2011;**99**:342—8.
9. te Pas AB, Davis PG, Kamlin CO, Dawson J, O'Donnell CP, Morley CJ. Spontaneous breathing patterns of very preterm infants treated with continuous positive airway pressure at birth. *Pediatr Res* 2008;**64**:281—5.
10. Schmölzer GM, Dawson JA, Kamlin CO, O'Donnell CP, Morley CJ, Davis PG. Airway obstruction and gas leak during mask ventilation of preterm infants in the delivery room. *Arch Dis Child Fetal Neonatal Ed* 2011;**96**:F254—7.
11. *Digital video recorders of Tral 3 series - Product information*. SMP Group Ltd.; 2006—09. Available at: http://www.smp-group.com/product-tral3.html. Accessed September 23, 2013.
12. Dawson JA, Kamlin CO, Vento M, Wong C, Cole TJ, Donath SM, et al. Defining the reference range for oxygen saturation for infants after birth. *Pediatrics* 2010;**125**:e1340—7.
13. Vento M, Cubells E, Escobar JJ, Escrig R, Aguar M, Brugada M, et al. Oxygen saturation after birth in preterm infants treated with continuous positive airway pressure and air: assessment of gender differences and comparison with a published nomogram. *Arch Dis Child Fetal Neonatal Ed* 2013;**98**:F228—32.
14. Fuchs H, Lindner W, Buschko A, Trischberger T, Schmid M, Hummler HD. Cerebral oxygenation in very low birth weight infants supported with sustained lung inflations after birth. *Pediatr Res* 2011;**70**:176—80.