

Neonatal resuscitation adhering to oxygen saturation guidelines in asphyxiated lambs with meconium aspiration

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BACKGROUND: The Neonatal Resuscitation Program (NRP) recommends upper and lower limits of preductal saturations (SpO₂) extrapolated from studies in infants resuscitated in room air. These limits have not been validated in asphyxia and lung disease.

METHODS: Seven control term lambs delivered by cesarean section were ventilated with 21% O₂. Thirty lambs with asphyxia with meconium aspiration were randomly assigned to resuscitation with 21% O₂ ($n = 6$), 100% O₂ ($n = 6$), or initiation with 21% O₂ followed by variable FIO₂ to maintain NRP target SpO₂ ranges ($n = 18$). Hemodynamic and ventilation parameters were recorded for 15 min.

RESULTS: Control lambs maintained preductal SpO₂ near the lower limit of NRP target range. Asphyxiated lambs had low SpO₂ ($38 \pm 2\%$), low arterial pH (6.99 ± 0.01), and high PaCO₂ (96 ± 7 mm Hg) at birth. Resuscitation with 21% O₂ resulted in SpO₂ values below the target range with low pulmonary blood flow (Qp) compared to variable FIO₂ group. The increase in PaO₂ and Qp with variable FIO₂ resuscitation was similar to control lambs.

CONCLUSION: Maintaining SpO₂ as recommended by NRP by actively adjusting inspired O₂ leads to effective oxygenation and higher Qp in asphyxiated lambs with lung disease. Our findings support the current NRP SpO₂ guidelines for O₂ supplementation during resuscitation of an asphyxiated neonate.

The use of 100% oxygen was routine during resuscitation of newly born infants (1) prior to the 2010 Neonatal Resuscitation Program (NRP) guidelines (2–4). Pulse oximetry studies of healthy term and preterm infants who did not require resuscitation at birth demonstrated that preductal oxygen saturation (SpO₂) is ~60% at birth and takes 5–10 min to reach 85–90% (5). The percentiles of SpO₂ at each minute of life have been identified and the goal saturation range has been approximately defined as interquartile ranges for healthy term infants (3). Current guidelines recommend starting resuscitation with 21% oxygen in term infants. Oxygen supplementation is then guided by preductal SpO₂ and adjusted to maintain

SpO₂ values in the goal saturation range at the corresponding minute of postnatal life (3,6,7).

However, it is important to recognize that infants with asphyxia or lung disease who needed resuscitation were excluded from these studies. Asphyxia results in hypoxemia and acidosis (8) resulting in lower SpO₂ values at the time of birth (9). Furthermore, in the presence of lung disease (such as meconium aspiration) and increased alveolar–arterial oxygen gradient, 21% inspired oxygen may not be sufficient to achieve the target SpO₂ values recommended by the NRP. Also, the combination of asphyxia and lung disease predisposes infants to persistent pulmonary hypertension of the newborn (10) that can lead to intra- and extrapulmonary right-to-left shunting of blood, further decreasing SpO₂ (11). The effect of maintaining preductal SpO₂ in the reference goal range recommended by the NRP on hemodynamics and gas exchange in the presence of perinatal asphyxia and lung disease is not known. Controversy remains as to whether a lower percentile SpO₂ target (that can potentially be achieved with 21% inspired oxygen) might be as effective and potentially safer in asphyxiated neonates (12).

The aim of our study was to evaluate gas exchange and pulmonary/cerebral hemodynamics during resuscitation in an ovine model of perinatal asphyxia (induced by umbilical cord occlusion) and lung disease (through instillation of meconium through the endotracheal tube) (9) adhering to the current NRP oxygen saturation target guidelines. We compared these results with lambs resuscitated with 21 and 100% inspired oxygen. We hypothesize that adjusting inspired oxygen to achieve goal NRP SpO₂ range in asphyxiated lambs with lung disease and persistent pulmonary hypertension of the newborn will result in hemodynamics and gas exchange similar to that observed in control lambs (without asphyxia or lung disease) ventilated with 21% O₂ at birth.

RESULTS

Thirty lambs were randomized, instrumented, asphyxiated, and delivered. Eighteen lambs were randomized to the variable FIO₂ group to keep preductal SpO₂ between 60 and 85% for the first 15 min after birth and six lambs each were randomized to

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receive inspired oxygen of 100 or 21% irrespective of SpO₂. To generate control data, seven healthy term lambs were ventilated with 21% O₂. Gestational age, birth weight, and gender distribution were similar among the groups. None of the animals required chest compressions or epinephrine. The gender distribution was equal (15 male and 15 female lambs) and no significant hemodynamic or gas exchange differences were observed between the genders.

Oxygenation

Asphyxia by umbilical cord occlusion resulted in a significant decrease in preductal SpO₂ compared to the control group (38 ± 2 vs. 53 ± 1.4%, respectively). Control lambs ventilated with 21% O₂ maintained preductal SpO₂ in the target range recommended by NRP (Figure 1). Asphyxiated lambs randomized to 21 and 100% inspired oxygen had SpO₂ values below and above the NRP target range, respectively. By design, asphyxiated lambs ventilated with variable FIO₂ maintained their SpO₂ values within the target range (Figure 1) but this required frequent titration of FIO₂ (Figure 2). Baseline fetal oxygen was similar in all the groups (23 ± 8 mm Hg). However, after meconium instillation and cord occlusion, the PaO₂ dropped significantly in asphyxiated lambs (15 ± 12 mm Hg) but improved with resuscitation and positive pressure ventilation (Figure 3a). The lambs that were ventilated with 100% inspired oxygen had significantly higher PaO₂ from birth until 15 min when compared to the other three groups (Figure 3a).

Arterial pH

Predelivery arterial pH was lower in the three asphyxiated groups (6.99 ± 0.01) when compared to controls (7.29 ± 0.09).

Asphyxiated lambs ventilated with 100% inspired O₂ had significantly higher pH throughout the 15 min of resuscitation when compared to the lambs ventilated with variable FIO₂ (Figure 3b). However, there was no difference in the base deficit between the two asphyxiated groups (-6 ± 3.8 in 100% inspired oxygen vs. -7.9 ± 2 in variable FIO₂).

Ventilation

Predelivery PaCO₂ was similar in the three asphyxiated groups (96 ± 7 mm Hg) at the onset of ventilation and was significantly higher than controls (56 ± 9.5 mm Hg). No significant difference was noted in PaCO₂ among asphyxiated lambs (Figure 3c). There was no difference between the ventilator rate and mean airway pressures among the three asphyxiated groups.

Systemic Hemodynamics

Baseline heart rate (HR) was similar among all the groups (154 ± 23/min) but umbilical cord occlusion caused significant bradycardia in the three asphyxiated groups (83 ± 37/min). With resuscitation by positive pressure ventilation, the HR for the first 15 min was similar between the asphyxiated lambs ventilated with variable FIO₂ and controls (Figure 4). Baseline fetal mean systemic blood pressure was similar among all the groups (47 ± 2.7 mm Hg). Mean systemic blood pressure in the three asphyxiated groups (52 ± 4.7 mm Hg) was significantly lower than the controls (71 ± 16.2 mm Hg) over the period of 15 min (Figure 5a). Left carotid blood flow was similar among all the groups (23.6 ± 2.27 ml/kg/min in asphyxiated group vs. 26.3 ± 2 ml/kg/min in controls) (Figure 6a).

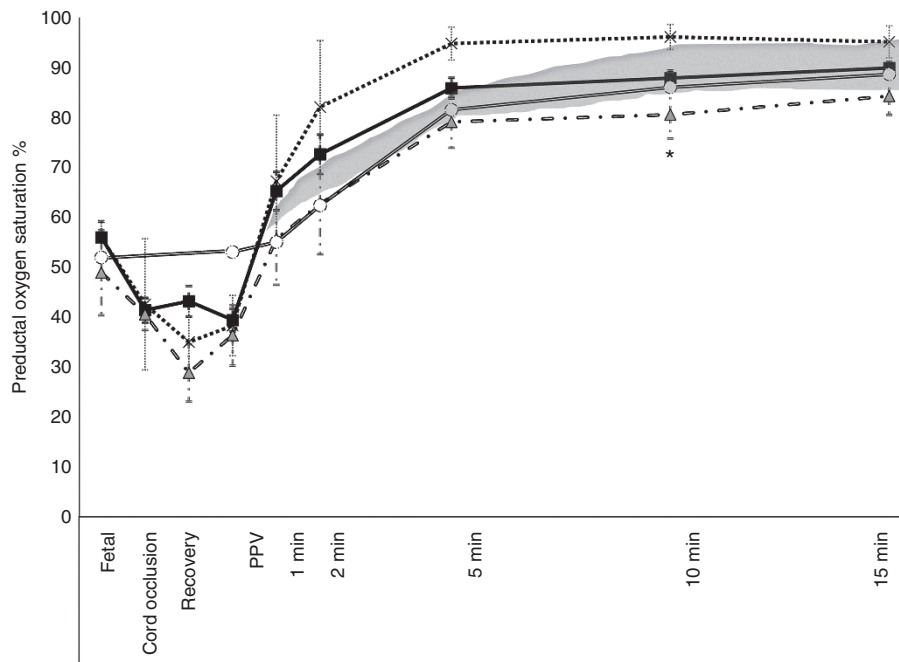


Figure 1. Changes in preductal oxygen saturation (SpO₂) during fetal life and the first 15 min of postnatal age in control lambs (open circle) and asphyxiated term lambs ventilated with 21% O₂ (gray triangle), 100% O₂ (cross), and inspired oxygen (FIO₂) titrated to keep the SpO₂ as per Neonatal Resuscitation Program (NRP) guidelines (black square). The shaded area represents the oxygen saturation range recommended by NRP. *P < 0.05 at 10 min time point by ANOVA (21% asphyxia and 100% asphyxia significantly different by Bonferroni post hoc test). PPV, positive pressure ventilation.

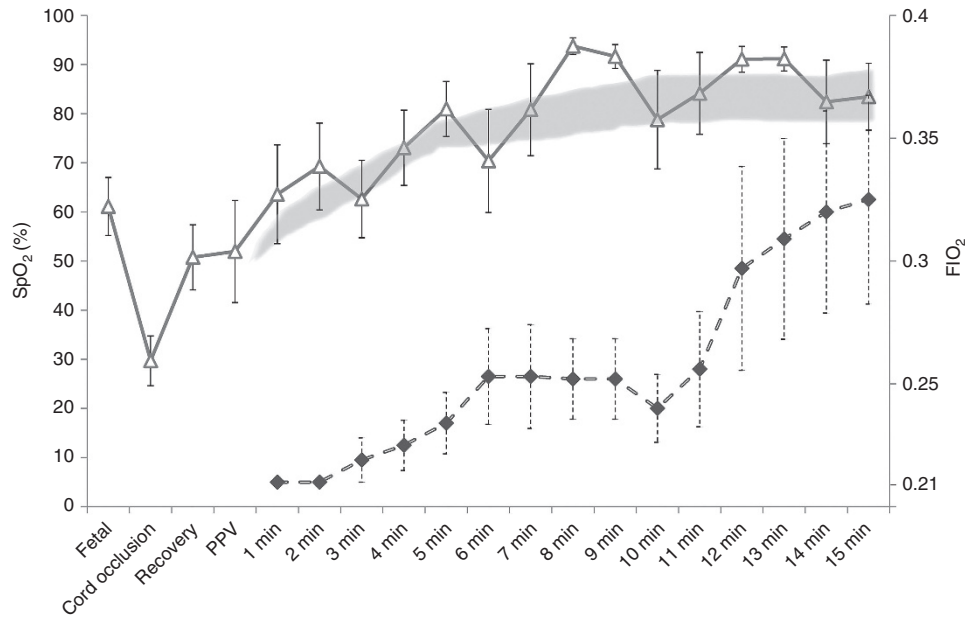


Figure 2. Titration of fraction of inspired oxygen (FIO₂, closed diamond) to maintain the preductal saturation (SpO₂, open triangle) between 85 and 95%. The X-axis represents fetal life, asphyxiation and resuscitation, and postnatal life in minutes. PPV, positive pressure ventilation.

Pulmonary Hemodynamics

Pulmonary blood flow (Q_p) was significantly lower in the asphyxiated 21% inspired oxygen group (42.3 ± 17 ml/kg/min) compared to variable FIO₂ (65.8 ± 10 ml/kg/min) and asphyxiated 100% group (64.1 ± 13 ml/kg/min) (Figure 6b). Interestingly, variable FIO₂ group had higher Q_p than controls (51.4 ± 5 ml/kg/min). Mean pulmonary artery pressure was higher in asphyxiated lambs ventilated with variable FIO₂ group (51 ± 3.4 mm Hg) when compared to asphyxiated lambs ventilated with 100% inspired O₂ (42 ± 4.4 mm Hg) and 21% inspired O₂ (44 ± 3.8 mm Hg) (Figure 5b). No difference was seen in mean pulmonary artery pressure between asphyxiated variable FIO₂ group and controls. There were no significant differences in pulmonary vascular resistance among the asphyxiated lambs (data not shown).

DISCUSSION

To our knowledge, this is the first study to evaluate pulmonary and systemic hemodynamics during resuscitation using the new preductal SpO₂ target guidelines (13) in a model of perinatal asphyxia with lung disease. This study demonstrates that initiating resuscitation with 21% oxygen and titrating inspired oxygen based on preductal SpO₂ in asphyxiated lambs results in hemodynamic changes similar to that achieved with room air in healthy lambs.

Baseline preductal SpO₂ at initiation of resuscitation in most nonasphyxiated neonates is in the 50s and 60s (5,14,15). However, HR and SpO₂ are significantly lower in severely asphyxiated neonates similar to the lambs in our study. It is encouraging to note that SpO₂ and HR can be restored to “normal” range by 60s of effective positive pressure ventilation (Figures 1 and 5) with 21% inspired oxygen.

Studies evaluating inspired oxygen in asphyxiated animal models have shown that resuscitation with 21% oxygen

is adequate to induce pulmonary vasodilation and “return of spontaneous circulation” (8,16–19). However, none of these animal models had lung disease and had low alveolar–arterial oxygen gradient (AaDO₂). Hence resuscitation with 21% oxygen was probably adequate to achieve SpO₂ in the target range. In the current study, we have used a model with meconium aspiration resulting in elevated AaDO₂ (264 ± 37 in asphyxiated lambs and 69 ± 11 mm Hg in control lambs) secondary to ventilation–perfusion mismatch and pulmonary hypertension (9). Resuscitation with 21% oxygen alone in this model did not achieve target SpO₂ (Figure 1) and limited the increase in pulmonary blood flow (Figure 6a). Adjusting FIO₂ significantly improved SpO₂ and pulmonary blood flow compared to the 21% oxygen resuscitation.

Why was pulmonary blood flow lower in asphyxiated lambs resuscitated with 21% oxygen and controls? We have previously shown that a preductal SpO₂ of approximately ≥90% is necessary to achieve optimal pulmonary vasodilation in lambs after birth (20,21). Only one asphyxiated lamb (out of six) in the 21% oxygen resuscitation group achieved SpO₂ >90% (Figure 1) and could have led to suboptimal pulmonary vasodilation (Figure 6a). In contrast, 15/18 lambs in the variable FIO₂ category achieved SpO₂ >90%. In addition, metabolic acidosis is known to decrease the threshold for hypoxic pulmonary vasoconstriction (22) and could have contributed to reduced pulmonary vasodilation in response to room air resuscitation in this study. We have shown in the past that maintaining PaO₂ between 45 and 65 mm Hg is necessary to avoid hypoxic pulmonary vasoconstriction and does not increase pulmonary arterial contractility (23). Our control lambs had an average PaO₂ of 34 ± 8 mm Hg at 10 min and reached 49 ± 6 mm Hg by 15 min. These low (albeit physiologic) PaO₂ values could have contributed to lower Q_p in lambs resuscitated with 21% oxygen.

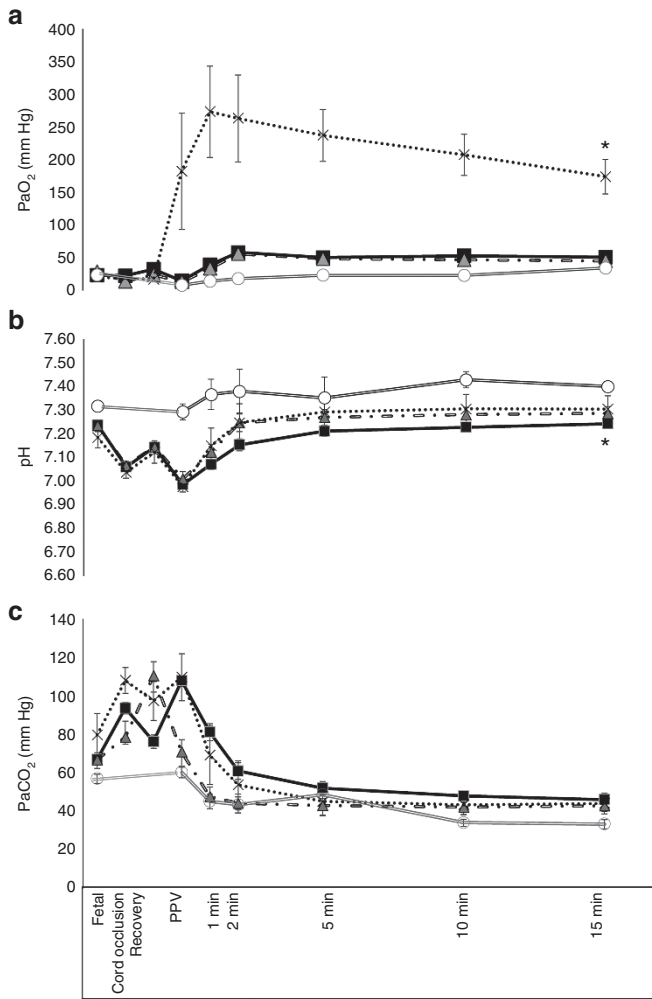


Figure 3. Partial pressure of oxygen in preductal right carotid arterial blood (PaO₂, panel **a**), arterial pH (panel **b**), and partial pressure of CO₂ in arterial blood (PaCO₂, panel **c**) during the first 15 min of postnatal age in control lambs (open circle) and asphyxiated term lambs ventilated with 21% O₂ (gray triangle), 100% O₂ (cross), and inspired oxygen (FIO₂) titrated to keep the SpO₂ as per Neonatal Resuscitation Program guidelines (black square). *P < 0.05, PaO₂ in 100% O₂ group is significantly higher than all other groups throughout the resuscitation period. PPV, positive pressure ventilation.

Recently, Kapadia *et al.* performed a novel clinical study to evaluate inspired oxygen titrated based on preductal SpO₂ in preterm neonates (24). Low oxygen strategy in this study was similar to the variable FIO₂ arm in the current study. Compared to 100% oxygen resuscitation, low O₂ strategy was associated with lower bronchopulmonary dysplasia. Our study demonstrates that 21% oxygen alone may not be adequate to induce pulmonary vasodilation in asphyxiated neonates with lung disease. We also demonstrate that adjusting FIO₂ based on preductal SpO₂ leads to pulmonary vasodilation similar to 100% oxygen resuscitation with considerably less oxygen exposure.

Resuscitation with 100% oxygen did not result in higher pulmonary blood flow compared to resuscitation with variable FIO₂. Clinical and translational studies (23,25) have

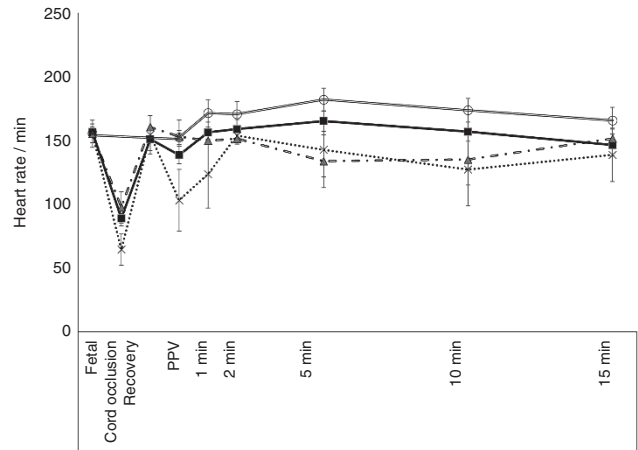


Figure 4. Variation in heart rate (beats per minute) in the first 15 min of life in control lambs (open circle) and asphyxiated term lambs ventilated with 21% O₂ (gray triangle), 100% O₂ (cross), and inspired oxygen (FIO₂) titrated to keep the SpO₂ between 85 and 95% (black square). PPV, positive pressure ventilation.

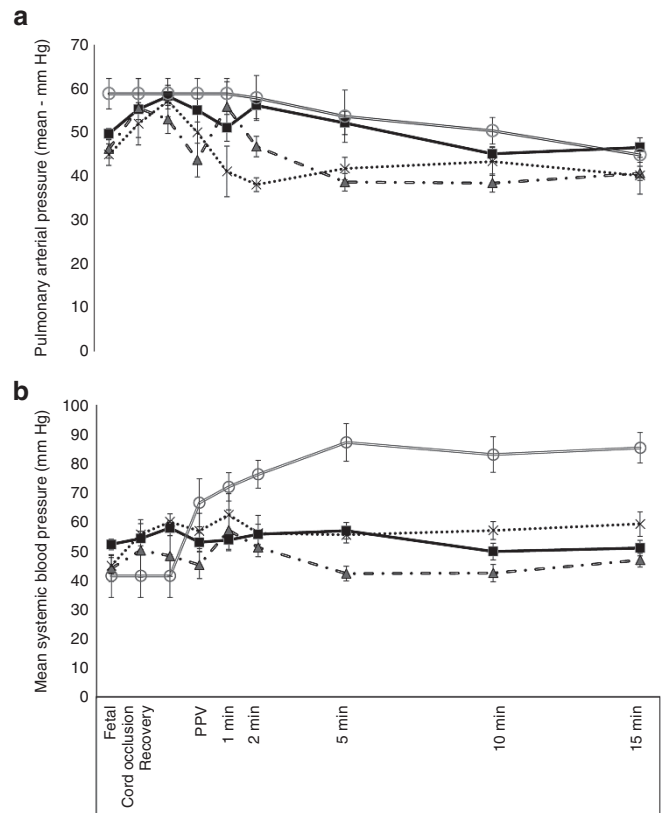


Figure 5. Mean systemic arterial pressure (panel **a**) and mean pulmonary blood pressure (panel **b**) during the first 15 min of postnatal age in control lambs (open circle) and asphyxiated term lambs ventilated with 21% O₂ (gray triangle), 100% O₂ (cross), and inspired oxygen (FIO₂) titrated to keep the SpO₂ as per Neonatal Resuscitation Program guidelines (black square). PPV, positive pressure ventilation.

demonstrated increased oxidative stress following resuscitation with 100% oxygen leading to increased pulmonary vasoconstriction (23). We speculate that resuscitation with variable

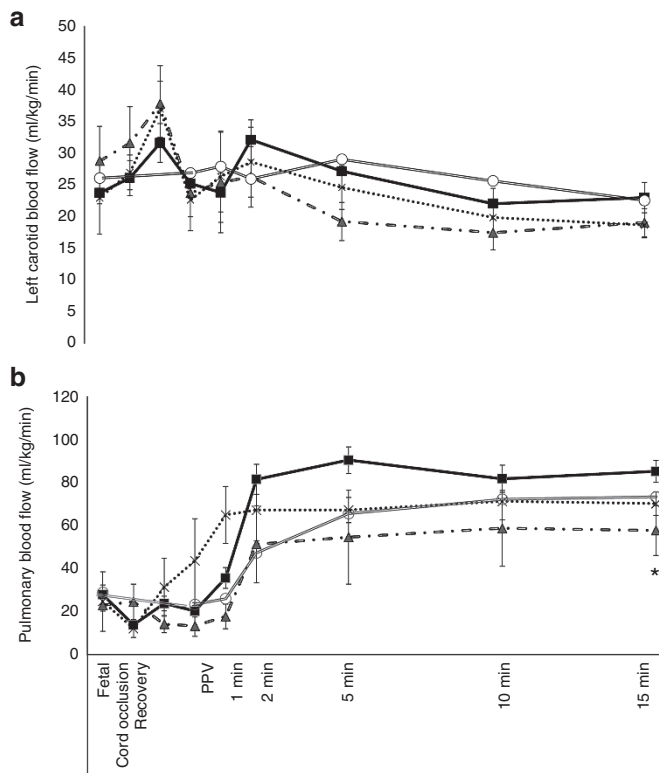


Figure 6. Variation in carotid blood flow (Q_{ca} , panel **a**) and pulmonary blood flow (Q_p , panel **b**) in the first 15 min of postnatal age in control lambs (open circle) and asphyxiated term lambs ventilated with 21% O_2 (gray triangle), 100% O_2 (cross), and inspired oxygen (FIO_2) titrated to maintain preductal SpO_2 as per Neonatal Resuscitation Program guidelines (black square). * $P < 0.05$ by ANOVA (21% asphyxiated and controls significantly lower than variable FIO_2 asphyxia by Bonferroni *post hoc* test). PPV, positive pressure ventilation.

FIO_2 resulted in an optimal balance between oxygen-mediated pulmonary vasodilation and oxygen free radical-induced vasoconstriction.

Adjusting FIO_2 to achieve target SpO_2 requires additional personnel and equipment. In the current study, an additional neonatal provider (a total of four resuscitators) was required to closely monitor SpO_2 and adjust FIO_2 . Absence of adequate providers during resuscitation may limit personnel availability to perform this function. In addition, many delivery suites/birthing rooms in level I nurseries in the United States and nurseries in developing countries are not equipped with oxygen blenders and pulse oximeters. Current clinical literature (26,27) and results from our study clearly indicate that resuscitation and effective ventilation of the lungs with 21% oxygen improves HR and systemic blood pressure and decreases pulmonary vascular resistance in a model of severe asphyxia, acidosis, and lung disease. Based on these results, if resources are limited during resuscitation of a severely asphyxiated neonate, the initial focus should be on effective ventilation of the lungs with room air and monitoring HR.

Recent evidence suggests that initiation of resuscitation and ventilation of the lungs before clamping the cord results in stable cerebral blood flow and influence SpO_2 and oxygen

delivery to the brain (28,29). Further studies to evaluate the impact of delayed cord clamping and ventilation before cord clamping on SpO_2 during resuscitation are warranted.

There are several limitations to this study. All lambs were intubated prior to delivery. Mask ventilation and the process of emergent intubation after delivery may result in lower SpO_2 values and were not evaluated in this study. The severity of lung disease, pulmonary hypertension, and hypoxemic respiratory failure was moderate (with oxygenation index in the mid-20s). Very severe persistent pulmonary hypertension of the newborn and profound hypoxemia may result in much higher oxygen requirement. A fixed positive end expiratory pressure of 5 cm H_2O was adapted in this study. A higher positive end expiratory pressure or use of sustained inflation may have established functional residual capacity earlier leading to lower FIO_2 requirement (30). Finally, this model only evaluates short-term acute lung injury. Long-standing asphyxial insult and lung injury, as seen in meconium aspiration, may lead to vascular remodeling and fixed pulmonary hypertension. Finally, we did not euthanize the lambs at the end of 15 min of resuscitation to evaluate oxidant injury to the lungs (as we did in our previous study) (8). As the lambs were part of a different study to evaluate optimal SpO_2 target at term gestation, we continued to ventilate them for 6 h.

In conclusion, adjusting FIO_2 to maintain preductal SpO_2 in the target range recommended by NRP, in asphyxiated lambs with lung disease, results in pulmonary hemodynamics similar to that observed in control nonasphyxiated lambs with normal lungs. However, in resource-limited and emergent situations, effective ventilation of the lungs with 21% oxygen leading to increased HR may be a reasonable approach as well. Clinical studies evaluating the efficacy of these recommendations are warranted.

METHODS

This study was approved by the Institutional Animal Care and Use Committee (IACUC) at State University of New York at Buffalo. Time-dated pregnant ewes (139–142 d gestation; term 145 d) (New Life Pastures, Attica, NY) were sedated, intubated, and ventilated with 2% isoflurane. Cesarean section was performed and the fetal lamb was partially exteriorized. Jugular and carotid lines were placed on the right side for access, preductal arterial blood gas sampling, and blood pressure monitoring. Catheters were placed in the main pulmonary artery and left atrium for pressure monitoring as previously described (20,21). Fetal lambs were asphyxiated by umbilical cord occlusion and meconium (5 ml/kg of 20% meconium suspended in ewe amniotic fluid) was instilled into their endotracheal tube as previously described (9). The lambs were then delivered, ventilated, and blood gases were obtained at fetal (predelivery), delivery, 1 min, 2 min, 5 min, 10 min, and 15 min. Thirty lambs were randomized into three groups (using sealed envelopes at 1:1:3 ratio): (i) FIO_2 1; (ii) FIO_2 0.21, irrespective of SpO_2 ; and (iii) initial FIO_2 of 0.21, titrated to keep preductal SpO_2 in the target range recommended by NRP (31). In group 3, attempts were made to maintain preductal SpO_2 between 60 and 65% in the first minute, 65 and 70% in the second minute, 70 and 75% in the third minute, 75 and 80% in the fourth minute, 80 and 85% in the fifth minute, and 85 and 95% between 5 and 15 min of postnatal age as per NRP guidelines. If preductal SpO_2 was outside this range, inspired oxygen was adjusted by 5% every 15 s by an attending neonatologist/neonatology fellow. Initial ventilation settings were peak inspiratory pressure of 30 cm H_2O , positive end expiratory pressure – 5 cm H_2O and rate – 40/min. Subsequent ventilation was adjusted using blood gas values.

The randomization described in the previous paragraph was part of a larger study where the variable FIO₂ group was further managed between 15 min and 6 h of postnatal age with different SpO₂ ranges (85–89%, 90–94%, and 95–99%). The second portion of the experiment (from 15 min to 6 h) is not described in this manuscript. Lambs were ventilated for 6 h and then sacrificed. For controls, seven healthy (nonasphyxiated) term lambs without lung disease were ventilated with 21% O₂ irrespective of SpO₂. Pulmonary and systemic hemodynamic parameters were compared between the groups.

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