Title

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Journal

American Journal of Perinatology, 40(6)

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Publication Date

2023-04-01

DOI

10.1055/s-0041-1730362

Peer reviewed

HHS Public Access

Author manuscript

Am J Perinatol. Author manuscript; available in PMC 2025 March 01.

Published in final edited form as:

Am J Perinatol. 2023 April ; 40(6): 630–637. doi:10.1055/s-0041-1730362.

Differential Alveolar and Systemic Oxygenation during Preterm Resuscitation with 100% Oxygen during Delayed Cord Clamping

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Abstract

Objective—Delayed cord clamping (DCC) and 21 to 30% O_2 resuscitation is recommended for preterm infants but is commonly associated with low pulmonary blood flow (Qp) and hypoxia. 100% O_2 supplementation during DCC for 60 seconds followed by 30% O_2 may increase Qp and oxygen saturation (SpO_2).

Study Design—Preterm lambs (125–127 days of gestation) were resuscitated with 100% O_2 with immediate cord clamping (ICC, $n = 7$) or ICC + 30% O_2, and titrated to target SpO_2 ($n = 7$) or DCC + 100% O_2 for 60 seconds, which followed by cord clamping and 30% O_2 titration ($n = 7$). Seven preterm (23–27 weeks of gestation) human infants received continuous positive airway pressure (CPAP) + 100% O_2 for 60 seconds during DCC, cord clamping, and 30% O_2 supplementation after cord clamping.

Results—Preterm lambs in the ICC + 100% O_2 group resulted in PaO_2 (77 ± 25 mm Hg), SpO_2 (77 ± 11%), and Qp (27 ± 9 mL/kg/min) at 60 seconds. ICC + 30% O_2 led to low Qp (14 ± 3 mL/kg/min), low SpO_2 (43 ± 26%), and PaO_2 (19 ± 7 mm Hg). DCC + 100% O_2 led to similar Qp (28 ± 6 mL/kg/min) as ICC + 100% O_2 with lower PaO_2. In human infants, DCC + CPAP with 100% O_2 for 60 seconds, which followed by weaning to 30% resulted in SpO_2 of 92 ± 11% with all infants >80% at 5 minutes with 100% survival without severe intraventricular hemorrhage.

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Authors' Contributions

S.L., A.K., P.V., P.K., and W.R. provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, and also supported in final approval of the version to be published. S.L., A.K., P.V., and P.K. supported in drafting the article or revising it critically for important intellectual content.

Conflict of Interest

None declared.

The clinical part of the study was approved by Sharp Mary Birch hospital IRB and consents were obtained from parents. Dr. Satyan Lakshminrusimha is a member of the Neonatal Resuscitation Program Steering Committee of the American Academy of Pediatrics (AAP). The opinions expressed in this manuscript are the author's own and does not reflect the official position of the AAP.

Conclusion—DCC + 100% O_2 for 60 seconds increased Qp probably due to transient alveolar hyperoxia with systemic normoxia due to “dilution” by umbilical venous return. Larger translational and clinical studies are warranted to confirm these findings.

Keywords

neonatology; delayed cord clamping; oxygen; resuscitaiton

Oxygenation at birth is largely determined by the entry of gas into the fluid-filled lung,[1] an increase in alveolar oxygen tension (PaO_2) leading to pulmonary vasodilation and a decrease in pulmonary vascular resistance (PVR).[2,3] Suboptimal increase in PaO_2 at birth may impair pulmonary vascular transition and increase risk of pulmonary hypertension (PH) and respiratory failure.[4]

The 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations (CoSTR) recommends the use of 21% O_2 for initial ventilation of term infants.[5] For preterm newborn infants (less than 35 weeks of gestation) who receive respiratory support at birth, CoSTR suggests starting with a lower oxygen concentration (21–30%) rather than higher initial oxygen concentration (60–100%).[6] CoSTR suggests the range of 21 to 30% oxygen because many trials used this range for the low oxygen concentration group. Subsequent titration of oxygen concentration using pulse oximetry is advised.

While 21% O_2 might be adequate in term babies, to stabilize extremely preterm infants in the delivery room, a higher fraction of inspired oxygen (FiO_2) may be required to compensate for inadequate lung aeration and achieve adequate alveolar and arterial oxygenation to stimulate pulmonary vasodilation.[2,7] The CoSTR suggestion to initiate resuscitation in extremely preterm infants with a low FiO_2 aims to reduce the risk of hyperoxia associated with increased production of free radicals and its resultant tissue damage.[8,9] The downside of this approach is an increased risk of hypoxemia with a potential negative effect on breathing effort. Hypoxemia (mean peripheral arterial oxygenation SpO_2 <80%) at 5 minutes after birth is associated with a higher risk of mortality and the development of severe intraventricular hemorrhage (sIVH).[10] This increased mortality may be caused by hypoxia-induced respiratory depression complicated by pulmonary vasoconstriction and respiratory failure.[10,11]

Several studies have questioned the use of 21 to 30% oxygen for initial resuscitation of extremely preterm infants. Rabi et al demonstrated that titrating up from 21% oxygen resulted in higher incidence of bradycardia (heart rate <100 beats per min [bpm]) compared with 100% oxygen in preterm infants ≤32 weeks of gestation.[12] Oei et al in a post hoc analysis of the Torpido trial concluded that using 21% oxygen (compared with 100%) to initiate resuscitation was associated with an increased risk of death (from respiratory failure) in infants <28 weeks of gestation.[13] Such respiratory failure with 21% oxygen resuscitation may be secondary to inadequate alveolar oxygenation, hypoxic pulmonary vasoconstriction, and PH.[14] A recent trial in infants <30 weeks of gestation by Dekker et al demonstrated initial stabilization with 100% oxygen led to less apnea at birth, a greater minute ventilation, higher tidal volumes, improved oxygenation, and a shorter duration of ventilation compared

with 30% O_2.[15] To date, no study has replicated these findings with an intact umbilical cord during delayed cord clamping.

We conducted a proof-of-concept translational and clinical pilot (feasibility) study. We hypothesized that the initiation of resuscitation with 100% oxygen with an intact umbilical cord for 1 minute in preterm lambs with subsequent abrupt weaning to 30% would promote early pulmonary vasodilation (due to alveolar hyperoxygenation), and SpO_2 ≥80% and heart rate ≥100 bpm by 5 minutes from birth without systemic hyperoxia (SpO_2 > 95% or PaO_2 > 80 mm Hg). The concept of "differential oxygenation" with transient alveolar hyperoxia and systemic normoxia due to "dilution" by umbilical venous blood is shown in ►Fig. 1.

Materials and Methods

Translational Study in Preterm Lambs

This study was approved by the Institutional Animal Care and Use Committees (IACUC) at University of California at Davis and University at Buffalo. We chose to compare three groups of preterm lambs: the first group to represent historical management with immediate cord clamping (ICC) and initiation of resuscitation with 100% O_2 routinely adapted prior to 2010[16]; the second group represented current standard of care (standard arm as per CoSTR recommendations) with immediate cord clamping and initiation of resuscitation at 30% with titration based on preductal SpO_2[5]; and the third (experimental) group of lambs were ventilated for 60 seconds with 100% oxygen with an intact umbilical cord (delayed cord clamping [DCC]), which followed by clamping and cutting the umbilical cord and abrupt weaning of oxygen to 30% and titration based on preductal SpO_2.

Time-date pregnant lambs seronegative for Q-fever underwent a cesarean section under general anesthesia at 125 to 127 days gestation as previously described.[14,17] Lambs were intubated with a cuffed endotracheal tube and excess lung liquid drained by gravity. A right carotid arterial, right jugular venous lines, and a left pulmonary arterial flow probe were placed as described in previous studies.[18] The lamb was completely exteriorized and three protocols were followed: (1) ICC, delivery to a radiant warmer and ventilation with 100% O_2 for 5 minutes; (2) ICC and ventilation with 30% O_2 and titration based on target SpO_2 as per the Neonatal Resuscitation Program (NRP) recommendations; or (3) DCC, ventilation with an intact cord with 100% O_2 for 1 minute followed by cord clamping and ventilation with 30% O_2 (with titration to target SpO_2 as per NRP standards. Positive pressure ventilation (PPV) was provided with a T-piece resuscitator with initial pressures of 35/5 cm H_2O at a rate of 40/min. Peak inflation pressure was adjusted based on chest rise. Right carotid blood gases, pulmonary, and carotid blood flow were monitored every minute. To assess our concept, the primary outcome was to evaluate pulmonary blood flow and arterial oxygenation (PaO_2) every minute in all three groups for the first 5 minutes. We also analyzed oxygen saturations and carotid blood flow during this period.

Clinical Protocol

Institutional review board approval was obtained from Sharp Mary Birch Hospital for Women and Newborns to test whether administration of 100% O_2 during DCC was feasible.

Individual parental consent was obtained for these seven infants (range = 24–29 weeks of gestational age). These seven infants received DCC + CPAP with 100% O_2 during 60 seconds of DCC. Following 60 seconds of DCC, the umbilical cord was clamped and cut and CPAP or PPV with 30% O_2 provided. Inspired oxygen was titrated to achieve target SpO_2 as per current NRP recommendations. Heart rate, preductal SpO_2, and FiO_2 at 5 minutes after expulsion of the neonate from the uterus were recorded. The incidence of sIVH (defined as IVH of grade 3 or 4) and mortality were documented.

Sample Size and Statistical Analysis

Lamb protocol: The primary outcome of pulmonary blood flow at 1 minute after birth was used for sample size calculation. Based on a previous study in preterm lambs, pulmonary blood flow was normally distributed with a standard deviation of 16 mL/kg/min.[14] To detect an anticipated difference of 28 mL/kg/min between 100 and 30% O_2 groups, we needed a sample size of six lambs in each group. With the current sample size of seven in each group, we have a power of 0.85.[19]

Human preterm infants: As the clinical evaluation was a proof-of-concept pilot trial, sample size was not calculated for human infants.

Statistics: Differences between the three groups were analyzed by ANOVA with post hoc Bonferroni correction using SPSS (version 27).

Results

Preterm Lambs

Seven lambs in each group (total 21) were evaluated. The mean gestational age and birth weight were similar between the three groups.

Oxygenation: Fetal blood gases, oxygen saturation from the right forelimb, and pulmonary and carotid flows were similar among all preterm lambs. ►Fig. 2 shows inspired oxygen (1), oxygen saturation (2), and preductal PaO_2 (3) from the three groups of lambs. Ventilation with 100% O_2 following ICC (ICC + 100% O_2 group) resulted in a marked increase in SpO_2 above the target range (►Fig. 2B). Preductal PaO_2 increased from fetal value of 23 ± 5.3 mm Hg to 77 ± 25 mm Hg by 1 minute and 321 ± 59 mm Hg by 5 minutes (►Fig. 2C). In the standard arm (ICC + 30% O_2 group), the cord was clamped and cut and PPV was initiated at 30% and gradually titrated up to 46 ± 16% by 5 minutes. In the experimental (DCC + 100% O_2) group, ventilation with 100% oxygen for 1 minute with an intact cord (DCC) resulted in a modest elevation of SpO_2 and PaO_2 (to 24 ± 5.8 mm Hg) at 1 minute (significantly lower than ICC and 100% oxygen, $p < 0.05$). Subsequently, the cord was clamped and inspired oxygen was abruptly decreased to 30% and then titrated up based on target SpO_2 to reach 60 ± 31% by 5 minutes. At 1 minute after birth, SpO_2 in the 30% oxygen ICC arm was significantly lower than the other two groups (►Fig. 2B). The PaO_2 results from 100% oxygen + DCC arm and 30% oxygen + ICC were not significantly different (►Fig. 2C).

Pulmonary blood flow (Qp): Fetal baseline left pulmonary arterial blood flow was similar in the three groups of lambs (►Fig. 3A). With ICC and PPV with 100% O_2, there was a threefold increase in Qp at 1 minute and a 10-fold increase by 5 minutes (fetal: 9.3 ± 3.8 mL/kg/min, 1 minute: 27 ± 9 mL/kg/min, 5 minutes: 91 ± 17 mL/kg/min). With ICC and initiation of PPV with 30% oxygen, Qp was significantly lower than with DCC + 100% O_2 at 1 minute although the PaO_2 in both groups were identical. With titration of FiO_2 and PPV, Qp increased to 50 ± 8 mL/kg/min by 5 minutes (►Fig. 3A). With DCC and PPV with 100% O_2, although there was minimal increase in PaO_2 (►Fig. 2C), there was a significant increase in Qp similar to that observed with ICC + 100% O_2 at 1 minute (28 ± 6 mL/kg/min; ►Fig. 3A). However, following the wean to 30% O_2 after the first minute, the rise in Qp was more gradual reaching 46 ± 3.8 mL/kg/min by 5 minutes (significantly lower than ICC + continuous 100% O_2).

Carotid blood flow: Carotid blood flow did not show a significant difference between the three groups (►Fig. 3B).

Clinical Results

All infants were resuscitated successfully and admitted to the NICU. The gestational age was 26 ± 2 weeks. Birth weight was 945 ± 317 g. The FiO_2 needed at 5 minutes after birth was 0.5 ± 0.21. The preductal SpO_2 achieved at 5 minutes was 92 ± 11%. Heart rate at 5 minutes was 155 ± 11 bpm. All infants achieved preductal SpO_2 >80% by 5 minutes. All seven infants survived to NICU discharge without sIVH.

Discussion

Current delivery room practice is to delay clamping and cutting the umbilical cord to allow for placental transfusion and hemodynamic stabilization. Supported by numerous randomized controlled trials[20–29] and meta-analyses,[30,31] this practice is endorsed by neonatal and obstetrical governing bodies.[32–34] Yet, data are very limited on optimal oxygenation during DCC in extremely preterm infants. In this manuscript, we demonstrate that providing 100% oxygen during 60 seconds of DCC increases pulmonary blood flow without increasing systemic PaO_2. If inspired oxygen is weaned immediately after cord clamping to 30% and then titrated up, the risk of systemic hyperoxia (PaO_2 > 80 mm Hg) was minimized in preterm lambs.

Oxygenation during the period when DCC is performed needs careful examination. In spontaneously breathing term infants, Padilla-Sanchez et al have demonstrated higher SpO_2 at 1 minute with a median (interquartile range [IQR] of 77% (68–85%)[35] compared with reference ranges obtained after immediate cord clamping (median 68%, IQR: 60–77%).[36] Similarly, Andersson et al demonstrated increased SpO_2 at 1 minute with DCC compared with early cord clamping with resuscitation with 21% in nonvigorous term infants (72 ± 9.3 vs. 62 ± 4.3%).[37] This difference may be due to continued umbilical venous return contributing to the left ventricular preload.[38] The normal umbilical venous SO_2 in the human fetus during the last trimester is 85 ± 9% by T2 MRI oximetry,[39] and this SO_2 can explain the increase in preductal SpO_2 observed in term infants breathing air with DCC at 1 minute.

While continued placental transfusion increases SpO_2 in infants breathing 21% oxygen, it is also likely to prevent hyperoxia when resuscitation is conducted with 100% O_2 (►Fig. 1). We speculate that DCC during 100% O_2 supplementation results in lower preductal PaO_2 because of dilution of left ventricular preload by umbilical venous SO_2 (~85%) that is lower than the pulmonary venous SO_2 (~100%). We describe this effect as "differential oxygenation" where alveolar hyperoxia associated with systemic normoxia can potentially offer an advantage during resuscitation of extremely preterm infants.

Unlike term infants, extremely preterm infants have less spontaneous breathing with immature lungs in the canalicular stage with a poorly developed alveolar-capillary interface.[7] Animal studies demonstrate that delaying clamping of the umbilical cord until breathing is established avoids adverse cerebral and cardiac hemodynamics, which may reduce bleeding in the brain or sIVH.[40–43] In a multicenter trial comparing DCC to umbilical cord milking, 76% of 23 to 27 weeks of gestation preterm newborns receiving DCC without respiratory support had initiated respirations prior to cord clamping.[44] Despite the onset of breathing in the majority of DCC infants, relative hypoxemia was common as demonstrated by a low 5-minute SpO_2, 73% (95% CI: 71.4–75.6).[45] The significance of this observation is evident from two recent analyses establishing that preterm infants with a 5-minute SpO_2 <80% were more likely to have sIVH or death.[10,46]

Providing respiratory support to aerate the lung prior to cord clamping has been advocated as an alternative to immediate cord clamping. To date, all studies of ventilation during DCC have used room air or low concentrations of oxygen (0.21–0.30), and none have shown reduction in morbidities.[47–49] Ventilation through a mask with low concentrations of oxygen may not be adequate in extremely preterm infants.[12,13] Noninvasive respiratory support during transition requires a patent airway to allow air to enter the trachea and aerate the lung. Spontaneous breathing is the most effective method of opening the airway for a newborn. Hypoxia inhibits breathing movements and contributes to a closed glottis,[15] which prevents lung aeration and subsequent benefits of DCC.

It would seem logical that provision of higher amounts of supplemental oxygen at birth would eliminate early hypoxia. Historically, too much oxygen during resuscitation of infants has been associated with death or organ injury.[50,51] A recent trial demonstrated that stabilization with a brief period of 100% O_2 postdelivery led to greater minute ventilation, higher tidal volumes, and improved oxygenation compared with 30% O_2.[15] Despite these data, several multicenter trials of resuscitation on the cord start with low oxygen concentrations,[52–54] but require 3 to 5 minutes to establish breathing prior to cord clamping. To test feasibility and safety, 100% oxygen for 1 minute with an intact cord in seven preterm lambs and seven extremely preterm infants have been included in this study. Preterm lambs receiving 100% O_2 showed higher pulmonary blood flow at 1 minute compared with lambs receiving 30% O_2(potentially due to higher alveolar PaO_2) without an increase in PaO_2 presumably due to continued umbilical venous return with an SO_2 of approximately 85% (►Figs. 2 and 3). Such dissociation between alveolar oxygenation and systemic oxygenation may be a rationale to enhance pulmonary vasodilation at birth in preterm infants without systemic oxygen toxicity (►Fig. 1).

We demonstrate that it is feasible to provide CPAP with 100% O_2 for 1 minute in extremely preterm infants. A higher alveolar oxygen tension may be critical to initial stabilization, improve diaphragmatic activity[55] pulmonary vasodilation[14] and oxygenation of the extremely preterm infant. Supplementation with 100% O_2 is likely to facilitate glottic opening[56,57] and increase alveolar PaO_2 resulting in pulmonary vasodilation.

There are several limitations to this study. Lambs delivered by cesarean section under general anesthesia may not be the ideal model to study placental transfusion. However, several studies have shown the hemodynamic benefits of placental transfusion in this ovine model.[38,58–60] In preterm lambs, we did not perform any studies to evaluate oxygen toxicity in plasma or tissues. We did not study an intermediate level of oxygen such as 60%. Preliminary data in three lambs with DCC and PPV with 60% O_2 for 1 minute resulted in a similar PaO_2 at PPV with 100% (23 ± 5.5 vs. 24 ± 6 mm Hg, respectively) but led to a smaller increase in pulmonary blood flow (23 vs. 28 mL/kg/min).

To conclude, supplemental oxygen at 100% for 60 seconds during DCC can potentially increase alveolar oxygenation and induce pulmonary vasodilation without systemic hyperoxia due to “dilution” of PO_2 by continued umbilical venous blood flow. Supplementation with 100% O_2 transiently during DCC is feasible in extremely preterm infants. Such dissociation between alveolar and systemic oxygen may be an effective approach to resuscitation of extremely preterm infants and warrants larger, multicenter, masked randomized controlled trials.

Funding

This study received financial support from Children’s Miracle Network (PV) (grant numbers: HD072929 [S.L.], K12 HL138052 [P.C.], and R03HD096510 [P.C.]).

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Key Points

- Transient alveolar hyperoxia during delayed cord clamping can enhance pulmonary vasodilation.
- Placental transfusion buffers systemic oxygen tension and limits hyperoxia.
- Use of 100% oxygen for 60 seconds during DCC was associated with SpO_2 ≥80% by 5 minutes.

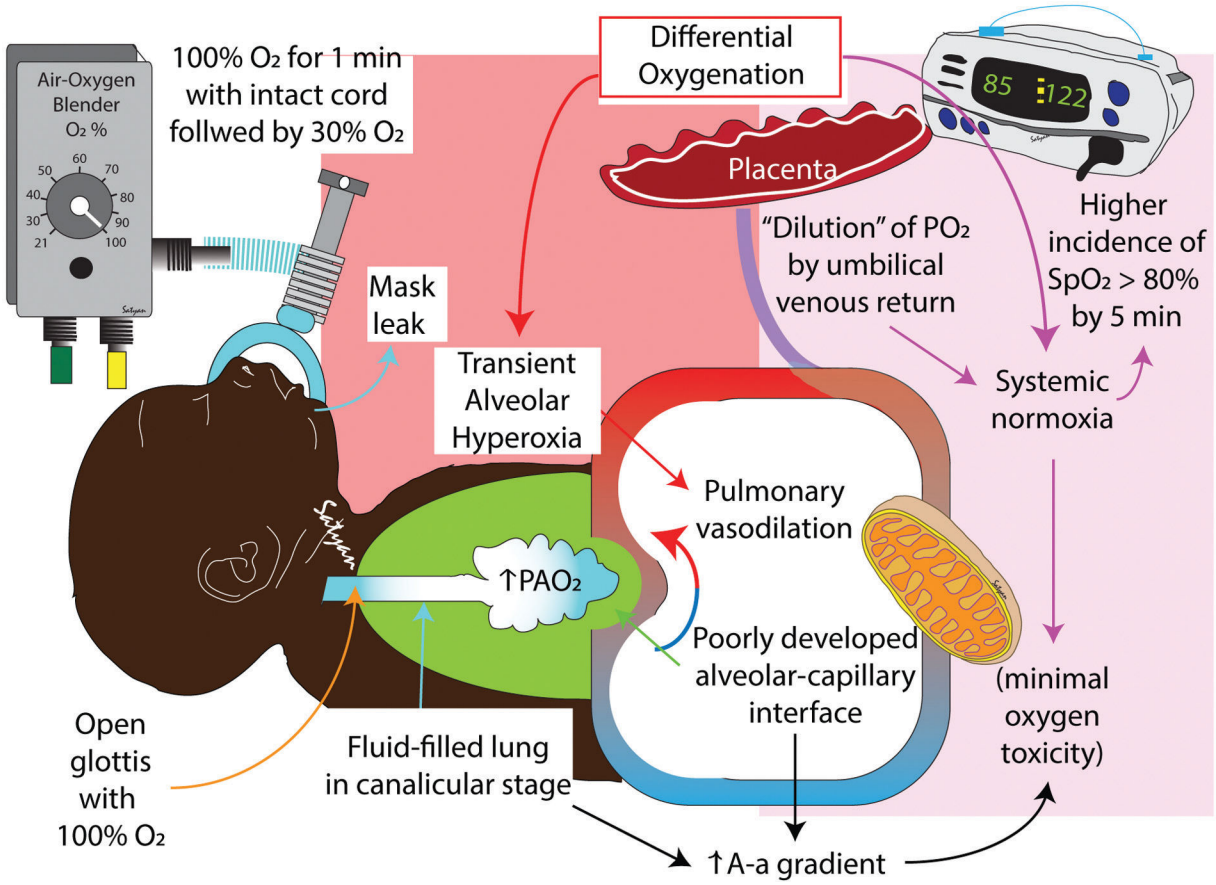

Fig. 1.

Hypothesis: "differential" oxygenation in extremely preterm infants mask ventilated with 100% oxygen. Due to high prevalence of mask leak in preterm infants, there is a high inspired-to-alveolar oxygen gradient. Supplementation with 100% oxygen is likely to facilitate glottic opening and increase alveolar PAO_2 resulting in pulmonary vasodilation. The high alveolar-arterial PO_2 gradient (A-a gradient) in extremely preterm infants reduces systemic PaO_2 and SpO_2. In addition, PO_2 in the pulmonary venous return is "diluted" by umbilical venous return (typical SO_2 of ~85%) further limiting oxygen toxicity to the infant. The red box indicates transient alveolar hyperoxia and the pink box suggests systemic normoxia. *Image courtesy*: Satyan Lakshminrusimha.

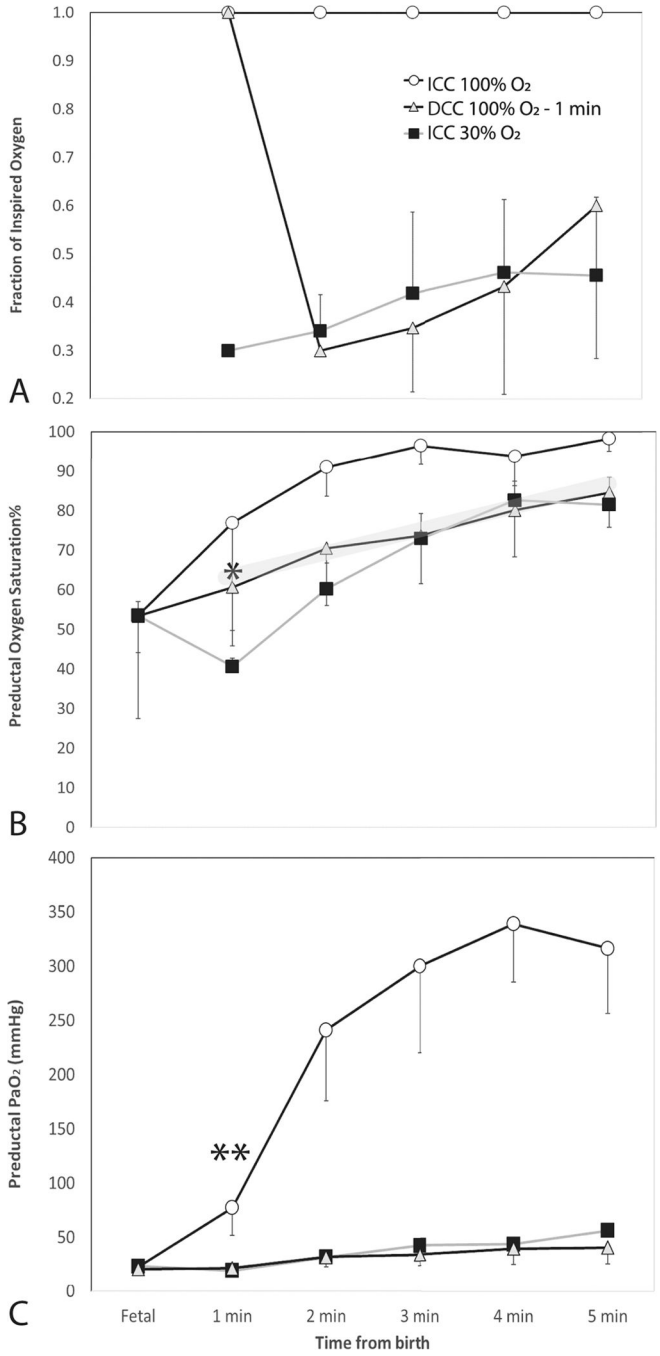

Fig. 2.

Oxygenation in preterm lambs. Fraction of inspired oxygen (**A**), right forelimb pulse oximetry (**B**) and preductal PaO_2 from the right carotid artery (**C**) in preterm lambs (seven in each group; open circle) ventilated for5 minutes with 100% oxygen with ICC, (gray triangle) delayed cord clamping for 1 minute with ventilation with 100% oxygen followed by cord clamping and ventilation with 30% oxygen with titration to target SpO_2 and (solid square) immediate cord clamping with ventilation with 30% oxygen with titration to target SpO_2. The shaded area in (**B**) represents the target range recommended by neonatal resuscitation

program; $^{**}p < 0.05$ compared with other groups by ANOVA repeated measures and $^{*}p < 0.05$ compared with 30% O_2 ICC group at 1 minute time point only. DCC, delayed cord clamping; ICC, immediate cord clamping.

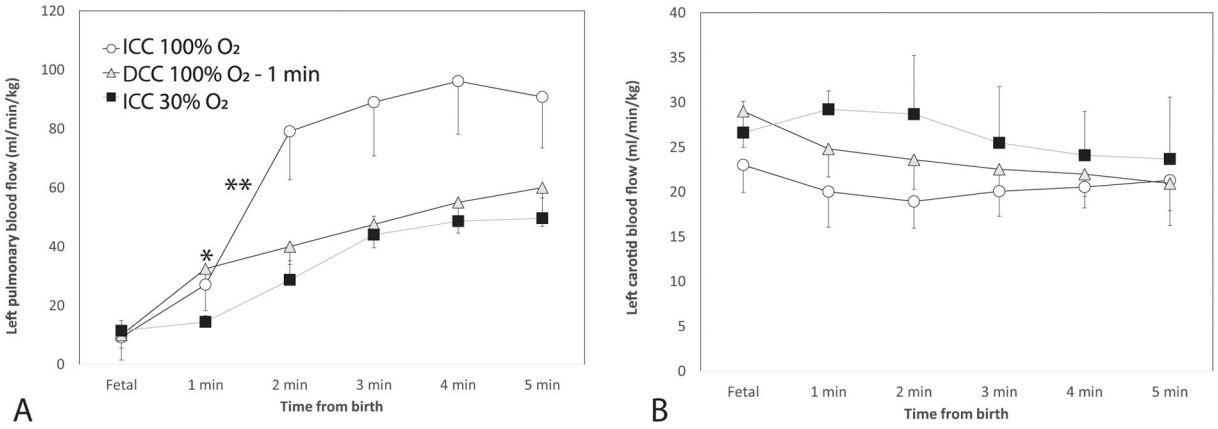

Fig. 3.

Left pulmonary blood flow (**A**) and left carotid blood flow (**B**) in preterm lambs (seven in each group; open circles) ventilated for 5 minutes with 100% oxygen with ICC (gray triangles) delayed cord clamping for 1 minute with ventilation with 100% oxygen followed by cord clamping and ventilation with 30% oxygen with titration to target SpO_2 and (solid squares) immediate cord clamping with ventilation with 30% oxygen with titration to target SpO_2. *$p < 0.05$ compared with other groups by ANOVA repeated measures and **$p < 0.05$ compared with 30% O ICC group at 1 minute time point only. DCC, delayed cord clamping; ICC, immediate cord clamping.