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Randomized Trial of Oxygen Weaning Strategies Following Chest Compressions During Neonatal Resuscitation

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Abstract

Background: The Neonatal Resuscitation Program (NRP) recommends using 100% O_2 during chest compressions and adjusting FiO_2 based on SpO_2 after return of spontaneous circulation (ROSC). The optimal strategy for adjusting FiO_2 is not known.

Methods: Twenty-five near-term lambs asphyxiated by umbilical cord occlusion to cardiac arrest were resuscitated per NRP. Following ROSC, lambs were randomized to gradual decrease versus abrupt wean to 21% O_2 followed by FiO_2 titration to achieve NRP SpO_2 targets. Carotid blood flow and blood gases were monitored.

Results: Three minutes after ROSC, PaO_2 was 229±32 mmHg in gradual wean group compared to 57±13 following abrupt wean to 21% O_2 ($p<0.001$). PaO_2 remained high in the gradual wean group at 10 min after ROSC (110±10 vs. 67±12, $p<0.01$) despite similar FiO_2 (~0.3) in both groups. Cerebral O_2 delivery (C-DO_2) was higher above physiological range following ROSC with gradual wean ($p<0.05$). Lower blood oxidized/reduced glutathione ratio (suggesting less oxidative stress) was observed with abrupt wean.

Conclusion: Weaning FiO_2 abruptly to 0.21 with adjustment based on SpO_2 prevents surge in PaO_2 and C-DO_2 and minimizes oxidative stress compared to gradual weaning from 100% O_2 following ROSC. Clinical trials with neurodevelopmental outcomes comparing post-ROSC FiO_2 weaning strategies are warranted.

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INTRODUCTION

Asphyxiated newly born infants often require resuscitation immediately after birth(1, 2). Cerebral ischemia and hypoxia during perinatal asphyxia initiates a cascade of deleterious biochemical events including a switch to anaerobic metabolism and secondary energy failure leading to neuronal death within hours to days after birth(3). Generation of reactive oxygen species at a rate that exceeds the capacity of the endogenous antioxidant systems to neutralize them results in oxidative stress and tissue damage(4). The developing brain is extremely vulnerable to free radical damage due to its lipid content, relatively high oxygen (O_2) consumption and low activity of antioxidant enzymes(5, 6). Previous studies have shown that brief exposure to 100% O_2 increases brain tissue O_2 tension(7), systemic oxidative stress and lung oxidative injury in ventilated term newborn lambs(8). Furthermore, the combination of perinatal asphyxia and early hyperoxemia is associated with higher incidence of moderate to severe hypoxic ischemic encephalopathy (HIE)(9). Approximately half of the infants with severe HIE are at risk for death or moderate to severe disability even in the era of therapeutic hypothermia(10, 11). Newborn infants who undergo intensive resuscitation and survive are at significant risk for neurodisability(12). Minimizing the risk of reperfusion injury with post-resuscitation hyperoxia(13) may potentially be associated with short-term and long-term reduction in mortality and morbidity.

The American Academy of Pediatrics/American Heart Association (AAP/AHA) Neonatal Resuscitation Program (NRP) provides guidance for preductal O_2 saturations (SpO_2) during resuscitation(14). The Textbook of Neonatal Resuscitation recommends 100% O_2 use during chest compressions (CC)(14, 15). The 2020 American Heart Association – Neonatal Resuscitation guidelines suggest that it is reasonable to use higher concentrations of O_2 when CC are needed(16). Due to poor perfusion during cardiac arrest in spite of CC, PaO_2 concentrations are very low (23.9±6.8 mmHg with 100% O_2) in animal studies(17). Moreover, it is clinically difficult to reliably monitor oxygenation status with pulse oximetry while delivering CC. After return of spontaneous circulation (ROSC) and heart rate is above 60 bpm, inspired O_2 is adjusted to meet target SpO_2 to reduce the risks associated with hyperoxia(16). This recommendation is based on expert opinion and is not based on scientific evidence. Inspired O_2 can be weaned gradually from 100% or abruptly to 21% and then titrated based on preductal SpO_2.

We hypothesized that abrupt weaning of inspired O_2 to 21% after ROSC will prevent a surge in cerebral O_2 delivery ($C\text{-}DO_2$), minimize oxygen toxicity and reduce oxidative stress as measured by oxidized to reduced glutathione (GSSG/GSH) ratio in whole blood samples compared to gradual weaning from 100% O_2 with titration based on preductal SpO_2 ranges recommended by NRP.

METHODS

Animal Preparation

The study protocol was approved by the Institutional Animal Care and Use Committee (IACUC) at the University of California, Davis. All experiments were performed according to animal ethical guidelines, in compliance with the ARRIVE guidelines(18). Time-dated

healthy pregnant ewes at near-term gestation (139–141 days gestation; term is 145 days) were procured from Van Laningham Farm, Arbuckle, CA, USA. Following an overnight fast, the ewe was medicated with intravenous diazepam and ketamine, and intubated with a 10.0 mm cuffed endotracheal tube (ETT). The ewe was ventilated with 21% O_2 and general anesthesia was provided with 2–3% inhaled isoflurane as previously described(19). The ewe was continuously monitored with a pulse oximeter and an end-tidal CO_2 ($ETCO_2$) monitor. Following a cesarean section, the fetal lamb was partially exteriorized and intubated with a 4.5 mm cuffed ETT. After draining the fetal lung fluid passively by gravity, the ETT was occluded to prevent entry of air. A left carotid arterial flow probe was placed to measure blood flow. A catheter was placed in the right carotid artery for invasive arterial blood pressure monitoring and to collect blood samples. The right jugular vein was catheterized for blood draws and for fluid and medication administration respectively. A pulse oximeter was placed on the right forelimb for continuous SpO_2 monitoring.

Experimental Protocol

The umbilical cord was occluded until asystole when the lamb's heart rate was zero and the carotid arterial pressure and flow waveforms were absent. The umbilical cord was then tied and cut. The lamb was transferred to a radiant warmer and weighed and a three-lead EKG applied. After 5 minutes of asystole, resuscitation was initiated with positive pressure ventilation (PPV) using peak inflation pressures (PIP) of 30 to 35 cm H_2O and PEEP of 5 cm H_2O with a rate of 40 breaths/min and 21% O_2 via a T-piece resuscitator(19). After 30 seconds of effective PPV through the ETT, CC were initiated and coordinated with PPV (3:1 ratio of CC:PPV) and the inspired O_2 was increased to 100%(16). In the lambs that did not achieve ROSC with CC and PPV, a dose of epinephrine (0.01–0.03 mg/kg) was administered intravenously by umbilical venous route at 3–5 minutes from the onset of resuscitation(1, 20). Epinephrine administration at the same dose was repeated every three minutes until ROSC or for a total of four doses. ROSC was defined as sustained heart rate greater than 100 bpm and systolic arterial blood pressure more than 40 mm Hg. Following ROSC, the lambs were randomized into two groups using opaque sealed envelopes:

Gradual wean (control) group: After ROSC, inspired O_2 was weaned down from 100% O_2 by 5% if preductal SpO_2 was 96–98% and by 10% if SpO_2 was ≥ 99% every 30 seconds as needed to maintain preductal SpO_2 within NRP recommended ranges (85–95%).

Abrupt decrease to 21% O_2/abrupt wean (experimental) group: Following ROSC, the inspired O_2 was abruptly weaned to 21% from 100%. Subsequently inspired O_2 was titrated up from 21% by 5% if preductal SpO_2 was 80–84% or by 10% if SpO2 was <80% every 30 seconds as needed to maintain preductal SpO_2 within 85–95%.

Monitoring

The lambs were placed on a conventional ventilator with settings adjusted to maintain $PaCO_2$ between 45–55 mmHg. Ventilator settings during the study period were peak inflation pressure of 25–35 cm H_2O, PEEP of 5 cm H_2O and rate of 30–40/min, targeting exhaled tidal volume of 6–8 ml/kg/min in both the groups. Carotid arterial blood flow and SpO_2 were continuously monitored until 30 minutes after ROSC. Arterial blood gas

samples were collected at fetal baseline, during cardiac arrest at the start of PPV, during CC, immediately after ROSC, every minute after ROSC for the first 5 minutes and at 10, 15 and 30 minutes after ROSC. Venous blood gases were obtained at fetal baseline, during cardiac arrest, during CC, immediately after ROSC and at 1, 2, 5 and 10 minutes after ROSC respectively. Each sample of blood drawn was replaced with equal volume of normal saline as flush. Arterial blood samples were obtained at fetal baseline and at 10 minutes after ROSC to measure the ratio of oxidized to reduced glutathione (GSSG:GSH ratio) in whole blood per manufactures instructions (Glutathione colorimetric detection kit, Invitrogen™, Thermo Fisher Scientific, MA USA) as a measure of oxidative stress.

Cerebral O_2 delivery and cerebral O_2 consumption (extraction) were calculated at various time points during resuscitation and after ROSC, as shown below:

$$C\text{-}DO_2\ (ml/kg/min) = Qca \times [(1.39 \times Hb \times SaO_2/100) + (PaO_2 \times 0.003)]$$

Cerebral O_2 consumption (ml/kg/min), Cerebral $AV\text{-}DO_2$= [Carotid arterial O_2 content (CaO_2)- Jugular venous O_2 content (CvO_2)] × Qca = [1.39 × Hb × (SaO_2-SvO_2)/100] × Qca

where

Qca = Carotid arterial blood flow (ml/kg/min)

Hb= Hemoglobin concentration (g/dl)

SaO_2= Carotid arterial O_2 saturation (%)

SvO_2= Jugular venous O_2 saturation (%).

PaO_2= Partial pressure of O_2 in carotid arterial blood (mm Hg)

Sample size calculation

Sample size was calculated for the primary outcome of $C\text{-}DO_2$. Based on published and pilot data from our laboratory, $C\text{-}DO_2$ in lambs 15–30 minutes after birth was normally distributed with standard deviation of 0.9 ml/kg/min(21). If the true difference in the experimental and control means was 1.25 ml/kg/min, we needed a total of 24 lambs with 12 lambs in each group to be able to reject the null hypothesis that the population means of $C\text{-}DO_2$ in the experimental groups (abrupt wean) and control (gradual wean) groups are equal with probability (power) of 0.9. The Type I error probability associated with this test of null hypothesis is 0.05.

Data Collection and Analysis

Hemodynamic variables were continuously monitored and recorded using a computer with data acquisition software (BIOPAC systems, Goleta, CA, USA). Continuous variables are expressed as mean and standard deviation (SD). Categorical variables are analyzed using χ^2 test with Fisher's exact test as required. Continuous variables are analyzed by ANOVA repeated measures between groups with Fisher's post hoc test within groups. Paired t-test was used to compare the whole blood oxidized and reduced glutathione and the ratio between the fetal baseline and at 10 min after ROSC. Unpaired t-test was used to compare the difference between GSSG/GSH ratio, GSSG and GSH concentrations at fetal baseline

and at 10 min after ROSC, between the 2 study groups. Statview 5.0.1 (SAS institute Inc., New York) was used for statistical analysis. Statistical significance was defined as $p < 0.05$.

RESULTS

Perinatal asphyxial arrest was induced by umbilical cord occlusion in 25 lambs. The lambs were resuscitated as per AHA Neonatal Resuscitation guidelines. All lambs achieved ROSC and were included in data analysis. Following ROSC, as per randomization, 12 lambs underwent gradual wean and 13 lambs had their FiO_2 abruptly weaned to 0.21. Characteristics of these lambs, including birth weight, sex, baseline hemodynamic parameters and arterial blood gas analyses were similar between the groups at fetal baseline and during cardiac arrest (Table 1). The time to cardiac arrest was also similar between groups. One lamb in each group achieved ROSC without epinephrine. Eight out of 12 lambs in the gradual-wean group and 11/13 lambs in the abrupt-wean group received epinephrine at 0.03 mg/kg, and the remainder of lambs in each group received 0.01 mg/kg. The mean (SD) of inspired O_2 concentration that was provided during resuscitation and after ROSC was significantly different between the two groups by design (Figure 1). There was no statistically significant difference in the left carotid arterial blood flow at fetal baseline, during resuscitation and after ROSC between the two groups (Figure 2).

Blood gas analyses

The arterial PaO_2 was significantly higher with gradual wean compared to abrupt wean during the 1– 10 minute period following ROSC ($p<0.05$, Figure 3A). Mean PaO_2 values were more than 200 mm Hg within a few minutes after ROSC and remained greater than 100 mm Hg at 10 minutes after ROSC with gradual weaning. With abrupt weaning to 21% O_2, mean preductal PaO_2 remained stable and less than 100 mmHg from 1 to 10 minutes after ROSC (Figure 3A). Arterial hemoglobin O_2 saturation (SaO_2) measured by blood gas analysis was significantly higher with gradual wean compared to abrupt wean between one and four minutes after ROSC ($p<0.05$, Figure 3B). Jugular venous partial pressure of O_2 (PvO_2) and venous hemoglobin O_2 saturation (SvO_2) obtained from venous blood gases were not different in the two weaning strategies (Figures 4A and 4B respectively). Preductal arterial partial pressure of carbon-dioxide ($PaCO_2$) was not different between gradual and abrupt wean strategies (Figure 5).

Cerebral oxygen delivery and cerebral oxygen consumption

Cerebral O_2 delivery during CC was low compared to baseline (0.03± 0.06 vs. 0.07± 0.10 ml/kg/min) despite 100% inspired O_2 in both groups (Figure 6). The first blood gas and C-DO_2 measurement obtained immediately after ROSC were similar between the two weaning strategies. However, during the 1 – 15 minute period after ROSC, the C-DO_2 was higher and above the physiological range (in healthy term newborn lambs: median [interquartile range] of 2.6 [1.98–3.55] ml/kg/min) with gradual wean compared to abrupt wean (Figure 6). The range of C-DO_2 in healthy term lambs was obtained from unpublished historical data from our laboratory. These values are similar to published data from asphyxiated lambs with meconium aspiration syndrome targeted to maintain preductal SpO_2 of 85– 95%(21). In contrast, the C-DO_2 was more stable and within the physiological range with abrupt

weaning to 21% O_2. Cerebral AV-DO_2 was not different between the two groups following ROSC (0.71± 0.32 vs. 0.47± 0.05 ml/dl with gradual wean and abrupt wean respectively at 5 min after ROSC).

Effect on glutathione metabolism

The GSSG/GSH ratio and oxidized glutathione (GSSG) concentration in whole blood samples were significantly lower at 10 min following ROSC compared to fetal baseline with abrupt weaning to 21% O_2 (Table 2). The concentration of reduced glutathione (GSH) was significantly lower with gradual weaning from 100% O_2 at 10 min after ROSC compared to fetal baseline.

DISCUSSION

The Textbook of Neonatal Resuscitation suggests increasing inspired O_2 concentration to 100% when chest compressions are started(14). Once heart rate is greater than 60 bpm, and a reliable SpO_2 signal is achieved, adjusting the oxygen concentration to maintain target SpO_2 is suggested(16). The current study demonstrates that abrupt weaning to 21% O_2 immediately following an increase in heart rate minimizes cerebral hyperoxemia and oxidative stress compared to gradual weaning over 5 minutes.

Normal postnatal transition at birth results in a gradual increase in PaO_2 from 25–30 mmHg in the fetus to 45–80 mmHg in the newborn infant over several minutes. This increase in alveolar and arterial O_2 results in pulmonary vasodilation(22) but may lead to a small increase in free radical production(23–25). When O_2 supplementation is needed during and after resuscitation, it adds to the prevailing vulnerability of the newborn to oxidative stress(23, 26). Following recovery from asphyxial arrest, the combination of reperfusion from increased cerebral blood flow, and hyperoxia can result in cerebral oxidative injury in addition to hypoxic-ischemic and reperfusion injury(7, 27, 28). Hyperoxic blood reperfusing the ischemic tissue can form free radicals, worsen oxidative stress, and exacerbate tissue injury(29–31). High PaO_2 (>140 mmHg) within 1 hour after birth has been shown to be associated with higher incidence of moderate to severe HIE(9). Hyperoxemia following ROSC was associated with higher mortality when compared to normoxemia in a large registry-based study of pediatric cardiac arrest(32). The 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations (CoSTR) for pediatric life support guidelines suggest targeting normoxemia after ROSC, with target SpO_2 of 94–99% as an alternative to measuring PaO_2, for titrating inspired O_2 when feasible to achieve normoxia(33). How to utilize oxygen following resuscitation in newborn infants is listed as a major gap in knowledge in the most recent neonatal resuscitation guidelines(16). The International Liaison Committee Neonatal Life Support Task Force is planning a future systematic review of this topic(2).

Several previous publications have compared the use of room air and pure O_2 during resuscitation in asphyxiated newborns(34–36). Linner et al reported high brain tissue PaO_2 with 100% O_2 during CC and similar time to ROSC with 21% O_2 in one-day old piglets(37). Solevag et al observed higher SpO_2 and higher left ventricular GSSG/GSH ratio after CC using 100% O_2(38, 39). Rawat et al reported that lambs ventilated with 100% O_2

during CC had marked increase in PaO_2 and pulmonary blood flow immediately following ROSC compared to those ventilated with room air(17). C-DO_2 was significantly lower during CC with both room air and pure O_2 comparable to that in the fetal lamb. However, following ROSC, C-DO_2 was significantly higher with 100% O_2. Rosenberg et al observed decreased cerebral O_2 consumption and fractional O_2 extraction immediately after recovery from asphyxia compared to control animals with no asphyxia(40). However, none of these studies evaluated optimal O_2 weaning strategies following successful recovery with chest compressions for perinatal cardiac arrest.

The presence of high $PaCO_2$ following prolonged asphyxia results in increased cerebral blood flow(41). Initial PPV with 100% O_2 and gradual weaning of inspired O_2 based on SpO_2 can be associated with ischemia-reperfusion compounded by hyperoxia(17) and a potential for cerebral tissue injury due to free radical exposure(42, 43). Recently, Badurdeen et al described the cerebral O_2 kinetics and hemodynamics immediately after ROSC in an asphyxiated term lamb model. Similar to our study, they demonstrated marked increase in C-DO_2 with gradual weaning of FiO_2 over 10–12 minutes targeting SpO_2 of 88–95%. Additionally, they noted a decrease in cerebral fractional O_2 extraction between 3–9 minutes after ROSC in comparison to fetal baseline, and fluctuations in cerebral blood flow and arterial blood pressure following ROSC. This study confirms that the gradual wean strategy for FiO_2 following ROSC results in excess C-DO_2 compared to consumption(13).

The present study has shown that abrupt weaning of inspired O_2 to room air immediately following ROSC could be protective against cerebral hyperoxia by limiting C-DO_2 while allowing for stable changes in PaO_2 and SaO_2 without compromising AV-DO_2. Furthermore, we report a decrease in GSSG and GSSG/GSH ratio in whole blood with abrupt weaning to room air and decrease in GSH concentration with gradual weaning from 100% O_2 at 10 min after ROSC compared to fetal baseline prior to cord occlusion. Glutathione (γ glutamyl-cysteinyl-glycine, GSH) is a crucial tripeptide involved in intracellular defense against reactive oxygen species mediated cell injury(44). In its reduced form, GSH combines with reactive oxygen species and functions as a free radical scavenger. Our findings may indicate preservation of antioxidant mechanisms with abrupt weaning to 21% O_2 and excessive oxidative stress with gradual weaning from pure O_2.

We acknowledge many limitations in the current study. Pulmonary artery blood flow and pressure were not measured. Tissues were not collected and analyzed to assess brain injury. Neurologic outcomes were not assessed. Even though the lambs were randomized by opaque envelopes, the resuscitation team was not blinded. Most lambs received 0.03 mg/kg dose of epinephrine, but 2 lambs had spontaneous ROSC with chest compressions without epinephrine and 3 lambs received 0.01 mg/kg. We did not evaluate intermediate concentrations of inspired O_2 (e.g., 30–50%) which may be more relevant in the presence of lung disease or pulmonary hypertension. However, this is the first study to evaluate abrupt weaning to 21% O_2 after recovery from perinatal asphyxial arrest and compare to gradual weaning from 100% O_2. Real time monitoring of physiological parameters including invasive blood flows and blood gases were performed. This model of perinatal asphyxial arrest by umbilical cord occlusion in lambs is a well-established large animal

model, with similar size and physiology as human neonates that allows for instrumentation and resuscitation(45).

CONCLUSION

In a term ovine model of perinatal asphyxial cardiac arrest, weaning down from 100% O_2 after ROSC resulted in cerebral hyperoxia and oxidative stress during the first 10 minutes after ROSC. The simple intervention of abrupt weaning to 21% inspired O_2 immediately after ROSC followed by titrating up not only limits excessive PaO_2 and C-DO_2, but also limits oxidative stress in the post-resuscitation period. Clinical studies assessing neurodevelopmental outcomes with different weaning strategies are warranted.

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Impact Statement:

- In a lamb model of perinatal asphyxial cardiac arrest, abrupt weaning of inspired oxygen to 21% prevents excessive oxygen delivery to the brain and oxidative stress compared to gradual weaning from 100% oxygen following return of spontaneous circulation.
- Clinical studies assessing neurodevelopmental outcomes comparing abrupt and gradual weaning of inspired oxygen after recovery from neonatal asphyxial arrest are warranted.

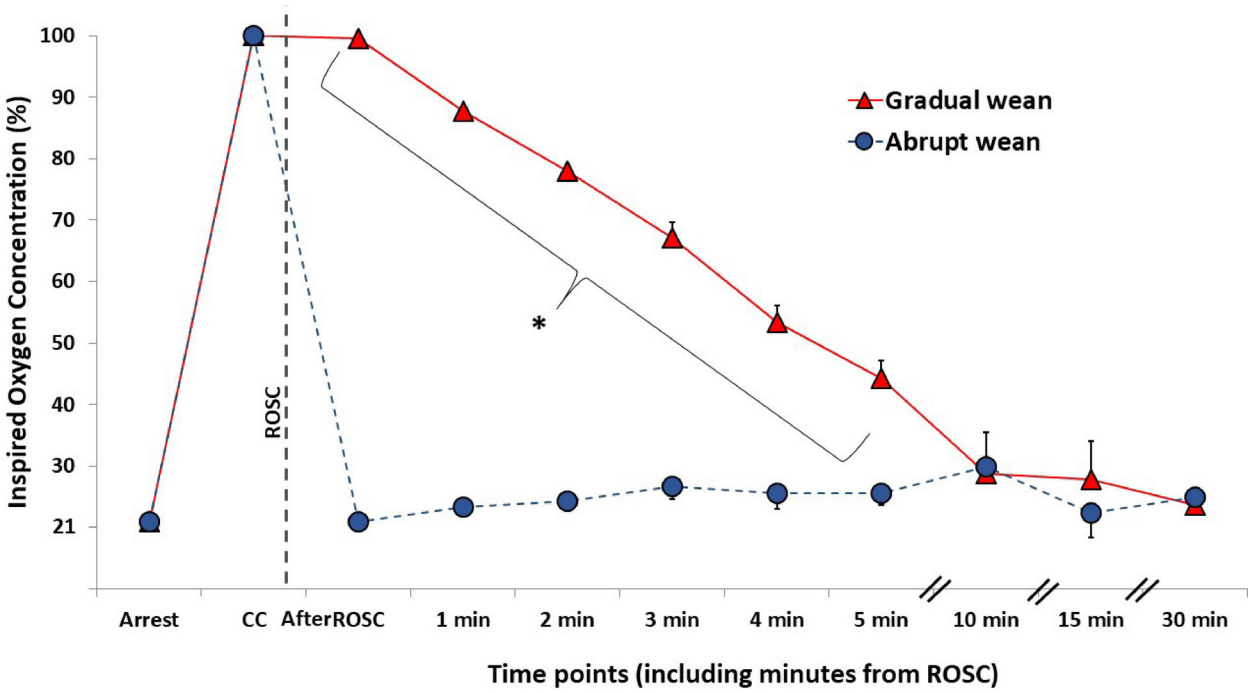

Figure 1:

The inspired O_2 concentration and weaning strategy in gradual wean and abrupt wean groups after ROSC. The inspired oxygen concentration was different between groups after ROSC. Data represented as mean and standard error of mean (SEM). *p value < 0.05 by ANOVA repeated measures.

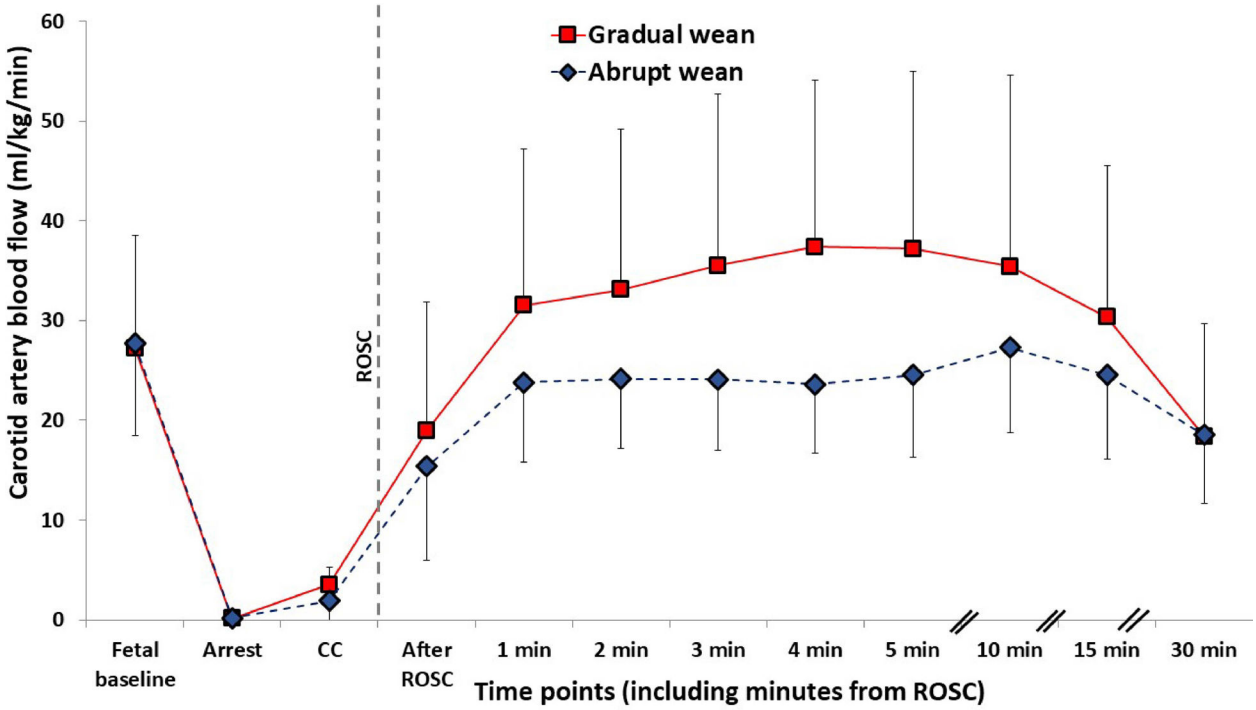

Figure 2:

The left carotid arterial blood flow during fetal baseline, asphyxia, resuscitation and ROSC. There were no differences at fetal baseline, asphyxia, during resuscitation and after ROSC between gradual wean and abrupt wean. Data presented as mean and standard deviation (SD).

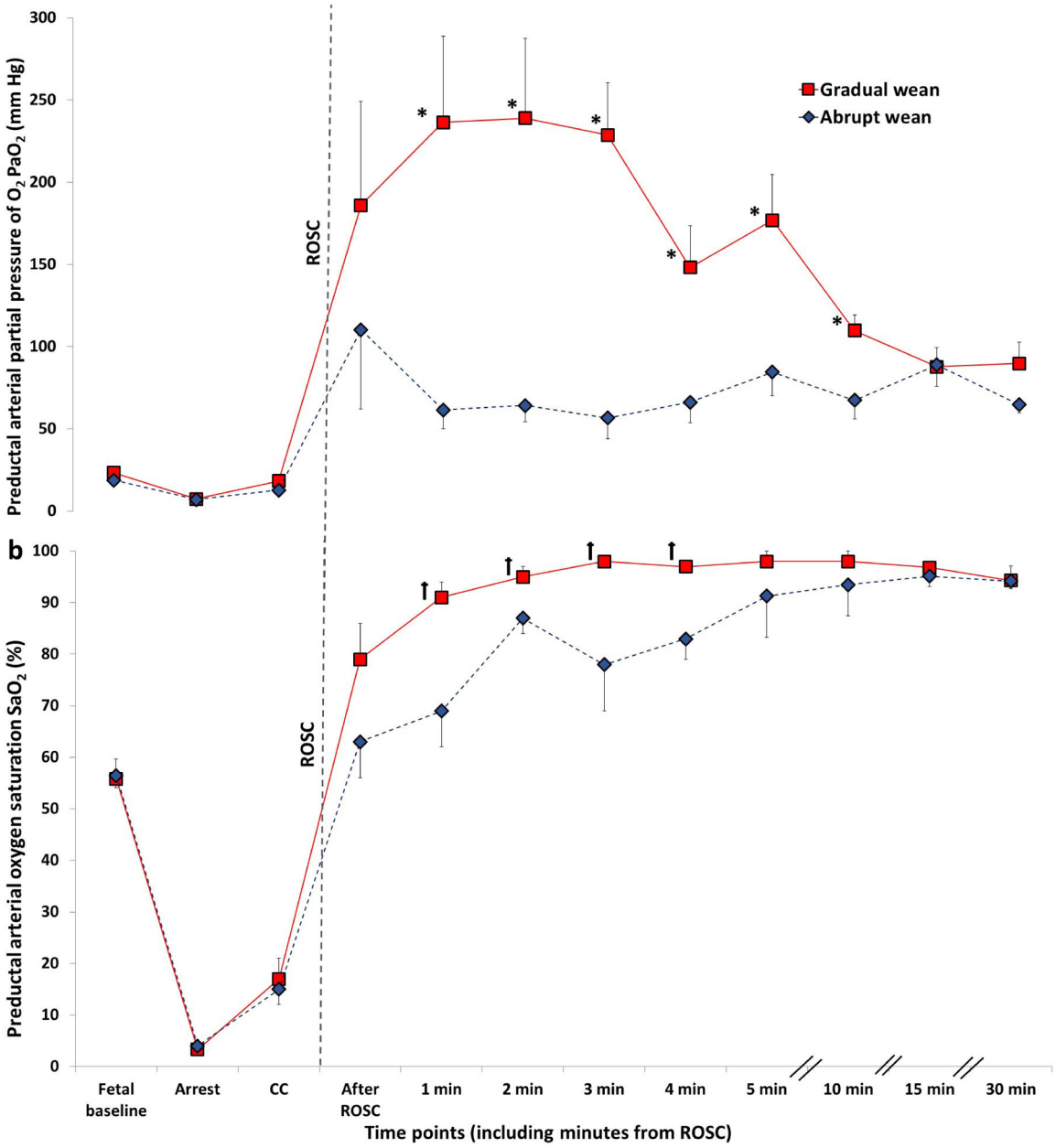

Figure 3:

Preductal arterial partial pressure of O_2 (PaO_2, Figure 3A) and arterial hemoglobin O_2 saturation (SaO_2, Figure 3B) obtained from serial blood gases in gradual wean and abrupt wean groups. These values were significantly higher with gradual wean compared to abrupt wean following ROSC. *p< 0.01, † p<0.05 by ANOVA repeated measures. Data presented as mean and SEM.

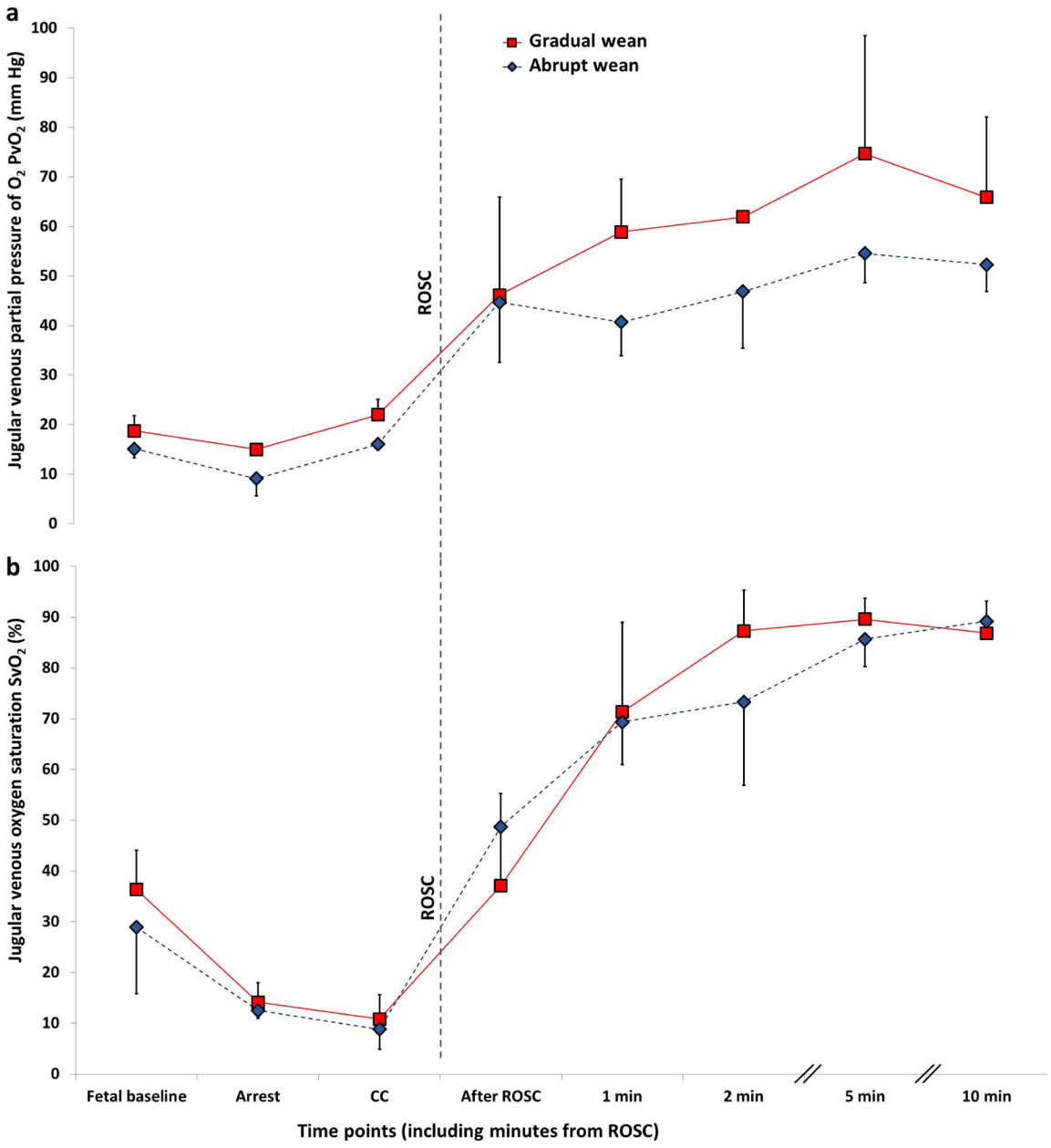

Figure 4:

The venous partial pressure of O_2 (PvO_2, Figure 4A) and venous hemoglobin O_2 saturation (SvO_2, Figure 4B) obtained from serial blood gases were not different between the two inspired O_2 weaning strategies. Data presented as mean and SEM.

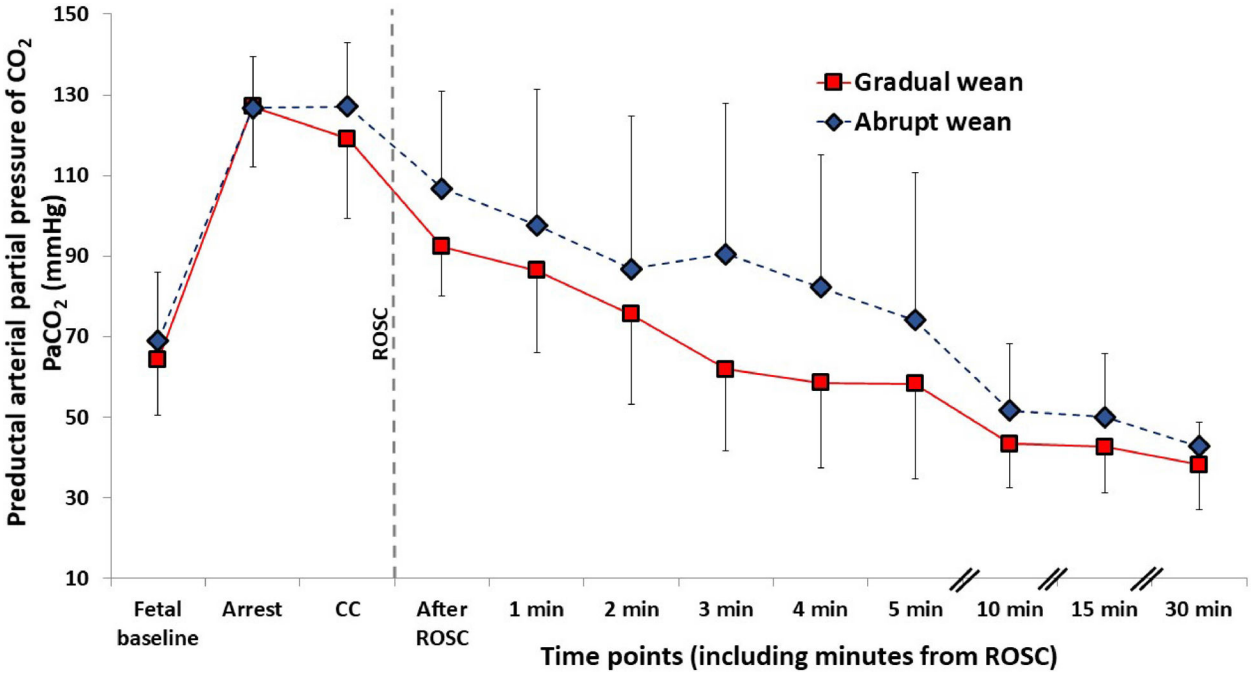

Figure 5:

Preductal arterial partial pressure of carbon dioxide ($PaCO_2$) was not different between the two inspired O_2 weaning strategies. Data presented as mean and SD.

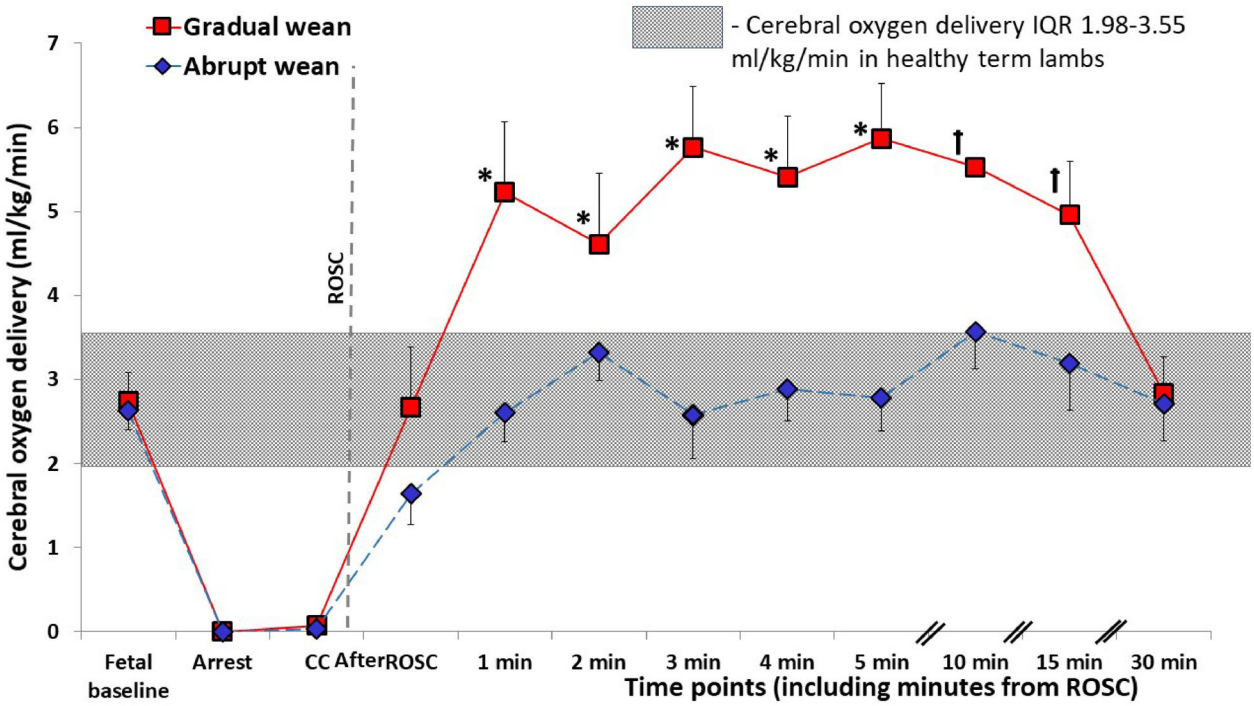

Figure 6:

Cerebral oxygen delivery ($C\text{-}DO_2$) was significantly higher with gradual wean compared to abrupt wean, potentially resulting in cerebral hyperoxia from supra-physiological $C\text{-}DO_2$. Data represented as mean and SEM. *$p< 0.01$, † $p<0.05$ by ANOVA repeated measures. ROSC: return of spontaneous circulation. The median (interquartile range) for $C\text{-}DO_2$ in normal term lambs breathing room air is shown by the shaded area (median= 2.6 ml/kg/min; IQR-1.98 to 3.55 ml/kg/min).

Table 1:

Characteristics of lambs including preductal arterial blood gas analyses at fetal baseline, cardiac arrest and ROSC in gradual wean and abrupt wean groups.

	Gradual wean (n=12)	Abrupt wean (n=13)	p- value
Weight (kg)	4.2 (1.3)	3.8 (0.7)	0.38
Sex M:F	6:6	5:8	0.56
Time to asystole (min)	12 (10–13)	14 (14–17)	0.05
ABG at fetal baseline before cord occlusion			
pH	7.22 (0.10)	7.17 (0.08)	0.28
$PaCO_2$ (mm Hg)	64 (14)	69 (17)	0.56
PaO_2 (mm Hg)	23.1 (5.9)	19.5 (6.9)	0.08
SaO_2 (%)	56 (13)	57 (9)	0.89
Hemoglobin (g/dL)	13 (1.2)	12.3 (2)	0.42
Lactate (mmol/L)	3.7 (2.1)	5.2 (3.8)	0.16
ABG at cardiac arrest			
pH	6.88 (0.08)	6.86 (0.06)	0.67
$PaCO_2$ (mm Hg)	127 (15)	127 (13)	0.94
PaO_2 (mm Hg)	4.3 (4.3)	4.4 (4.8)	0.82
SaO_2 (%)	3 (3)	4 (4)	0.61
Hemoglobin (g/dL)	13.6 (1.8)	12.2 (1.6)	0.06
Lactate (mmol/L)	9.1 (2.7)	8.9 (4.1)	0.96
ABG immediately after ROSC			
pH	6.91 (0.10)	6.86 (0.06)	0.14
$PaCO_2$ (mm Hg)	92 (12)	106 (24)	0.08
PaO_2 (mm Hg)	139 (194)	72 (129)	0.08
SaO_2 (%)	78 (22)	63 (27)	0.08
Hemoglobin (g/dL)	12.6 (1.5)	11.5 (1.6)	0.15
Lactate (mmol/L)	11.6 (2.9)	11.6 (4.6)	0.85

Continuous variables are reported as mean (standard deviation) and median (interquartile range). ABG: preductal arterial blood gas; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; SaO_2: arterial oxygen saturation. ROSC: return of spontaneous circulation.

Table 2:

Whole blood oxidized to reduced glutathione ratio at 10 min after ROSC compared to fetal baseline between gradual wean and abrupt wean.

Parameter	Gradual wean	Abrupt wean
GSSG/GSH ratio		
Fetal baseline	0.012 (0.002)	0.018 (0.006)
10 min after ROSC	0.061 (0.139)	0.012 (0.005)
p-value	0.37	0.02 *
GSSG (μM/ml)		
Fetal baseline	16.6 (3.3)	17.6 (3.2)
10 min after ROSC	12.2 (3.3)	10.3 (3.3)
p-value	0.25	0.03 *
GSH (μM/ml)		
Fetal baseline	1564 (344)	1188 (167)
10 min after ROSC	1137 (272)	1031 (149)
p-value	0.04 *	0.21
Difference in GSSG/GSH ratio between fetal baseline and 10 min after ROSC	+0.049 (0.051)	−0.006 (0.002)
Difference in GSSG concentration between fetal baseline and 10 min after ROSC (μM/ml)	−4.4 (2.6)	−7.3 (2.7)
Difference in GSH concentration between fetal baseline and 10 min after ROSC (μM/ml)	−427 (166)	−157 (112)

Variables are reported as mean (SEM). Fetal baseline: prior to cord occlusion. GSSG: oxidized glutathione. GSH: reduced glutathione. GSSG/GSH ratio: oxidized to reduced glutathione ratio. ROSC: return of spontaneous circulation.

* $p<0.05$ by paired t-test.

Difference in GSSG:GSH ratio, GSSG and GSH concentrations between fetal baseline and 10 min after ROSC were compared between gradual wean and abrupt wean groups by unpaired t-test, and were not statistically different.