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Optimal oxygen use in neonatal advanced cardiopulmonary resuscitation—a literature review

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Abstract

Background and Objectives: Oxygen (O_2) use during neonatal cardiopulmonary resuscitation (CPR) remains a subject of controversy. The inspired O_2 concentration during neonatal CPR, that hastens return of spontaneous circulation (ROSC), allows adequate cerebral and myocardial O_2 delivery, and enhances survival to discharge, is not known. The optimal FiO_2 during CPR should decrease incidence of hypoxia but also avoid hyperoxia, and ultimately lead to improved neurodevelopmental outcomes. Due to infrequent need for extensive resuscitation, and emergent circumstances surrounding neonatal CPR, conducting randomized clinical trials continues to be a challenge. The goal of this study was to review the evolution of oxygen use during neonatal CPR, the evidence from animal and clinical studies on oxygen use during neonatal CPR and after ROSC, the pertinent physiology including myocardial oxygen consumption and cerebral oxygen delivery during CPR, and outcomes following CPR in the DR and in the neonatal intensive care unit.

Methods: This narrative review is based on recent and historic English literature in PubMed and Google scholar over the past 35 years (January 1, 1985 – May 1, 2021).

Key Content and Findings: Several studies in animal models have compared ventilation with different inspired O_2 concentrations (mostly 21% and 100%) during chest compressions and after ROSC. These studies reported no difference in short-term outcomes, even with as low as 18% O_2. However, in lamb models of cardiac arrest and CPR, 100% O_2 during chest compressions is associated with better oxygen delivery to the brain compared to 21% O_2. Abrupt weaning to 21% O_2 following ROSC followed by titration to achieve preductal SpO_2 of 85–95% minimizes

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systemic hyperoxia and oxidative stress compared to slow weaning from 100% O_2 following ROSC.

Conclusions: Clinical research is needed to arrive at the best strategy for assessment of oxygenation and choice of FiO_2 during neonatal CPR that lead to improved survival and outcomes. In this article, we have reviewed the literature on evidence behind O_2 use during neonatal advanced CPR and after ROSC.

Keywords

Oxygen (O_2); neonatal resuscitation; neonatal cardiopulmonary resuscitation; hyperoxia; chest compressions (CC)

Introduction

Newly born infants infrequently need advanced resuscitation including endotracheal intubation, chest compressions (CC), medications such as epinephrine, and fluid administration (1-3). Neonates surviving extensive cardiopulmonary resuscitation (CPR) are at risk for poor neurodevelopmental outcomes (4). Oxygen (O_2) is the most frequently used drug in newborns during resuscitation in the delivery room (DR). During extensive CPR including CC for neonatal bradycardia and cardiac arrest, the International Liaison Committee on Resuscitation (ILCOR) advocates increasing inspired O_2 to 100%. However, researchers have reported similar outcomes with the use of lower inspired O_2 compared to 100% O_2 during CC (Table 1). Furthermore, evidence has emerged over the past decade that hyperoxia may be harmful in the post-resuscitation period (5). Optimal oxygen use during CPR in the neonatal intensive care unit (NICU) especially among preterm infants with bronchopulmonary dysplasia (BPD) or pulmonary hypertension is not known. Judicious use of O_2 during advanced neonatal resuscitation based on robust evidence is warranted to minimize further tissue injury during resuscitation and post-resuscitation period, as well as improve long-term outcomes. We present this article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-21-74/rc).

Methods

This narrative review is based on recent and historic English literature in PubMed and Google scholar over the past 35 years (January 1, 1985 – May 1, 2021). More detailed methods could be found in Table 1.

Evolution of oxygen use in neonatal CPR

Oxygen has been an integral component of neonatal resuscitation for almost two centuries. Use of 100% O_2 in newborns requiring positive pressure ventilation (PPV) in the DR remained unquestioned until recently, since perinatal asphyxia is associated with hypoxic ischemic injury to the brain. However, multiple animal studies have reported increases in inflammation in the lung, heart, and brain, neurological and brain injury, elevated pulmonary vascular reactivity, oxidative stress, and activation of transcription factors with neonatal

exposure to 100% O_2 at birth (6-9). Towards the end of the 20th century, efforts of investigators resulted in randomized and quasi-randomized trials that demonstrated higher neonatal mortality, prolonged time to first breath, increased duration of resuscitation, and higher exposure to O_2, lower 5-minute Apgar score, more myocardial and kidney injury, higher oxidative stress and increased risk of childhood leukemia and cancer when neonatal resuscitation was initiated with 100% O_2 as compared to 21% O_2 in term neonates (10-16). Thus, there was a clear change in approach towards use of room air at initiation of ventilation in asphyxiated term neonates by the end of the first decade of 21st century, with a shift in focus towards improved effectiveness of ventilation (17,18). A recent meta-analysis by ILCOR supports this approach in term infants (19), although the optimal initial inspired O_2 concentration for preterm neonates remains unknown (20).

The goal of neonatal resuscitation is effective ventilation to switch the site of gas exchange from the placenta to the lungs. When effective ventilation fails to raise the heart rate >60 beats per min (bpm), CC are indicated (in addition to PPV) to pump deoxygenated blood from the right ventricle (RV) to the lungs for oxygenation, and oxygenated blood from the left ventricle (LV) to the coronary and cerebral circulations until return of spontaneous circulation (ROSC) is achieved (21). Neonatal resuscitation guidelines continue to recommend increasing the inspired O_2 to 100% (based on expert opinion) when CC are needed for severe bradycardia while acknowledging that there is a dearth of evidence in this topic (21). This stems from an attempt to maximize O_2 delivery during CPR to the myocardium to hasten recovery and improve chances of survival, and to the brain in hopes of improving overall neurodevelopmental and cognitive outcomes by minimizing cerebral hypoxic injury.

Assessment of oxygenation status during CPR

During CPR, neonates are monitored for adequate chest rise, bilateral breath sounds (in response to effective PPV) and rise in heart rate by auscultation and electrocardiogram (in response to effective PPV and/ or CC) (22). Color of the infant is a poor indicator of tissue oxygenation status (23). An increasing heart rate by electrocardiogram (EKG) [with palpable pulsations at the base of the umbilical cord to rule out pulseless electrical activity (PEA)] is the most reassuring sign of effective resuscitation.

When a pulse oximetry probe is placed on the right upper extremity to assess the preductal capillary O_2 saturation (SpO_2), the oximetry reading is either absent or inaccurate during severe bradycardia, asystole and during CC owing to poor peripheral perfusion. Cerebral regional oxygen saturation ($CrSO_2$) can be recorded non-invasively during neonatal resuscitation by near-infrared spectroscopy. Badurdeen *et al.*, and Zeinali *et al.*, evaluated the utility of $CrSO_2$ monitoring in ovine models of perinatal cardiac arrest, and found that $CrSO_2$ correlated better with cerebral O_2 delivery than SpO_2 (24,25). $CrSO_2$ may be more sensitive compared to SpO_2 in the DR to assess cerebral oxygenation, detect ROSC, and titrate inspired O_2, and requires further investigation (25). We speculate $CrSO_2$ is more reliable than SpO_2 as it does not depend on pulsatile flow and reflects oxygen delivery (oxygen content × blood flow) to the brain. In addition, oxygen consumption by the brain is significantly impaired soon after asphyxia (Figure 1A) (24,26,27). The arteriovenous

oxygen difference ($AVDO_2$; Figure 1B) in the immediate post-resuscitation period following cardiac arrest is 1.86±0.6 mL/dL (carotid arterial oxygen content =15.3±2.7 mL/dL; jugular venous oxygen content =13.5±2.4 mL/dL) (27). In lambs with asphyxial bradycardia and meconium aspiration (without arrest), the $AVDO_2$ in the immediate post-resuscitation period following cardiac arrest is 0.9±0.4 mL/dL (Carotid arterial oxygen content =14.6±2.5 mL/dL; jugular venous oxygen content =13.9±2.7 mL/dL) (28). These results suggest that oxygen consumption by the brain is low in neonatal lambs soon after an asphyxial episode. This results in cerebral venous oxygen saturation fairly similar to arterial oxygen saturation during the immediate post-asphyxial period.

Several investigators have evaluated oxygenation in the fetus and during fetal-to-neonatal transition. The fetus is exposed to a PaO_2 of 27–35 mmHg from the oxygenated umbilical venous blood (29). Soon after delivery, a healthy newly born infant breathing room air has a PaO_2 of 45–80 mmHg. Exposure to room air with 21% O_2 is adequate to raise the alveolar PO_2 (PAO_2) and hence the arterial PO_2 (PaO_2), that along with lung aeration results in pulmonary vasodilation and decrease in pulmonary vascular resistance (PVR) (30,31). However, in the clinical setting, it is not possible to obtain repeated invasive measurements including arterial blood gases to assess the oxygenation and ventilation. Many researchers diligently performed studies in both perinatal and postnatal animal models of asphyxial arrest in an endeavor to determine the optimal inspired O_2 concentration during CPR.

Evidence from animal studies (Table 2)

Linner *et al.* evaluated asphyxiated and bradycardic newborn piglets and compared PPV with air *vs.* 100% O_2 for 3 or 30 min during CC (32). The authors observed no difference in speed of circulatory recovery and cerebral oxygenation (32). The duration of CC was relatively short in this model of bradycardia. However, 100% O_2 during CC for bradycardia resulted in very high brain tissue PO_2 (32). In the setting of inadequate ventilation, the same authors observed earlier ROSC with one O_2 breath per minute compared to air (33). Dannevig *et al.* compared 21% and 100% O_2 during CPR and reported no difference in time to ROSC and markers of lung or cerebrospinal fluid inflammatory response (34,35). Solevåg *et al.* similarly compared 21% and 100% O_2 during CPR in post-natal piglets and reported no differences in mean arterial blood pressure, heart rate, pH, pCO_2, IL-1ß or lactate/pyruvate ratios (36). At the same token, there was an inherent bias in this study towards 21% O_2 (Table 2). Additionally, they observed higher SaO_2 and $CrSO_2$ in animals resuscitated with 100% O_2 (36). Subsequently, Solevåg *et al.* also demonstrated lower myocardial oxidative stress (oxidized/ reduced glutathione ratio 0.1 (0.09–0.12) *vs.* 0.13 (0.11–0.2), P=0.04, with 21% *vs.* 100% O_2 during CC respectively) and improved cardiac function with the use of room air compared to 100% O_2 during CPR (37). Recently, Solevåg *et al.* randomized newborn piglets to receive 18%, 21% and 100% O_2 concentrations during CPR, and did not find any difference in time to ROSC or myocardial and frontoparietal cortical oxidative stress from hypoxia or hyperoxia (38). Thus, from these postnatal piglet models of cardiac arrest/ bradycardia, room air resuscitation appeared to be safe, and as effective, but may not be superior to the current practice of using 100% O_2.

Perinatal ovine models of asphyxial arrest provide a window of opportunity to evaluate the hemodynamics during the fetal-to-neonatal transition with the fetal shunts (patent foramen ovale and ductus arteriosus), fluid filled lungs and high pulmonary vascular resistance (39-41). Perez-de-Sa *et al.* noted very high brain tissue PO_2 with prolonged ventilation with 100% O_2 in severe near-term ovine asphyxia without cardiac arrest (39). Rawat *et al.* observed low PaO_2 (21.6±1.6 mmHg with 21% O_2 and 23.9±6.8 mmHg with 100% O_2) and cerebral O_2 delivery (0.05±0.06 mL/kg/min with 21% O_2 and 0.11±0.09 mL/kg/min with 100% O_2) during CC in term perinatal ovine asphyxial arrest, that were significantly lower than fetal baseline values (40). Furthermore, they reported significantly higher cerebral O_2 delivery at peak of CC and excessive PaO_2 post-ROSC among lambs ventilated with 100% O_2 during CC (Table 1). A meta-analysis showed no difference in mortality or time to ROSC between use of 21% and 100% O_2 during CC (43). However, resuscitation with 21% O_2 may lead to inadequate oxygenation, delayed pulmonary transition and elevated PVR which could further extend the window of hypoxic ischemic injury (44). Therefore, the optimal inspired O_2 during CC remains controversial.

Lack of human trials

There are no clinical trials evaluating O_2 use during neonatal CPR. Emergent situation and ethical issues preclude performance of such a study in human neonates. Clinical trials are difficult to conduct due to the infrequent need for CC, emergent clinical circumstances with inadequate time to obtain parental informed consent. While planning clinical trials, other factors that contribute to poor outcomes, including etiology of cardiac arrest, duration of cardiac arrest, need for and number of epinephrine doses, duration of resuscitation, availability of trained personnel in the DR capable of advanced resuscitative interventions, should be accounted for as confounding variables while evaluating inspired O_2 concentrations during CPR. Multicenter prospective observational studies to collect clinically important information are being conducted and might be a good source of information in the absence of randomized clinical trials (4).

Observational studies of infants undergoing CPR and with low Apgar scores provides some information regarding short- and long-term follow-up of neonates undergoing CC. evidence in term infants and preterm infants are presented below. These results demonstrate a high incidence of mortality and neurodevelopmental impairment following advanced CPR at birth further emphasizing the importance of optimal cerebral oxygenation during CC.

Evidence in term infants

Harrington *et al.* conducted a systematic review of literature to investigate the outcomes of infants who had an Apgar score of zero at 10 minutes in the pre-therapeutic hypothermia era (infants born between January 1991 and December 2004) (45). Eighty-five cases were identified of which 9 within the Oxford database were closely evaluated. Six died before discharge, one with severe quadriparesis and microcephaly died at 11 months. One infant had severe spastic quadriparesis and global delay. One infant had mild disability at 2 years follow-up. Evaluation of all 94 infants (85 from the literature and 9 in this case series), 88 (94%) either died or had severe handicap; 2 infants (2%) had moderate handicap and

1 (1%) had mild handicap. Three infants were lost to long-term follow-up. The authors concluded that an Apgar score of zero at 10 minutes is associated almost universally with a poor outcome (45). In 2007, in an accompanying editorial, Drs. Carlo and Schelonka commented on the limitations of Harrington *et al.* and concluded that at the present time (in 2007), evidence suggests that resuscitation beyond 10 minutes in neonates without cardiac activity or other signs of life may not be justified. However, they pointed out that outcomes of these infants could be significantly improved with therapeutic hypothermia (46). The AAP/AHA NRP recommendations in 2015 specified that an Apgar score of zero at 10 minutes was a strong predictor of mortality and morbidity in late preterm and term infants (47). If heart rate was undetectable after 10 minutes of resuscitation, it was reasonable to stop assisted ventilation in the pre-hypothermia era. However, an individualized decision based on effectiveness of resuscitation, availability of therapeutic hypothermia and advanced neonatal care, and family wishes was recommended.

Laptook *et al.* evaluated 208 infants in a secondary analysis of term infants (≥36 weeks' gestation at birth) infants enrolled in the NICHD NRN cooling trial (48). Twenty-seven percent of these infants had Apgar scores of 0 to 2 at 10 minutes. Death or disability occurred in 76% of infants with a 10-minute Apgar score of 0 (19/25). Death occurred in 48% and among 13 survivors, 7 (54%) had moderate to severe disability. Six infants survived without moderate or severe disability with a Mental Developmental Index (MDI) of 87±9 (range, 73–100) (48).

Shah *et al.* evaluated 13 infants (gestational age ≥35 weeks) with Apgar score of zero at 10 minutes admitted to the NICU in the era of therapeutic hypothermia from Western Australia (49). Out of the 5 survivors, three had normal cognitive scores (100, 100 and 110) on Bayley III assessment at 2 years of age and one infant had a normal Griffiths score of 103 at 1 year. Only one infant developed severe spastic quadriplegia (49). A recent systematic review by ILCOR included 579 newborns from 16 studies with ongoing need for CPR at 10 min after birth for asystole, bradycardia or PEA. Newborns with ongoing need for CPR at 10 min after birth are at increased risk for mortality and neurodisability, although survival without neurodevelopmental impairment is possible (4). These results have led to revision of guidelines. The revised NRP recommendations state that in a newly born baby with confirmed absence of heart rate after all appropriate steps are performed, cessation of resuscitation efforts may be considered around 20 minutes after birth. This decision should be individualized based on patient and contextual factors (50).

Evidence in preterm infants

Sproat *et al.* studied 22 babies with no detectable heart beat at 10 minutes of age among 35,805 births between 2009 and 2013 (51). These included 7 infants between 24 and 31 weeks' gestation. In four of these preterm infants, heart rate was detected at 15, 12, 35 and 17 minutes but they all died at 30 minutes, 48 h, 10 h and 72 h respectively. The other 3 preterm infants could not be resuscitated. In contrast, 55% of term (>37 weeks gestation) babies survived and 67% of survivors had a normal 2-year neurodevelopmental outcome in this study (51).

Similarly, the Canadian Neonatal Network reported poor survival (35%) among infants <32 weeks gestation at birth with an Apgar score of zero at 10 minutes compared to term (≥36 weeks gestation) infants with a survival to discharge of 61%. Among preterm infants <32 weeks gestation with an Apgar score of zero at 10 minutes, only 5/31 (16%) survived to NICU discharge without brain injury. In this preterm <32 weeks gestation category, mortality before hospital discharge remained high (39%) even when the Apgar score was 1–2 or 3–5 at 10 minutes (52).

We need multicenter observational studies that record inspired oxygen used during CPR. Although invasive monitoring of hemodynamics and recurrent blood sampling for assessment of gas exchange may be challenging in the clinical settings, human trials can collect data on FiO_2, $CrSO_2$, and SpO_2 and will enable long term follow-up for assessment of survival and neurodevelopmental outcomes.

Myocardial energy and oxygen demand during CPR

Animal models of neonatal bradycardia and cardiac arrest have helped investigators explore myocardial energy and oxygen demand during CC. Newborns who remain persistently bradycardic in the DR have failed to respond to early effective ventilation, and have poor pulmonary vascular transition, hypoxemia and severe metabolic acidosis (53). In such severe asphyxia, the myocardium has been depleted of its energy substrates such as ATP (54). In these neonates, CC are indicated to allow adequate coronary arterial blood flow to kick-start the heart. Coronary blood flow occurs solely in diastole in a normal cardiac cycle and during the “decompression” phase of CC due to high right atrial pressures during the compression phase of CC (Figure 2A-2C) (54). Delivery of oxygenated blood to the myocardium can potentially facilitate aerobic metabolism with mitochondrial generation of ATP to restore the myocardial function. Additionally, CPR is followed by an intense sympathoadrenal response increasing the systemic vascular resistance and enabling blood flow to the brain (55). A particular challenge in newly born infants is the presence of ductus arteriosus which prevents buildup of diastolic pressure during CC for cardiac arrest. Vali *et al.* have reported low diastolic pressures such as 9 mmHg associated with successful ROSC in the perinatal lamb model (56). During decompression phase, such low diastolic pressures appear to lead to adequate coronary perfusion pressure and coronary flow (Figures 2,3) (53). Immediately after birth, following clamping of the umbilical cord and ventilation of the lungs with 21% oxygen, carotid flow, aortic pressure and pulmonary flow rapidly increase (Figure 4A). The pulmonary flow is predominantly forward with minimal retrograde flow during diastole due to high PVR and bidirectional ductal shunting (Figure 4A). In contrast, pulmonary flow is bidirectional with minimal forward flow during chest compressions but significant retrograde flow during the decompression phase (Figure 4B). This results in minimal effective pulmonary flow to support gas exchange during CPR for cardiac arrest. Hence, providing 100% oxygen during CC for cardiac arrest might benefit by reducing the duration of CPR and increase oxygen content in the low flow volume of pulmonary venous return (Figure 4B).

Meanwhile, the pumping of deoxygenated blood from the RV to the lungs is a requirement to enable adequate gas exchange and oxygenation, especially following early cord clamping

and removal of placental source of oxygenated blood. Furthermore, the presence of fetal shunts with persistent high PVR (due to hypoxic pulmonary vasoconstriction) diverts deoxygenated blood away from the lungs and towards the systemic circulation (57). Effective ventilation of the lungs with supplemental O_2 can potentially mediate increased pulmonary blood flow and therefore, enable gas exchange at the alveolar-capillary membrane (58). For the fetus who was exposed to a maximum PO_2 of 27–35 mmHg from the umbilical venous blood, any amount of O_2 supplementation (even 21% O_2) may be surplus in aiding pulmonary vasodilation (29). Simultaneously, adequate cerebral perfusion in order to minimize brain injury is desired. The goal is to supplement with just enough inspired O_2 that bring about decrease in PVR along with lung aeration strategies during CPR, with optimal coronary and cerebral perfusion, while not causing toxicity from hyperoxia. However, Rawat *et al.* demonstrated that gas exchange during CPR is suboptimal (40). The carotid blood flow, PaO_2 and cerebral O_2 delivery are very low during CPR both with 21% and 100% O_2 supplementation. Thus, more intricate research in warranted to decipher the optimal strategy of oxygenation during CPR.

Epinephrine is a catecholamine with inotropic, chronotropic, lusitropic, and vasoconstrictor properties. Vasoconstriction mediated by effect of epinephrine on α adrenergic receptors are primarily responsible for its effects on increasing systemic vascular resistance and coronary perfusion pressure during neonatal CPR (59,60). However, β-adrenergic effects of epinephrine may increase myocardial work and oxygen demand (61). In addition, epinephrine is a pulmonary vascular constrictor that increases pulmonary vascular resistance further reducing the oxygen uptake and is associated with persistent pulmonary hypertension (62).

Cerebral oxygen delivery and consumption after ROSC

In the immediate post-ROSC period, hypercapnia from the accumulated arterial PCO_2 results in post-ischemic cerebral hyperemia. Following ROSC, there is a swift increase in cerebral blood flow, cerebral vascular blood pressure and oxygen saturation (SaO_2) resulting in an increase in cerebral oxygen delivery (24). Gradual weaning of inspired O_2 down from 100% based on NRP recommended preductal SpO_2 targets in asphyxiated term lambs after ROSC is accompanied by a rapid increase in cerebral O_2 delivery and PaO_2 that remained higher and above the physiological range in term newborn lambs ventilated with room air until 10–15 min after ROSC (27). Moreover, the increased cerebral O_2 delivery following ROSC is associated with a decrease in cerebral O_2 consumption due to slowed metabolism (24-27), that may result in cerebral hyperoxemia, generation of excessive oxygen free radicals and potential toxicity with cerebral tissue injury.

Infants surviving severe hypoxic ischemic encephalopathy (HIE), especially after requiring extensive resuscitation including CC are at risk of poor neurodevelopmental outcomes (4). These poor outcomes are attributed to cerebral reperfusion injury over several hours following the perinatal asphyxial event. However, the excess oxygen free radicals in the cerebral circulation that are not being consumed may contribute to further tissue injury and need further investigation. Kapadia *et al.* observed an association between high PaO_2 at 1 hour after birth with increased incidence of moderate to severe HIE in newborn infants

with perinatal metabolic acidosis (5). Additional brain injury can potentially be averted by avoiding excessive O_2 supplementation after ROSC. The Pediatric Life Support guidelines from the 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations (CoSTR) recommend targeting normoxemia as soon as ROSC is established (63). Optimal O_2 supplementation in the post-ROSC period is listed as a knowledge gap by the recent neonatal resuscitation guidelines (21).

Optimal oxygen supplementation following chest compressions

Existing neonatal resuscitation guidelines recommended titrating inspired O_2 down as soon as the heart rate recovers to >60 bpm and a reliable SpO_2 signal is obtained (21). Once the neonate recovers with a sustained spontaneous heart rate following CC, there is a dramatic increase in reperfusion of organs, especially to the brain, even in the presence of varying degrees of myocardial dysfunction (64). During this phase, aiming to decrease excessive cerebral O_2 delivery, researchers have investigated abrupt weaning of inspired O_2 to 21% immediately following ROSC (27). In a perinatal asphyxial cardiac arrest lamb model, gradual weaning of inspired O_2 down from 100% O_2 (standard of care) was compared to abrupt weaning of inspired O_2 to 21% as soon as ROSC occurred. Abrupt decrease to room air followed by titrating up to target preductal SpO_2 per NRP resulted in stable PaO_2, cerebral O_2 delivery and SaO_2 following ROSC (27). In stark contrast, gradual weaning down from 100% O_2 resulted in excessive cerebral O_2 delivery and PaO_2, with no difference in cerebral O_2 extraction between the two weaning strategies. Moreover, abrupt weaning to room air was protective against oxidative stress [assessed by measurement of whole blood oxidized (GSSG), reduced (GSH), and oxidized to reduced glutathione ratios (GSSG/GSH)] when compared to gradual weaning down from 100% O_2 (Table 2) (27). These findings were corroborated by Badurdeen *et al.*, who identified deep grey matter hyperoxia and mitochondrial dysfunction with gradual wean (current standard), whereas rapid wean to 21% after ROSC reduced hyperoxia and mitochondrial dysfunction while maximizing blood O_2 content during CPR (42). Thus, an intervention as simple as decreasing to room air and subsequently titrating up on O_2 if needed to target preductal SpO_2 per NRP guidelines may minimize any further and unnecessary cerebral O_2 exposure and oxidative stress. However, preterm newborns and bradycardic neonatal models have not been evaluated. Additionally, it is not known if delayed cord clamping or umbilical cord milking during CC may be helpful in diluting the higher PaO_2 by the lower PaO_2 from the umbilical venous blood post-ROSC after 100% O_2 resuscitation.

During delivery room resuscitation, it may be practically difficult to titrate inspired O_2 every 30 seconds to achieve normoxemia, especially because PaO_2 is not measured by repeated blood gases. Furthermore, some infants may have lung parenchymal diseases, such as meconium aspiration syndrome or surfactant deficiency, and may require more inspired O_2 to achieve target preductal SpO_2.

Outcomes and optimal oxygenation during CPR in the NICU

Neonatal CPR has been reported in 1–3% of all the NICU admissions (65). However, the incidence of NICU-CPR among extremely preterm infants is as high as 10–34% (66). Foglia *et al.* performed a single center retrospective cohort study of NICU patients <1 year of age requiring CPR over a 4-year-period, that included 162 CPR events in 113 infants (~2.2% of all NICU admissions) with median gestational age of 28 weeks (65). Respiratory compromise was the primary etiology of the event in 77% whereas primary cardiopulmonary arrest occurred in 20%, and 81% of events occurred while on invasive mechanical ventilation. Epinephrine was administered in 30% of the events. Ninety-one percent of the infants (103/113) achieved ROSC, 81% (92/113) survived at least 24 hours after CPR, and 61% (69/113) survived to hospital discharge. Duration of CPR {median [interquartile range]: 1 min [1–4] in survivors *vs.* 5 min [2–24] in non-survivors}, and epinephrine administration (1% of survivors *vs.* 61% of non-survivors) were different among survivors and non-survivors, while inotrope infusion prior to CPR and epinephrine administration independently affected survival to discharge (65). These findings were corroborated by Ahmed *et al.*, with higher NICU-CPR incidence with decreasing gestational age and worse outcomes with increasing CPR duration in a multicenter retrospective study over 6 years from 10 centers (67). Similarly, Ali *et al.* conducted an elegant multicenter retrospective study from 4 quaternary NICUs in USA over a 5-year period (68). CPR was required in 1.2% of the NICU admissions (200/17,358). Majority of newborns who received CPR in NICU were preterm {median [IQR] gestational age 29 [26–36] weeks}, were receiving mechanical ventilation (79%, 157/200), with acute respiratory compromise as the etiology in 91% (182/200), and 45.5% survived to hospital discharge. Mechanical ventilation, vasopressor, antibiotic and inhaled nitric oxide therapies at time of arrest decreased likelihood of survival to discharge (68). None of these published studies mention about oxygen supplementation or oxygenation characteristics during CPR in the NICU. Further, it is not known if continued mechanical ventilation (especially high frequency ventilation) can improve oxygenation and hasten ROSC during CPR in the NICU when compared to bag and mask ventilation.

Long term impact of oxygen exposure during neonatal CPR

There are no published studies comparing long-term effects of neonatal exposure to O_2 specifically during CPR. Newborn animal models of asphyxia and persistent pulmonary hypertension have clearly demonstrated objective evidence of hyperoxia in the form of high brain tissue PaO_2 and increase in oxygen free radicals following 100% O_2 ventilation (39,69). Even brief exposure to O_2 can be toxic in a newly born infant and is associated with adverse outcomes in the long run (10,13-16). These are illustrated by the clinical studies in asphyxiated neonates demonstrating increased mortality, oxidative stress and childhood leukemia (70).

Conclusions

During CC for cardiac arrest, pulmonary, coronary, and cerebral blood flow along with PaO_2 are very low. In this situation, the current recommendation to use 100% inspired O_2 appears

prudent based on current animal data. During CC for bradycardia, the optimal FiO_2 is not known and there does not appear to be a significant difference with the use of 21% or 100% oxygen. Following ROSC, there is evidence of cerebral hyperoxia and hyperoxemia in the post-resuscitative period with slow weaning from 100% O_2. Evidence from recent animal studies suggest that post-ROSC hyperoxia can be avoided by abrupt/rapid decrease of inspired O_2 immediately after ROSC. Clinical trials that are well designed, sufficiently powered, and well executed comparing various inspired O_2 concentrations during CPR and O_2 weaning strategies after ROSC are essential to answer these key questions but are difficult to conduct. In the absence of clinical trials, large observational databases collecting information on neonatal CPR provide the best evidence. In addition, follow-up of recruited neonates to assess the survival, short-term pulmonary and cardiovascular outcomes, and long-term cardiovascular and neurodevelopmental outcomes is of paramount importance.

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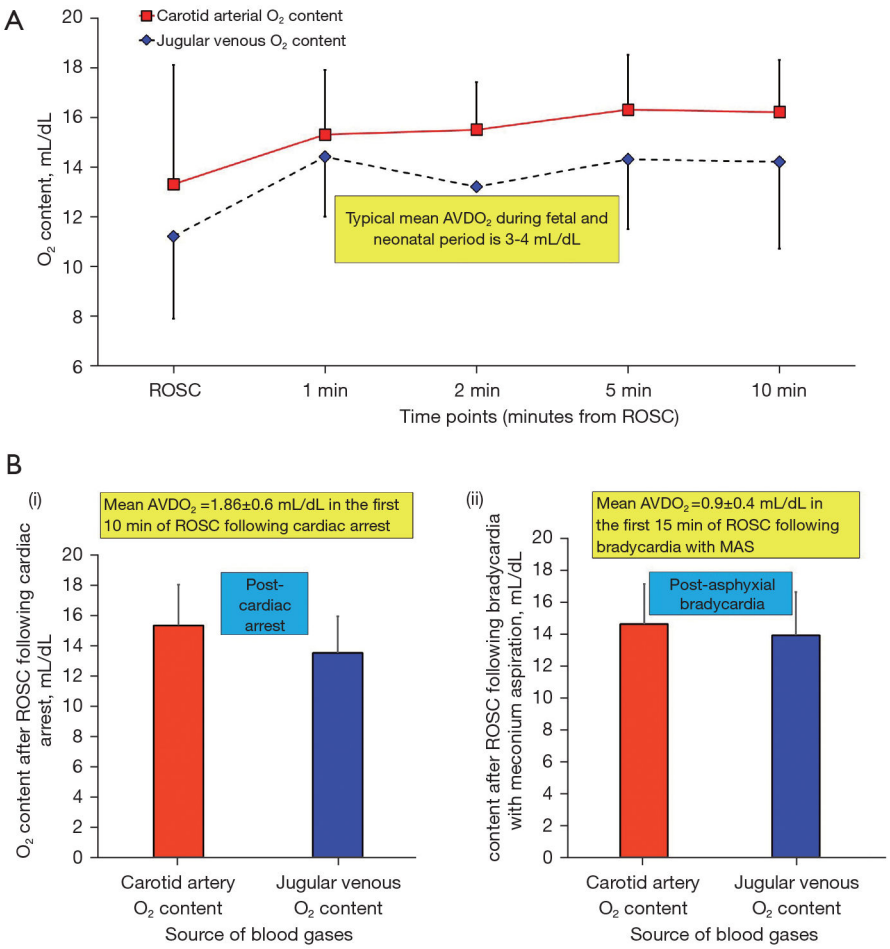

Figure 1.

Change in carotid arterial and jugular venous oxygen content after recovery from cardiac arrest and bradycardia. Change in carotid arterial and jugular venous O_2 content following ROSC in a lamb model of cardiac arrest are shown in (A). The $AVDO_2$ is low in the first 10 min after ROSC indicating reduced cerebral O_2 consumption after recovery from asphyxial arrest in term newborn lambs. The typical $AVDO_2$ in fetal and neonatal lambs is shown in the yellow box in (A). Carotid arterial and jugular venous oxygen content, and arteriovenous differences ($AVDO_2$) after ROSC from lamb models of cardiac arrest induced by umbilical cord compression [B, (i)] and bradycardia [with meconium aspiration, (B), (ii)] are presented as bar graphs. These suggest that oxygen consumption by the brain is low in neonatal lambs following recovery from cardiac arrest and bradycardia. Copyright Satyan Lakshminrusimha. O_2, oxygen; ROSC, return of spontaneous circulation; $AVDO_2$, arteriovenous difference in oxygen content.

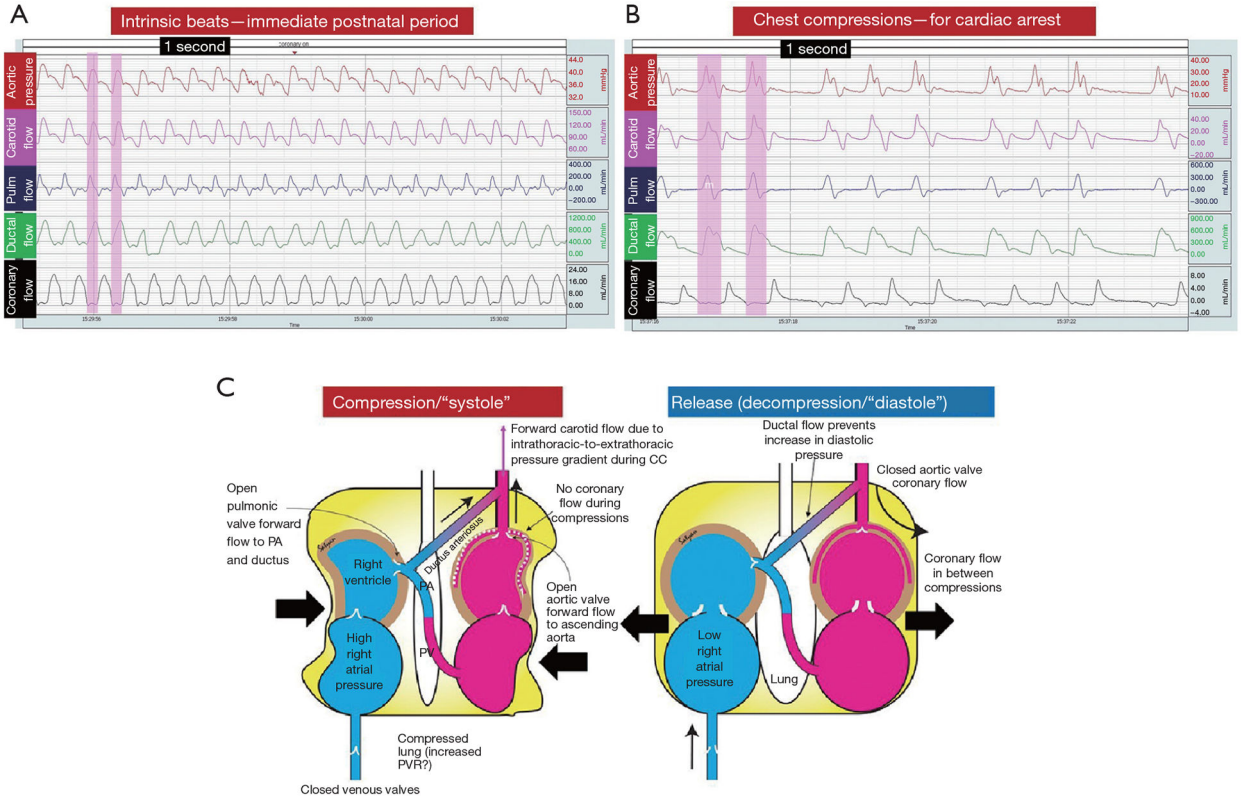

Figure 2.

Changes in hemodynamics and timing of flows during intrinsic heart beats in a BIOPAC snapshot and an illustration. Changes in aortic pressure, carotid artery blood flow, pulmonary blood flow, ductus arteriosus blood flow and coronary artery blood flow during spontaneous heartbeat are depicted in (A). Pink highlight indicates timing of systole during an intrinsic heartbeat. Except forward coronary flow that occurs during diastole, all the other blood flows (carotid, pulmonary and ductal) occur during systole (A). During chest compressions (B), there is forward flow across the aorta, carotid artery, pulmonary artery and ductus arteriosus (right-to-left) depicted by the positive deflection in the BIOPAC snapshot (pink highlight indicating time of chest compressions). However, there is no forward blood flow across the coronary artery during chest compressions, and the forward flow occurs during the decompression phase (diastole). Illustration of pressure and flow changes in the heart chambers during chest compressions for cardiac arrest are shown in (C). During chest compressions/"systole" (left hand side of the figure), the venous valves are closed (preventing back flow of blood in inferior vena cava), the right atrial pressure is increased, along with open pulmonary and aortic valves, allowing forward flow to the PA, ductus arteriosus (ductus) and ascending aorta. However, there is no forward coronary blood flow during CC as there is no gradient between aortic pressure and right atrial pressure. The pulmonary flow may be limited by compressed lung with increased pulmonary vascular resistance during CC. On the other hand, during decompression phase of CC/"diastole", the venous valves and atrioventricular valves are open, allowing forward flow from atria to ventricles, but the pulmonary and aortic valves are closed, and forward blood flow occurs in the coronary arteries in between the CC. Furthermore, the flow from left to right across

the ductus arteriosus during the decompression phase prevents the increase and build-up of diastolic pressure. Copyright Satyan Lakshminrusimha. PA, pulmonary artery; CC, chest compressions; PV, pulmonary veins; PVR, pulmonary vascular resistance.

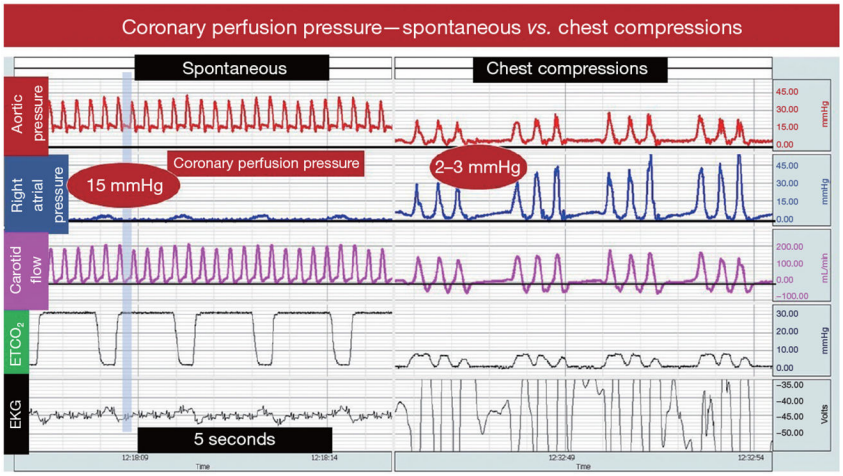

Figure 3.

Coronary perfusion pressure during spontaneous heartbeats compared to during CC. During spontaneous heartbeat, the aortic pressure is normal, with very low right atrial pressure (BIOPAC snapshot), allowing a gradient between diastolic blood pressure and right atrial pressure of ~15 mmHg which is the coronary perfusion pressure. Forward carotid blood flow, $ETCO_2$ and EKG are also shown. However, during CC (right hand side of the figure) for cardiac arrest, the aortic diastolic pressure is lower, and the right atrial pressure is higher approaching the diastolic pressure, thus decreasing the difference to 2–3 mmHg resulting in lower coronary perfusion pressure. Reduced carotid artery blood flow (forward flow during CC/systole) and dampened $ETCO_2$ (due to low pulmonary circulation) are also depicted. Copyright Satyan Lakshminrusimha. CC, chest compressions; $ETCO_2$, end tidal carbon dioxide; EKG, electrocardiogram.

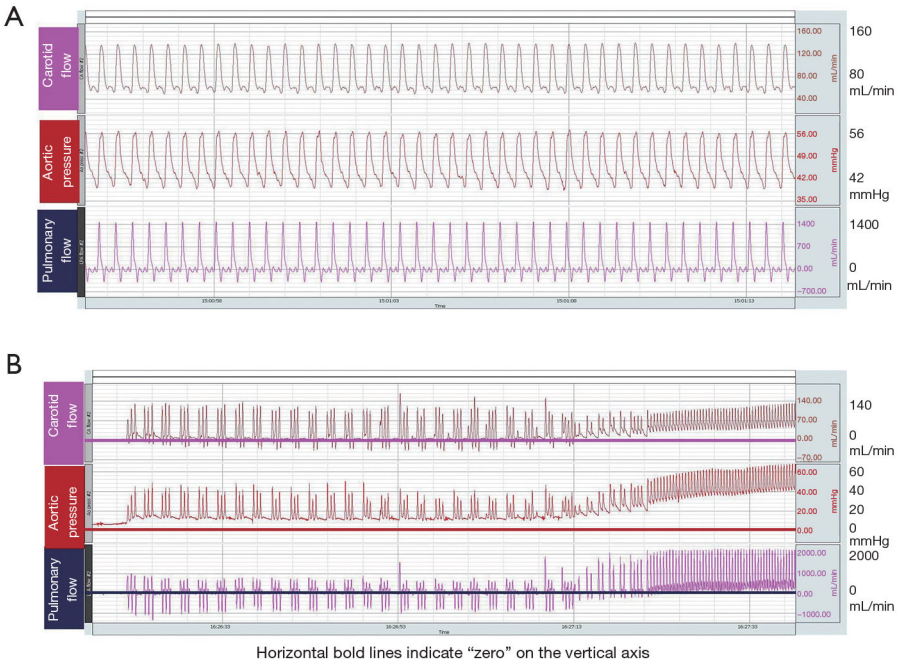

Figure 4.

Differences in carotid and pulmonary hemodynamics during CC. (A) Shows carotid flow, aortic pressure, and pulmonary flow during spontaneous heart beats immediately after birth in term lambs ventilated with 21% Oxygen after cord clamping from a BIOPAC snapshot in non-asphyxiated lambs. Immediately after birth, following clamping of the umbilical cord and ventilation of the lungs with 21% oxygen, carotid flow, aortic pressure and pulmonary flow rapidly increase. The carotid flow is always antegrade both during systole and diastole. The pulmonary flow is predominantly forward with minimal retrograde flow during diastole due to high pulmonary vascular resistance and bidirectional ductal shunting (A). Whereas, (B) is a BIOPAC snapshot depicting changes in hemodynamics during CC and at ROSC. The pink, red and blue horizontal bold lines indicate “zero” value for the carotid flow, aortic pressure and pulmonary flow respectively. During CC, pulmonary flow is bidirectional with minimal forward flow during chest compressions but significant retrograde flow during the decompression phase (B). This results in minimal effective pulmonary flow to support gas exchange during CPR for cardiac arrest. Hence, providing 100% oxygen during CC for cardiac arrest might benefit by reducing duration of CPR and increasing oxygen content in the low flow volume of pulmonary venous return (B). In contrast, carotid flow is predominantly antegrade with only minimal retrograde flow during the decompression phase. We speculate that these differences are secondary to extrathoracic location of carotid vessels—resulting in positive pressure gradient during chest compressions vs. intrathoracic location of pulmonary vessels (as shown in Figure 2C). Copyright Satyan Lakshminrusimha. CC, chest compressions; ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation.

Table 1

The search strategy summary for this narrative review

Items	Specification
Date of search	May 1, 2021
Databases and other sources searched	PubMed and Google scholar
Search terms used	“oxygen during neonatal chest compressions”, “oxygen in neonatal cardiac arrest”, “oxygen in neonatal resuscitation”
Timeframe	January 1, 1985 – May 1, 2021
Inclusion and exclusion criteria	Original articles and review articles, textbooks, limited to English language
Selection process	Conducted by the first author and subsequently consensus obtained among the three authors

Table 2

Studies comparing different inspired O_2 concentrations during CC

Study	Species and age	Asphyxiation method	Heart rate at randomization	Intervention arm (s)	Control arm	Results	Comments
Studies comparing different inspired O_2 concentrations during CC							
Linner *et al.*, (32)	Newborn piglets (12–36 h old)	Hypoventilation (rate 5 breaths/min) with air for 20 min, then disconnecting ventilator	HR <50 bpm and mean arterial pressure <25 mmHg	Room air [1] and 30-min 100% O_2 [2]	3-min 100% O_2	No differences in time from PPV to increase in HR >150 bpm {67 [60–76] sec with 21% O_2, 88 [76–126] sec with 3 min of 100% O_2, and 68 [56–81] sec with 30 min of 100% O_2} time to reach 30% $CrSO_2$ or time to increase in $PbtO_2$ by 0.75 mmHg from its nadir	During CC for bradycardia, use of 100% O_2 can lead to cerebral hyperoxia. Circulatory recovery is as fast with air compared to 100% O_2
Linner *et al.*, (33)	Newborn piglets (12–36 h old)	5 min hypoventilation, 5 min hypoxic ventilation and a max of 8 min apnea	HR <60 bpm and/or mean BP <30 mmHg	Ventilation with room air [1] or 100% O_2 [2] once per minute	None	Continued need for CC at 10 min in 21% O_2 group, but not in 100% O_2 group. Time to ROSC was 60 sec in 100% O_2 and 845 sec in 21% O_2	In the setting of inadequate ventilation, one oxygen breath reduces time to ROSC
Dannevig *et al.*, (34)	Newborn piglets (14–34 h old)	Hypoxia to 8% and adding CO_2 aiming $PaCO_2$ >52.5 mmHg and decreasing ventilator rate by 10 breaths/min every minute until asystole	Asystole with mean BP of 0 mmHg, a flat ECG and cardiac auscultation.	Initial ventilation period 30 sec (*vs.* 60 *vs.* 90 sec), 3:1 *vs.* 9:3 CC:PPV ratio and 21% O_2	Initial ventilation period 30 sec, 3:1 CC:PPV ratio and 100% O_2	21% *vs.* 100% O_2, and 3:1 vs 9:3 CC:PPV ratios: No difference in time to ROSC and gene expression of TNFα, MMP2, MMP9 and ICAM-1 (inflammatory markers) in lung tissues (BAL), increased markers with 30 sec PPV *vs.* 60 sec	21% O_2 is as good as 100% O_2 with respect to time to ROSC and lung inflammatory markers
Dannevig *et al.*, (35)	Newborn piglets (12–36 h old)	Hypoxia to 8% and adding CO_2 aiming $PaCO_2$ >52.5 mmHg, and decreasing ventilator rate by 10 breaths/min every minute until asystole	Asystole with mean BP of 0 mmHg, a flat ECG and cardiac auscultation.	Initial ventilation 30 sec (*vs.* 60 *vs.* 90 sec), 3:1 *vs.* 9:3 *vs.* 15:2 CC:PPV ratio and 21% O_2	Initial ventilation period 30 sec, 3:1 CC:PPV ratio and 100% O_2	No difference in CSF concentrations of inflammatory markers, S-100 and IL-6, between air and 100% O_2 ventilation during CC	21% vs 100% O_2 and different CC:PPV ratios did not modulate brain inflammatory markers. S100 higher with 90s than 30 or 60 s initial PPV
Solevåg *et al.*, (36)	Newborn piglets (14–36 h old)	Adding CO_2 to achieve hypercarbia (pCO_2 >52.5 mmHg), hypoxia with decrease in inspired O_2 to 8% and ventilator rate reduced by 10 breaths/min every min	Mean BP 0 mmHg and loss of pulsatility and auscultation to confirm asystole for 20 seconds	Ventilation with 21% O_2 during CC (3:1 ratio)	Ventilation with 100% O_2 during CC (3:1 ratio)	Median time to ROSC not different between 21% and 100% O_2 groups. No differences in mean BP, heart rate, pH, pCO_2, IL-1ß or lactate/pyruvate ratios. Systemic and regional cerebral O_2 saturations were higher with 100% O_2 during CC	21% O_2 safe and effective as 100% O_2 during CPR. Inherent bias towards 21% O_2 (as 2 piglets in 100% group with no ROSC assigned 1000 sec as time to ROSC, and 1 piglet in 21% group with prolonged bradycardia excluded)
Solevåg *et al.*, (37)	Newborn piglets (1–3 d old)	Hypoventilation (reduction of ventilator rate by 10 breaths/min every 10 min) and hypoxia (use of 8%	PEA defined as a peak flow velocity across aortic valve of <0.5 m/s, carotid artery flow <5 mL/min	3:1 CC:PPV with 21% O_2 [1], Continuous CC with asynchronous ventilation (CCaV) with 21% O_2 [2] and	3:1 CC: PPV with 100% O_2	Time to ROSC and mortality were not different. 21% O_2 CPR associated with higher LV stroke volume after ROSC and less myocardial oxidative stress	In asphyxia induced cardiac arrest, 21% O_2 during CPR may reduce myocardial oxidative stress and improve

Study	Species and age	Asphyxiation method	Heart rate at randomization	Intervention arm (s)	Control arm	Results	Comments
		inspired O_2) for 30 min, followed by ETT clamping 3–5 min	and no heartbeat on auscultation	CCaV with 100% O_2 [3]		compared to 100% O_2 groups. CCaV had lower mean BP and higher myocardial lactate than 3:1	myocardial function compared to 100% O_2
Solevåg *et al.*, (38)	Newborn piglets (1–3 d old)	30 min of normocapnic hypoxia followed by disconnection from ventilator and clamping ETT until asystole	Asystole was defined as no audible heartbeat during auscultation and zero carotid blood flow	3:1 CC: PPV with 18% [1], 21% [2] or 100% O_2 [3]	Sham without hypoxia or asphyxia	No difference in time to ROSC, inflammatory markers or markers of oxidative stress (lactate, GSH, GSSG, GSSG/GSH ratio in myocardial and frontoparietal cortex) between 18%, 21% and 100% O_2 use during CC	No differences in outcomes between 18%, 21% and 100% O_2 during CC
Perez-de-sa *et al.*, (39)	Perinatal lambs (141–142 d gestation)	Cord clamped and lamb delivered. Ventilation onset 10 min after delivery	50–100 bpm	PPV with 21% O_2 for 30 min [1], 100% O_2 for 3 min then by 21% O_2 [2] and 100% O_2 for 30 min [3]. CC and epinephrine as needed	No asphyxia. PPV with 21% O_2, then 100% O_2 for 30 min, then decreased to 21% O_2	With 100% O_2 ventilation for 30 min, Pbt_{O2} increased from <0.75 mmHg to 420 [225–458] mmHg, whereas in those given 100% O_2 for 3 min Pbt_{O2} peaked at 31.5 (21.8–345) kPa and 21.8 (6–40.5) mmHg in 21% O_2 ventilated lambs	High brain tissue PO_2 with 100% O_2 ventilation, but not with 21% O_2 or brief 100% O_2 ventilation followed by 21% O_2
Rawat *et al.*, (40)	Perinatal lambs (139–141 d gestation)	Umbilical cord compression and ETT occlusion until asystole	Absence of carotid blood flow, arterial blood pressure, and audible heart rate	21% O_2 during CC	100% O_2 during CC	PaO_2, SaO_2, cerebral O_2 delivery and carotid blood flow were similar. Maximal cerebral O_2 delivery at peak of CC was higher with 100% O_2. After ROSC, PaO_2 was higher with 100% O_2 CPR	During cardiac arrest with no flow, CC with 100% O_2 may provide better oxygen delivery to the brain
Vali *et al.*, (41)	Perinatal lambs (139–141 d gestation)	Umbilical cord compression and ETT occlusion until asystole	Absence of carotid blood flow, arterial blood pressure, and audible heart rate	100% O_2 during CCaV	100% O_2 with 3:1 CC:PPV	CCaV with 100% O_2 resulted in higher PaO_2 (22±5.3 vs. 15±3.5 mmHg), higher carotid blood flow (7.5±3.1 vs. 4.2±2.6 mL/kg/min) and cerebral O_2 delivery (0.4±0.15 vs. 0.13±0.07 mL/kg/min) compared to 3:1 CC:PPV with 100% O_2	CCaV with 100% O_2 improved carotid blood flow, PaO_2 and cerebral O_2 delivery compared to 3:1 CC:PPV ratio with 100% O_2
Studies comparing different inspired O_2 weaning strategies after ROSC							
Sankaran *et al.*, (27)	Perinatal lambs (139–141 d gestation)	Umbilical cord compression and ETT occlusion until asystole	HR 0 bpm for 5 min followed by CPR (use of 100% O_2 during CC)	After ROSC, abrupt wean of inspired O_2 to 21% followed by titrating targeting 85–95% SpO_2	After ROSC, gradual wean of O_2 from 100% to achieve 85–95% SpO_2	PaO_2, SaO_2 and cerebral O_2 delivery were higher with gradual wean compared to abrupt wean, with cerebral O_2 delivery remaining higher until 15 min after ROSC. Oxidative stress (blood GSSG/GSH and GSSG) lower with abrupt wean	Clinical trials comparing inspired O_2 weaning strategies after ROSC are warranted
Badurdeen *et al.*, (42)	Perinatal lambs (139±1 d gestation)	Umbilical cord clamping until asystole and pH <7.0	Asystole with HR 0 bpm	100% O_2 CC and rapid wean to 21% after ROSC with titration after 5 min (rapid wean), and 21% O_2 CC and until 5 min, then target SpO_2 >90%	100% O_2 during CC and until 5 min after ROSC, followed by titrating to achieve SpO_2	PaO_2, caudate/thalamic tPO_2 and $CrSO_2$ were below fetal levels during CPR, but significantly elevated after ROSC with standard 100% O_2 group compared to rapid wean and 21% O_2 group. Standard and 21% O_2 groups had decreased	Rapid weaning of inspired O_2 to 21% after ROSC following CC improves cerebral mitochondrial bioenergetics

Study	Species and age	Asphyxiation method	Heart rate at randomization	Intervention arm (s)	Control arm	Results	Comments
					>90% (standard)	C1 and CIV-driven respiration and reduced maximal electron transfer capacity	

O_2, oxygen; CPR, cardiopulmonary resuscitation; CC, chest compressions; PPV, positive pressure ventilation; HR, heart rate; Bpm, beats per minute; ROSC, return of spontaneous circulation; ETT, endotracheal tube; GSSG and GSH, oxidized and reduced glutathione respectively; PEA, pulseless electrical activity; SpO2, pulse oximetry oxygen saturation.