NEONATAL AND PEDIATRIC CEREBRO-CARDIOPULMONARY RESUSCITATION

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NEONATAL AND PEDIATRIC CEREBRO-CARDIOPULMONARY RESUSCITATION

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Neonatal and pediatric cerebro-cardiopulmonary resuscitation.
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Pediatric resuscitation medicine has witnessed significant advances with improved understanding of the pathophysiology of cardiac arrest and resuscitation. Multiple mechanisms of neurological injury have been identified, outlining potential avenues for neuroprotection following cardiac arrest. Resuscitation science exists at multiple levels of analysis, from biomechanics of chest compressions to implementation of best training procedures in real time, from epidemiology of cardiac arrest survival to molecular mechanisms of cellular injury due to ischemia and reperfusion. What next steps in research and in clinical practice will ensure the best possible neurologic outcome among children who survive cardiac arrest? How can we leverage novel technologies in neuroimaging, nanomaterials, drug delivery, biomarker-based risk stratification and next generation sequencing, among others, to resuscitate and to protect the Central Nervous System (CNS)? How can we improve clinical trial design and data analyses to maintain a robust clinical research infrastructure and to ensure validity and applicability? These are just some of the questions will addressed in this Research Topic.

Using evidence-based algorithms and public health approaches to disseminate them, the last decade has seen a paradigm shift in pediatric resuscitation with significantly improved survival from pediatric cardiac arrests. However, neurologic outcome in

survivors remains far from optimal. High quality CPR is increasingly recognized as a key factor for improving neurologic outcomes. Advanced technologies allow monitoring the quality of CPR and just-in-time feedback to improve the quality of CPR. Further research is needed to evaluate impact of these technologies on neurologic outcome. The recent American Heart Association CPR guidelines emphasis on Circulation-Airway-Breathing (CAB) approach to CPR needs a careful evaluation in children, in whom timely airway and breathing support are as important as circulation. The growing controversy regarding use of epinephrine, and alternative routes of administration of epinephrine during CPR, warrants further evaluation in the setting of pediatric CPR.

Improved outcome of hemodynamic goal-directed CPR over standard CPR in animal models of cardiac arrest has initiated interest in physiology-based CPR, especially in the in-hospital cardiac arrest. Basic and applied-science research have become relevant for specific subpopulations of pediatric cardiac arrest victims and circumstances (e.g., ventricular fibrillation, neonates, congenital heart disease, extracorporeal cardiopulmonary resuscitation). Just-in-time and just-in-place simulation training, which have evolved as training strategies to improve quality of CPR, are being evaluated for outcomes. The concept of just-in-time and just-in-place coaching of CPR providers on high quality CPR is a novel concept which has emerged recently and remains unstudied.

Whilst there have been significant advances in newborn stabilization over the last decade many questions remain unanswered. These include the role of delayed cord clamping in preterm infants and term newborns requiring resuscitation, the role of sustained inflations as a method of respiratory support and the role of epinephrine and volume administration in neonatal resuscitation. Novel methods of assessment including the use of end tidal CO2 monitoring, respiratory function monitoring and near infrared spectroscopy warrant further evaluation. The use of transitioning animal models that accurately replicate the newborn circulation with patent fetal shunts are emerging but more assessments in these are required to better establish CPR strategies in newborn infants. Newborn resuscitation training programs have resulted in a reduction in neonatal mortality in the developing world, but key questions remain around the frequency of training, team training methods and the role of simulation training. Post resuscitation interventions, in particular therapeutic hypothermia, has resulted in significant improvements in long-term outcome and there is now a growing interest in adjunct therapies, such as use of melatonin, erythropoietin, or other neuroprotective molecules to improve therapeutic benefits of cooling.

Therapeutic hypothermia did not provide any higher benefit than normothermia in children following out of hospital cardiac arrest, although three is considerable debate in the community whether 14% probability of observing a similar outcome if the study were repeated a 100 times applies to an individual child in the PICU. Exciting research is occurring in unraveling connection between inflammation, immune dysregulation and neuroinjury. This will further support research on the use of anti-inflammatory agents and immunomodulators for neuroprotection after cardiac arrest and birth asphyxia.

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EDITORIAL
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Editorial: Neonatal and Pediatric Cerebro-Cardio-Pulmonary Resuscitation (CCPR): Where Do We Stand and Where Are We Heading?

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Editorial on the Research Topic

Neonatal and Pediatric Cerebro-Cardio-Pulmonary Resuscitation (CCPR): Where Do We Stand and Where Are We Heading?

An overwhelming response followed my inaugural article in Frontiers in Pediatric Critical Care in 2015, which focused on hypoxic ischemic injury in the developing brain (1). My article sparkled a renewed interest in neonatal and pediatric cerebro-cardio-pulmonary resuscitation (CCPR). In reviewing the research investment into neonatal deaths, only 10% of research expenditure is directed toward 90% of the world's global burden of disease—the so called "10/90 gap" (2). The Millennium Development Goal to reduce the under-five mortality by two-thirds by 2015 was not achieved (3), and neonatal death remains a significant contributor to this category of childhood mortality (4).

To address these concerns, we gathered a team of neonatal and pediatric CCPR experts from across the globe and proposed a research topic on neonatal and pediatric CCPR. The topic received a robust response from across the world and we received original research articles and review articles from neonatal and pediatric resuscitation experts.

Whilst prolonged mechanical ventilation has been well established to induce injury to preterm brain, ventilation-induced brain injury may occur as early as the initiation of ventilation in the delivery room and seems to be a potentially preventable contributor to brain injury (5). An original investigation conducted by Alahmari et al in our research topic tested the hypothesis that neuropathology associated with *in utero* inflammation is exacerbated by inappropriate delivery room ventilation in preterm lambs (12). The findings of the study not only supported the concept of neuroinjury in preterm babies worsened by hyperventilation in the delivery room but it also defined neuroimaging changes and neuroprotective ventilation strategies in the delivery room. Using a neonatal resuscitation simulator, Solveg and co-authors investigated volume-controlled delivery room ventilation (5). The study compared a new volume-controlled resuscitator (The Next Step^{TM}) with four other available devices used for stabilization in the delivery room. The study showed that routinely used newborn resuscitators delivered excess tidal volume, whereas the Next Step^{TM} under delivered in the low compliant test lung (5). These findings published clearly bridge important knowledge gaps in the area of delivery-room ventilation and its impact on neurologic outcome in preterm infants.

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While studying an optimum technique and technology to deliver safe ventilation in the delivery room, Solveg and co-authors also raise an equally important question on optimal chest compression (CC) rate and compression to ventilation (C:V) ratio during delivery room resuscitation (5, 6). Despite a lack of scientific evidence supporting CC at 90/min and C:V ratio of 3:1, the investigation of alternative CC interventions in human neonates is ethically challenging. Also, the infrequency of CPR in the delivery room make randomized controlled trials difficult to perform. Therefore the physiology of CPR has been investigated in animal and mannequin models. Neither continuous CCs with synchronous ventilation nor higher C:V ratios of 9:3 or 15:2 have been associated with better outcomes as compared to C:V ratio of 3:1 in neonatal resuscitation (6, 7). Infact, uninterrupted or less interrupted CCs have been associated with poor quality CCs due to provider fatigue (8, 9) The authors appropriately bring up un-answered questions as potential future directions—biomechanical aspect of CPR using mechanical/automated devices and feedback systems during neonatal CPR have not been explored. Also, video recording of delivery room CPR and outcomes have yet to be reported (6).

On one hand, the investigators are looking at post-partum measures such as placental transfusion to improve outcomes of neonatal asphyxia (7) and on the other hand, investigators are exploring antepartum measures such as maternal dietary supplements to support fetal metabolism and reduce severity of organ injury caused by intrapartum asphyxia (8). In their review article, Katheria and co-authors discuss the current evidence on placental transfusion in neonates requiring resuscitation. Placental transfusion using techniques such as delayed cord clamping or cord stripping or milking have been described over last several decades (10, 11). Though RCTs on these techniques have shown beneficial effects, a number of logistic challenges such as maintaining sterile field and ergonomic difficulties of providing effective ventilation while attached to the placenta need exploration. Future trials on effects of placental transfusion on outcome will help determine guidelines on use of placental transfusion during delivery room resuscitation, especially in preterm newborns. LaRosa and colleagues provide an extensive review of existing information on organ injury following intrapartum asphyxia. The authors also shed light on maternal therapies, specifically creatine, to minimize organ injury related to intrapartum asphyxia (8). Prior animal studies have shown promising results on neonatal mortality and protection of organs such as brain, diaphragm, kidney and skeletal muscles after maternal dietary supplementation with creatine during antepartum period (12, 13). There is a need for bench-to-bedside research exploring the role of creatine in pregnant women (14).

Current guidelines recommend monitoring of vital signs which do not include monitoring of the brain, the most vulnerable organ especially to hypoxia during transition immediately after birth. Doppler sonography allows non-invasive monitoring of the perfusion in different regions of the brain. However, this method is limited since it does not allow continuous monitoring, it is difficult during transition after birth and it is prone to motion artifacts, especially in infants (15). In the last decade, several studies have demonstrated feasibility of cerebral oxygenation monitoring using Near Infrared Spectroscopy (NIRS) during immediate transition in healthy term neonates (16–21), preterm neonates (22, 23), and even during resuscitation with chest compressions (24). Cerebral oxygenation changes within the first minutes after birth do not correlate with arterial oxygen saturation, heart rate, or even peripheral tissue oxygenation (20, 25). The authors discuss the studies on cerebral tissue oxygenation in relation to interventions such as delayed cord clamping and sustained lung inflation. Monitoring cerebral tissue oxygenation with NIRS and interventions to correct the cerebral oxygenation changes as detected by NIRS can reduce cerebral hypoxia. A large randomized controlled trial to investigate the effect of cerebral NIRS monitoring in combination with intervention guidelines on short- and long-term outcomes in preterm neonates is currently underway.

Dix et al in their review paper discuss about the importance of cerebral oxygenation monitoring in the first 3 days of life, particularly during neonatal resuscitation and beyond resuscitation (10). Apart from discussing the evidence on cerebral oxygenation monitoring during interventions such as ventilation, management of hypotension and during neonatal surgery, they also discuss the findings of a large international randomized controlled trial, the SafeboosC study (Safeguarding the brains of our smallest children). The percentage of time spent outside a predetermined "normative" range of rScO2 (55–85%), was significantly lower in the group with NIRS monitoring as compared to the blinded control group (median 36.1 vs. 81.3%) (26). The authors also highlight the current evidence on low cerebral oxygenation and/or abnormality of cerebral autoregulation as measured by NIRS and poor neurologic outcomes in neonates. More data is needed to define how assessment of neonatal brain oxygenation could guide clinical management, prevent brain injury and provide important information regarding the infant's prognosis.

Vesoulis and co-authors present a very comprehensive review on techniques of assessing cerebral autoregulation and current evidence on role of cerebral autoregulation in the pathogenesis of brain injury in premature infants (11).

The next steps are assessing a cerebral autoregulation quantification system, which is a hybrid of currently available techniques, and neuroprotective interventions directed toward autoregulation targets. Due to ischemia-reperfusion, neuronal injury continues beyond resuscitation. It is therefore important to understand cerebral perfusion and autoregulation in post-resuscitation period. Monitoring of cerebral perfusion and management of disturbance of cerebral autoregulation are important not only during resuscitation but also in the post-resuscitation period. Lordanova and colleagues discuss changes in cerebral blood flow during post-arrest period and methods to assess cerebral perfusion during post-resuscitation period (15). There has been a growing interest in use of NIRS for non-invasive monitoring of the cerebral perfusion. Though transcranial doppler is a promising modality to monitor cerebral blood flow after resuscitation, it is not well utilized in clinical practice. Though monitoring of cerebral blood flow and oxygenation are crucial during and beyond resuscitation, a multimodality

monitoring incorporating simultaneous monitoring of blood flow, oxygenation and electroencephalogram is more likely to provide a global status of neurologic function during and after resuscitation.

The EEG is exquisitely sensitive to any impairment in oxygen delivery to the brain. A reduction in oxygen leads to an immediate suppression of synaptic transmission with a reduction (often complete suppression) in EEG amplitude. A sustained change in the EEG signals a risk of impending brain injury. EEG activity should recover immediately following restoration of oxygen delivery to the brain, if EEG activity does not return immediately post-resuscitation or activity is severely disrupted, this indicates that the infant is at risk of hypoxic-ischemic brain injury. Dr. Finn and co-authors describe the rationale for using delivery room EEG, explored the current evidence on feasibility of delivery room EEG monitoring and the role of DR EEG monitoring on neurologic outcome. Though delivery room EEG is feasible, it is challenging to apply within minutes after delivery. The EEG pattern correlates with cerebral oxygen saturation and oxygen extraction and therefore it provides useful information about neonates' status during transition after delivery. This could potentially identify neonates who might benefit from early cooling within first 3 h of delivery. Prospective, randomized controlled studies are needed to support the authors' statements on use of EEG in delivery room, especially to determine early (<3 h after delivery) vs. late (3–6 h after delivery) cooling.

In summary, the field of cerebro-cardiopulmonary resuscitation is evolving significantly but many questions still remain unanswered. There is a growing interest in monitoring of cerebral function through non-invasive modalities such as NIRS and understanding the effects of interventions such as placental transfusion, ventilation and use of epinephrine during neonatal resuscitation. Multi-center, prospective, randomized controlled trials focused on multi-modality monitoring of brain function and goal-directed interventions will potentially help us bridge the knowledge gaps.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Ventilation Strategies during Neonatal Cardiopulmonary Resuscitation

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Approximately, 10–20% of newborns require breathing assistance at birth, which remains the cornerstone of neonatal resuscitation. Fortunately, the need for chest compression (CC) or medications in the delivery room (DR) is rare. About 0.1% of term infants and up to 15% of preterm infants receive these interventions, this will result in approximately one million newborn deaths annually worldwide. In addition, CC or medications (epinephrine) are more frequent in the preterm population (~15%) due to birth asphyxia. A recent study reported that only 6 per 10,000 infants received epinephrine in the DR. Further, the study reported that infants receiving epinephrine during resuscitation had a high incidence of mortality (41%) and short-term neurologic morbidity (57% hypoxic-ischemic encephalopathy and seizures). A recent review of newborns who received prolonged CC and epinephrine but had no signs of life at 10 min following birth noted 83% mortality, with 93% of survivors suffering moderate-to-severe disability. The poor prognosis associated with receiving CC alone or with medications in the DR raises questions as to whether improved cardiopulmonary resuscitation methods specifically tailored to the newborn could improve outcomes.

Keywords: infants, newborn, delivery room, neonatal resuscitation, chest compression

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INTRODUCTION

Chest compression (CC) is an infrequent event (0.08%) in newborns delivered at near-term and term gestation, and happens at higher frequency (~10%) in preterm deliveries (1–5). In addition, outcome studies of deliveries requiring resuscitation or CC have reported high rates of mortality and neurodevelopmental impairment in surviving children (1–5). The poor prognosis associated with resuscitation requiring CC alone and/or medications in the delivery room (DR) raises questions as to whether improved cardiopulmonary resuscitation (CPR) techniques specifically tailored toward the newborn infant could improve outcomes.

ASPHYXIA AT BIRTH

Asphyxia, a condition of impaired gas exchange with simultaneous hypoxia and hypercapnia leading to a mixed metabolic and respiratory acidosis, is the most common reason that newborns fail to make successful transition (6, 7). Asphyxia could result from either failure of placental gas exchange before

delivery (e.g., abruption and chorioamnionitis) or deficient pulmonary gas exchange immediately after birth (e.g., apnea, airway obstruction, and respiratory distress syndrome) (6, 7). Asphyxia depresses myocardial function leading to cardiogenic shock, pulmonary hypertension, mesenteric reperfusion, and acute renal failure. Newborn infants present with serve bradycardic or asystole at birth as a consequence of asphyxia. Current resuscitation guidelines recommend to initiate CC if heart rate remains <60/min despite adequate ventilation with supplementary oxygen for 30 s; CC should be then performed at a rate of 90/min with 30 ventilations 3:1 C:V (**Figure 1A**) (8) to achieve adequate oxygen delivery (9–11).

RATIONALE FOR USING 3:1 COMPRESSION TO VENTILATION RATIO

Neonatal bradycardia or cardiac arrest is caused by hypoxia rather than primary cardiac compromise; therefore, providing ventilation is more beneficial (9–11). However, the optimal C:V ratio that should be used during neonatal resuscitation to optimize coronary and cerebral perfusion while providing adequate ventilation of an asphyxiated newborn remains unknown.

Animal studies on cardiac arrest induced by asphyxia in newborn piglets demonstrated that combining CC with ventilations improves ROSC and neurological outcome at 24 h compared to ventilations or CC alone (12–14). Solevåg et al. performed a study investigating alternating nine CC and three ventilations in asphyxiated piglets with cardiac arrest with the hypothesis that nine CC would generate higher diastolic blood pressure (15). The time to ROSC was similar between the two approaches (150 and 148 s for 3:1 and 9:3 C:V, respectively). Similarly, C:V ratios of 3:1 and 15:2 were compared using the same model (16). Although the 15:2 C:V ratio provided higher mean CC per minute (75 versus 58 for 3:1), time to ROSC was similar between groups (median time of 195 and 150 s for 15:2 and 3:1, respectively) (16). These studies suggest that during neonatal CPR, higher C:V ratios do not improve outcomes, and potentially a higher ventilation rate is needed.

This is further supported by manikin studies showing higher ventilation rates during simulated CPR using 3:1 C:V compared with higher C:V ratios (17–19). A more recent neonatal manikin study examined respiratory parameters during neonatal CPR and reported that a 3:1 C:V ratio delivered significantly higher minute ventilation of 191 mL/kg compared to the minute ventilation at 9:3 and 15:2 C:V ratios (140 and 77 mL/kg/min, respectively) (20). A further manikin study compared 3:1 C:V with continuous CC with asynchronous ventilations (CCaV) using 90 CC and 30 non-synchronized inflations and reported significantly higher minute ventilation in the CCaV group compared to the 3:1 group (221 versus 191 mL/kg/min, respectively) (21). Schmölzer et al. compared 3:1 C:V CPR with CCaV in a piglet model of neonatal asphyxia and reported similar minute ventilation (387 versus 275 mL/kg) (22). There was also a similar time to ROSC (143 and 114 s for 3:1 and CCaV, respectively) and survival (3/8 and 6/8, respectively). The same manikin (21) and animal study (22) also reported similar tidal volume (V_T) delivery between 3:1 C:V and CCaV [manikin study V_T 6.4 and 5.6 mL/kg (21), respectively and animal study V_T 14.7 versus 11.0 mL/kg (22)]. In a secondary analysis of the study by Schmölzer et al. (22), Li et al. reported that during 3:1 C:V a cumulated loss of V_T of 4.5 mL/kg occurs for each 3:1 C:V cycle (**Figure 2A**) (23). Similarly, during CCaV, a cumulated loss of V_T of 9.1 mL/kg for each cycle of three CC and one inflation were observed (23). This suggests a potential loss in V_T during CC, which could cause lung derecruitment, hence hamper oxygenation and therefore ROSC. A recent pilot randomized trial in the DR reported that the exhaled CO_2 was significantly higher in the CC + sustained inflation (SI) group with 11 (9) mmHg compared to 2 (1) mmHg ($p < 0.001$) in the 3:1 C:V ratio group during CPR suggesting improved gas exchange in the CC + SI group (24). Further, an argument of synchronized CPR is the potential interference of non-synchronized CC with V_T delivery, resulting in impairment of oxygen delivery. However, the study by Schmölzer et al. observed that 29 and 25% of manual inflations were similarly affected during CC using CCaV or 3:1 C:V CPR (22), respectively. These studies suggest that no advantages (e.g., oxygen delivery and V_T or minute ventilation) of using CCaV compared to 3:1 C:V.

RATIONAL FOR USING CONTINUOUS CCs WITH SI

Reoxgenation and adequate blood flow are the cornerstones of neonatal CPR. Any effective resuscitative maneuver should increase blood flow and optimize oxygen delivery. In addition to standard CPR, maneuvers that raise intrathoracic pressure can significantly increase carotid blood flow during CPR. Chandra et al. provided ventilation at a high airway pressure while simultaneously performing CC in an animal model and demonstrated increased carotid flow without compromising oxygenation (25). Further, studies in preterm lambs have demonstrated that an SI also increases intrathoracic pressure without impeding blood flow (26). In the resuscitation of asphyxiated newborn piglets, Schmölzer et al. recently reported that passive ventilation during CC, achieved by superimposing CC with an SI (CC + SI) (**Figure 1B**) (8), significantly improved hemodynamics, minute ventilation, and time to ROSC compared to the current approach of using a 3:1 C:V ratio (mean arterial pressure: 51 versus 31 mmHg; pulmonary arterial pressure: 41 versus 31 mmHg; mean minute ventilation: 936 versus 623 mL/kg; and median time to ROSC: 38 versus 143 s, respectively) (8). However, the study by Schmölzer et al. used a CC rate of 120/min (in the CC + SI group), which is higher than the currently recommended CC rate of 90/min, which could have also added to the improved outcomes. A recent study using a perinatal cardiac arrest lamb model with transitioning fetal circulation and fluid filled lungs reported that CC + SI is as effective as 3:1 C:V ratio in achieving ROSC (27).

Rate of CC

A recent mathematical model suggests that CC rates higher than the currently recommended 90 CC/min could optimize systemic perfusion (28). This model further suggests that the most effective CC rate depends on body size and weight, which would translate

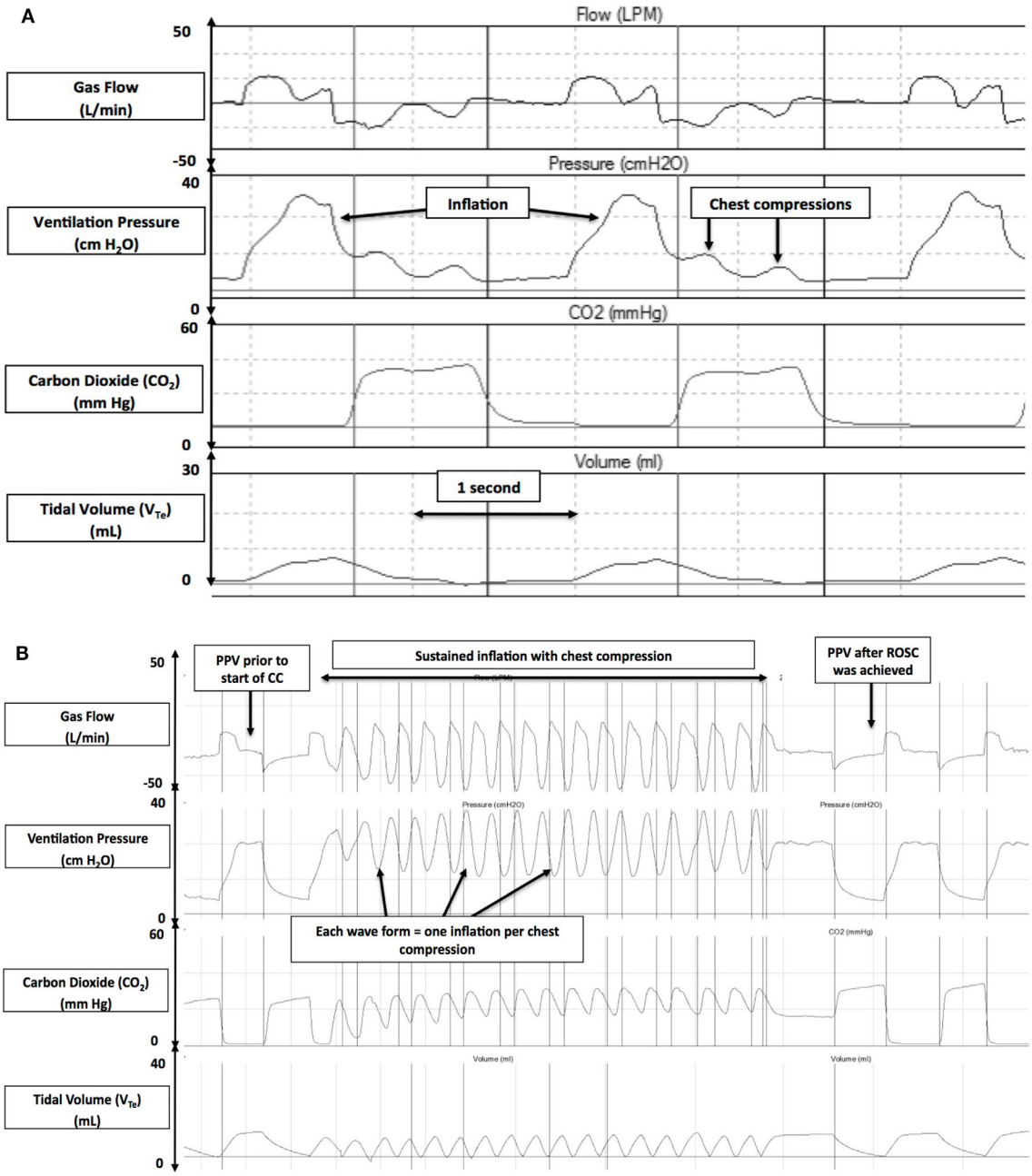

FIGURE 1 | Respiratory waveforms during cardiopulmonary resuscitation in the 3:1 compression:ventilation ratio (3:1 C:V) **(A)** and chest compression (CC) + sustained inflation (SI) **(B)** groups (gas flow, airway pressure, ECO_2, and tidal volume). Reproduced with permission from Schmölzer et al. (8).

to 180 CC/min for term infants and even higher rates for preterm infants (28). However, a recent simulation study comparing various CC rates (e.g., 90 versus 120 CC/min) reported faster fatigue with increasing CC rates (29). Overall, using CC rates of 90 CC/min was the least fatiguing and the most preferred method of neonatal CPR compared to that using 120 CC/min (29). This is further supported by a study by Solevåg et al. who quantified the force used during CC and reported fatigue occurring faster with increasing CC rates (30). These studies suggest that a rate of 90 CC/min would be the least fatiguing rate. Further, a recent randomized animal trial compared CC + SI using CC rates of 90 versus 120 CC/min and reported similar time of ROSC, survival rates, and respiratory parameters during CPR (31). During CC, carotid blood flow, mean arterial pressure, and percentage change in ejection fraction and cardiac output were higher in the CC + SI 90/min group compared to CC + SI 120/min (31). This further supports that higher CC rates do not improve systemic perfusion and that the current recommendation of 90 CC/min

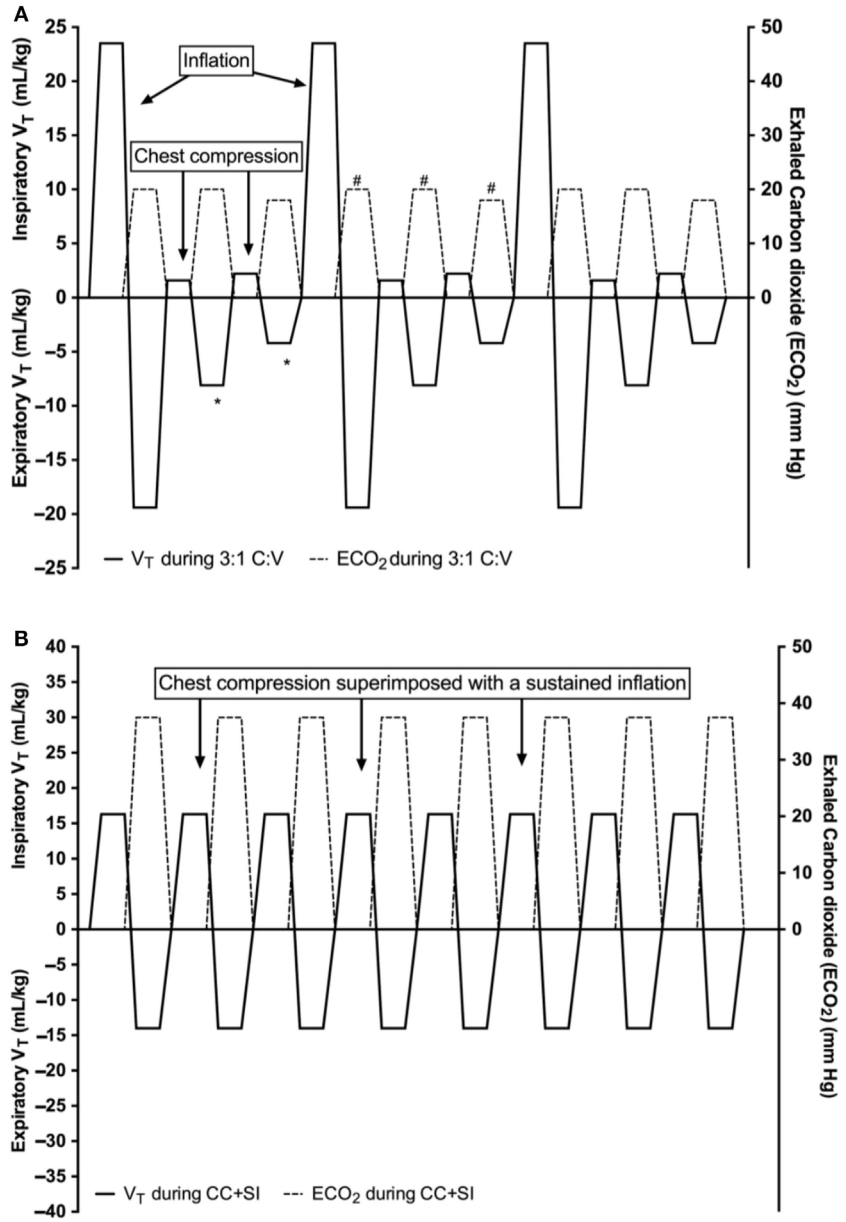

FIGURE 2 | Tidal volume (mL/kg) changes during 3:1 compression:ventilation ratio (3:1 C:V) **(A)** and continuous chest compressions (CCs) superimposed by sustained inflations (SIs) (CC + SI) **(B)**. Reproduced with permission from Li et al. (23).

are sufficient to achieve systemic perfusion. This is further supported by a randomized animal trial comparing CC + SI using a rate of 90/min with 3:1 C:V. CC + SI significantly reduced the median (IQR) time of ROSC, i.e., 34 s (28–156 s) versus 210 s (72–300 s) in the 3:1 group ($p = 0.048$). CC + SI also significantly reduced the requirement for 100% oxygen, improved respiratory parameters, and resulted in a similar hemodynamic recovery (32). Furthermore, the study reported no significant differences in the concentrations of interleukin (IL) IL-1β, IL-6, IL-8, or tumor necrosis factor in lung tissue homogenates (32). This suggests that SI does not increase the risk of brain injury as recently suggested in two meta-analyses (33, 34).

Adequate Ventilation during CC

Providing adequate ventilation to achieve reoxgenation is a cornerstone of neonatal CPR. Current best practice is to provide 90 CC and 30 ventilations that are coordinated during a pause (9). The purpose of inflations during CC is to deliver an adequate V_T to facilitate gas exchange. However, delivery of an adequate V_T during CPR remains difficult. Several DR studies reported that mask ventilation is the most difficult task during neonatal CPR. V_T delivery could be compromised due to mask leak or airway obstruction (35–43), causing inadequate oxygen delivery to any asphyxiated newborn. A recent case by Li et al. reported a large mask leak during mask ventilation in

the DR, which resulted in severe bradycardia and the need for neonatal CC (44). In addition, once CC was started, mask leak further increased (44). This is further supported by manikin studies, which reported decreased expiratory V_T once CC were started (20, 45, 46). Binder-Heschl et al. examined human or monitor feedback during simulated neonatal CPR using a leak-free manikin and reported lower expiratory V_T in all groups compared with mask ventilation alone (46). These studies suggest a decrease in expiratory V_T once CCs are initiated. A loss in expiratory V_T could cause lung derecruitment, which could hamper oxygenation and therefore ROSC. This has been recently confirmed in an animal model of neonatal CPR. In a secondary analysis of the study by Schmölzer et al. (22), Li et al. reported that during a significant loss of expiratory V_T compared to inspiratory V_T over each 3:1 C:V cycle (mean total inspiratory V_T was 27.2 mL/kg and mean total expiratory V_T 31.7 mL/kg = a loss of 4.5 mL/kg per 3:1 C:V cycle) (**Figure 2A**) (8, 23). In contrast, no V_T loss was observed in CC + SI. Instead, continuous lung recruitment and establishment of functional residual capacity were observed (mean total inspired V_T was 16.3 mL/kg and mean total expiratory was 14 mL/kg = a gain of 2.3 mL/kg/CC + SI cycle) (**Figure 2B**) (8, 23). This improvement in V_T delivery might lead to better alveolar oxygen delivery and lung aeration. More importantly, the initial study by Schmölzer et al. (22) and secondary analysis by Li et al. (23) describe passive V_T delivery during each CC cycle. Similar observations have been reported by Tsui et al. (47) in children under the age of 17 years undergoing any surgery requiring general anesthesia and endotracheal intubation. Tsui et al. compared V_T after induction of general anesthesia before and after intubation by applying a downward force on the chest, which was not greater than the patient's weight in seven infants (47). Overall, median (IQR) V_T generated before and after intubation was 2.4 (0.8–4.0) and 2.0 (0.4–3.6) mL/kg, respectively (47). Although, Tsui et al. only applied gentle chest pressure, they could achieve ~33% of an infant's physiological V_T of 5–7 mL/kg. During CC, the mean applied forced is ~10 kg (3–4 times the weight of the newborn infant) (30), which would result in adequate V_T delivery during CC + SI. Further, Solevåg et al. determined the distending pressure needed to achieve sufficient V_T delivery using different models (manikin and cadaver piglets) during CC + SI (48). Distending pressure and V_T correlated in cadaver piglets ($r = 0.83$, $p < 0.001$), manikin ($r = 0.98$, $p < 0.001$), and combined data ($r = 0.49$, $p < 0.001$). V_T was delivered during chest recoil during CC in both models. In cadaver piglets, a distending pressure ~25 cmH_2O was needed to achieve an adequate V_T. This study suggests that chest recoil generates V_T depending on an adequate distending pressure, and that a pressure of ~25 cmH_2O will be needed to achieve adequate V_T delivery. In addition, this has been recently shown in the first randomized controlled trial in the DR by Schmölzer et al. (24). Overall, the mean (SD) time to ROSC was significantly shorter in the CC + SI group with 31 (9) s compared with 138 (72) s in the 3:1 C:V group ($p = 0.011$). Infants in the CC + SI group had significantly higher respiratory rates with 91 (1) versus 29 (2) inflations/min in the 3:1 C:V group ($p = 0.0001$). The delivered tidal volume ranged between 0.6 and 4.4 mL/kg in the CC + SI group and 0.8 and 4.5 mL/kg in the 3:1 C:V group. Median (IQR) minute ventilation was significantly higher in the SI + CC group compared to the 3:1 C:V group 165 (85–216) versus 101 (48–110) mL/kg/min ($p = 0.0001$). This is currently further studied in a multicenter cluster randomized trial "CC + SI versus 3:1 C:V ratio during neonatal CPR (SURV1VE)—NCT02858583" to study this in a larger patient population.

QUALITY AND DEPTH OF CC AND/OR THE ADMINISTRATION OF EPINEPHRINE

Improved left ventricular ejection fraction have been postulated after review of computer tomography images of neonates when CC with a 1/3 anterior–posterior chest diameter was compared with a 1/4 anterior–posterior chest diameter (49). The current neonatal resuscitation guidelines recommend a 1/3 anterior–posterior chest diameter during CPR (9–11). Adequate CC depth is important to optimize cardiac output. However, compressing to deep could cause rib fractures, cardiac contusion, and other thoracic injuries (7). While compressing to shallow might not create the required cardiac output or diastolic blood pressure (50, 51). A retrospective review of six infants (2 weeks to 7.3 months old) with indwelling arterial blood pressure monitoring reported that CC with a 1/2 anterior–posterior chest diameter produced significantly higher systolic blood pressure but similar diastolic blood pressure compared with CC using a 1/3 anterior–posterior chest diameter. However, the optimal CC depth has not been rigorously evaluated in neonates. Furthermore, no study has examined tidal volume delivery with different anterior–posterior chest diameter.

CONCLUSION

Successful resuscitation from cardiac arrest or severe bradycardia requires the delivery of high-quality CC while providing adequate ventilation. However, until now, no study has examined different CC techniques during neonatal resuscitation in asphyxiated newborn infants, and randomized controlled trials are urgently needed.

AUTHOR CONTRIBUTIONS

Concept, literature search, review of the data, writing of the manuscript, and review of the manuscript: NB, MO, CF, SO, P-YC, and GS.

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Alterations in Cerebral Blood Flow after Resuscitation from Cardiac Arrest

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Greater than 50% of patients successfully resuscitated from cardiac arrest have evidence of neurological disability. Numerous studies in children and adults, as well as in animal models have demonstrated that cerebral blood flow (CBF) is impaired after cardiac arrest. Stages of cerebral perfusion post-resuscitation include early hyperemia, followed by hypoperfusion, and finally either resolution of normal blood flow or protracted hyperemia. At the level of the microcirculation the blood flow is heterogeneous, with areas of no flow, low flow, and increased flow. CBF directed therapies in animal models of cardiac arrest improved neurological outcome, and therefore, the alterations in CBF after cardiac arrest likely contribute to the development of hypoxic ischemic encephalopathy. Current intensive care after cardiac arrest is centered upon maintaining systemic oxygenation, normal blood pressure values for age, maintaining general homeostasis, and avoiding hyperthermia. Assessment of CBF and oxygenation is not routinely performed after cardiac arrest. Currently available and underutilized techniques to assess cerebral perfusion include transcranial doppler, near-infrared spectroscopy, and arterial spin labeling magnetic resonance imaging. Limited clinical studies established the role of CBF and oxygenation monitoring in prognostication after cardiac arrest and few studies suggest that guiding critical care post-resuscitation to mean arterial pressures above the minimal autoregulatory range might improve outcome. Important knowledge gaps thus remain in cerebral monitoring and CBF and oxygen goal-directed therapies post-resuscitation from cardiac arrest.

Keywords: cerebral perfusion, cerebral blood flow, cardiac arrest, post-cardiac arrest syndrome, transcrianial Doppler, arterial spin labeling, hypoperfusion, hyperemia

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INTRODUCTION

In the hours and days following successful resuscitation from cardiac arrest, various organs are recovering from global ischemia–reperfusion. The two key organs that determine the ultimate prognosis of pediatric patients resuscitated from cardiac arrest are the heart and the brain. Hypoxic ischemic encephalopathy persists and evolves during the days and weeks after cardiac arrest and is the major limiting factor in the full recovery of the victims of cardiac arrest. In the immediate period after cardiac arrest, there are important disturbances at the level of cerebral blood flow (CBF), cerebral oxygenation, and cerebral metabolism. The function of the neurovascular unit is disrupted. Despite great advances in the understanding of the cerebral pathophysiology post-resuscitation and

several successful therapeutic advances in animal models, presently there are no therapies proven to be beneficial for improving neurological outcome in pediatric patients after cardiac arrest. Moreover, brain metrics are currently not routinely assessed after cardiac arrest.

The goal of this review is to reveal the knowledge gaps regarding post-resuscitation CBF disturbances in pediatric and adult patients, and ultimately to stimulate the development of cerebral goal-directed therapies for cardiac arrest. We will present several methods used for assessment of cerebral perfusion, and review the evolution of CBF during the after cardiac arrest first in animal models and then in humans.

METHODS USED FOR EVALUATION OF CEREBRAL PERFUSION

Multiple methods are available for the assessment of CBF and cerebral perfusion. Some methods are strictly limited to use in animal models, while others may also be utilized at the bedside. **Table 1** summarizes the various methods available for evaluation of cerebral perfusion in animals and humans.

Methods for CBF Assessment in Animal Models

Various methods of CBF assessment have been used in animal models of cardiac arrest. A review of these methods is important to appreciate the benefits and additional information that can be acquired from research in animal models, as well as to aid in interpretation of blood flow data considering the limitations of each method. In animal models of cardiac arrest, available methods for the assessment of cerebral perfusion may be categorized regarding brain tissue penetration (invasive or non-invasive), and further categorized regarding the area assessed (regional vs. global), and time post-resuscitation (one time point vs. serially) (**Table 1**).

Invasive and Minimally Invasive Methods of Quantification of Cerebral Perfusion in Animal Models

Assessment of CBF can be performed invasively using intraparenchymal Laser Doppler probes (1), intravenously injected microspheres (2) or ^{14}C iodoantipyrene autoradiography (3), laser speckle flowmetry (4, 5), and optical imaging (6, 7). Laser Doppler probes are inserted locally and can serially assess cerebral perfusion in a small area limited to the region surrounding the probe. Intravenously injected microspheres and autoradiography methods require harvesting of the brain to quantify the concentration of microspheres or intensity of the tracer. Thus, these methods can assess CBF at only one time point after cardiac arrest, but have the advantage of providing regional maps of CBF for various brain regions. Laser speckle flowmetry is a minimally invasive method for assessment of serial perfusion. In pediatric and neonatal aged rodents the scalp is incised and deflected and imaging is performed though the intact skull allowing perfusion measurements for large cortical areas, whereas in adult rats a craniotomy is often necessary and perfusion can be measured over an area of a few millimeters. At a microscopic level, the novel optical technologies of dark field imaging and *in vivo* multiphoton microscopy allow assessment of perfusion in animal models from the pial surface to cortical depths of 100–400 μm over a small area of a few millimeters. These techniques provide detailed analysis of the cortical microcirculation and allow for measurement of microvessel diameter, red blood cell speed and density, plasma transit time in the microcirculation, cell interactions at the neurovascular unit, and important assessments of the effect

TABLE 1 | Current methods for assessment of cerebral blood flow (CBF) in animals and humans.

Method	Animals vs. humans	Invasive vs. non-invasive	Area measured	Serial vs. one time point	Comments
Laser Doppler	Animals	Invasive	Regional/small area	Serial	Measures perfusion in a localized area around the probe
Microspheres	Animals	Invasive	Regional	One time point	Requires sacrifice of the animal for analysis of blood flow
^{14}C autoradiography	Animals	Invasive	Regional	One time point	Requires sacrifice of the animal for analysis of blood flow
Laser Speckle Flow	Animals	Invasive	Regional	Serial	Assesses cortical areas only. Requires deflection of the scalp and craniotomy in adult animals
In vivo multiphoton microscopy	Animals	Invasive	Regional/small area	Serial	Assesses perfusion in several areas of 50–100 μm over a 2 mm cortical window
Xenon CT	Animals	Non-invasive	Regional	Serial	Used for humans exclusively in research
Arterial spin labeling magnetic resonance imaging, PET, SPECT	Animals and humans	Non-invasive	Regional	Serial	Current gold standard for CBF measurements
Transcranial Doppler ultrasound	Animals and humans	Non-invasive	Regional/small area	Serial	Measures velocity at the level of middle cerebral artery. Indirect assessment of cerebral microvasculature
Near-infrared spectroscopy	Animals and humans	Non-invasive	Regional/small area	Serial	Measures tissue oxygenation in a localized area under the sensor
Thermal Diffusion flowmetry	Animals and humans	Invasive	Regional/small area	Serial	Utilized in humans after traumatic brain injury

of clinically relevant as well as novel therapeutic agents on the microcirculation (7, 8).

Non-Invasive Methods for Use in Animal Models

Xenon CT (9), arterial spin labeling magnetic resonance imaging (ASL-MRI) (10), TCD, positron emission tomography (PET), single-photon emission computed tomography (SPECT), and dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI) allow non-invasive measurement of perfusion. These methods have the ability to assess regional CBF at multiple time points after cardiac arrest. Details on these techniques are provided in the following section.

Methods for CBF Assessment in Humans

Limited evaluation of CBF has been performed in humans after CA, due to the availability of only a few non-invasive means and portable devices. For human use, an ideal tool for CBF assessment post-resuscitation should be employable early post-resuscitation and be portable, non-invasive, not interfere with clinical care, and allow for serial assessments. Post-resuscitation research is still in search of this tool, and this represents the largest knowledge gap and the greatest impediment to goal-directed cerebral resuscitation.

Cerebral perfusion can currently be assessed in children and adults after cardiac arrest using three techniques: TCD, ASL-MRI, or Xenon CT. Additionally, implantable CBF monitors such as thermal diffusion flowmetry are available invasive methods which have been used to assess perfusion in isolated case reports of cardiac arrest (11) and have been extensively used in patients with traumatic brain injury and subarachnoid hemorrhage (12, 13). In the past, valuable CBF data were obtained in adults using tracers (^{133}Xe) (14) or thermodilution methods (15); however, with the advent of the newer, less invasive technologies enumerated above, these two techniques have not been used recently.

Transcranial Doppler

Transcranial Doppler may be used immediately after cardiac arrest. It can provide serial assessment of cerebral perfusion, does not interfere with clinical care, and provides immediate results. TCD measures cerebral perfusion by assessing blood flow in the middle cerebral artery (MCA). It does not directly assess microvascular perfusion, although several parameters can be used to infer the status of cerebral microcirculation, especially in a global cerebral insult such as cardiac arrest. TCD uses a sonographic probe that is placed on the temporal area anterior to the ear and detects changes in the frequency of sound waves deflected by intravascular erythrocytes. Velocity, direction, and presence of blood flow in the MCA artery may be obtained using TCD (16, 17). As blood flow velocity in the MCA can increase due to local factors (vasoconstriction) or due to increased cardiac output, the ratio between MCA velocity and intracranial carotid artery (ICA) velocity [Lindegaard ratio (LR)] is used to differentiate between cerebral vasoconstriction and decreased cardiac output. Cerebral vasospasm or vasoconstriction will increase the MCA velocity while the ICA velocity would be unaffected, resulting in an increased LR $>$ 3, whereas increased cardiac output would increase both MCA and ICA velocities, resulting in LR $<$ 3 (17). A useful index for measuring microvascular perfusion is the pulsatility index (PI), which takes into account the systolic and diastolic velocities in the MCA and the mean flow velocity to differentiate between normal (PI = 0.6–1.1), low resistance conditions (PI $<$ 0.6, hyperemia vs. vasospasm vs. stenosis), high resistance (PI = 1.2–1.6, in case of microvascular derangements or mild increase in intracranial pressure), or very high resistance (PI = 1.7–1.9, severe increase in ICP), or absent CBF (PI = 2, cerebral asystole) (18). TCD is an available tool for assessment of cerebral perfusion, and it is currently underutilized in clinical care post-resuscitation.

Arterial Spin Labeling Magnetic Resonance Imaging

Arterial spin labeling magnetic resonance imaging is currently the gold standard technique for assessment of CBF (19). It provides data on regional CBF, and it allows for correlation with cerebral metabolism if nuclear magnetic resonance spectroscopy is acquired in the same patient. ASL-MRI requires patient transport to the MRI suite, it cannot be done in the presence of metal devices, and the scan time is 30–60 min. Therefore, ASL-MRI is not feasible during the early period after resuscitation, as patients require intense monitoring, titration of blood pressure medication, and may undergo other various therapies such as therapeutic hypothermia. In two recent studies, ASL-MRI was performed at 6 ± 4 days after cardiac arrest in one study, and in another at a median time of 5 days, range of 1.6–10.4 days after cardiac arrest (20, 21). Future advancement in ASL-MRI scanning techniques to shorten the scan time, availability of MRI scanners in close proximity to intensive care units, and a move toward universal MRI safe equipment for critically ill patients may allow in the future obtaining MRI images to assess structure, perfusion, and metabolism after the initial stabilization post-resuscitation.

Xenon Computer Tomography (Xe-CT)

Xenon computer tomography is another method of quantitative CBF measurement, which could theoretically be used at the bedside. The Xe-CT methods detect the distribution of the tracer in the brain. When the method was initially developed, Xe^{133} was injected in the carotid artery, and CBF was calculated from its clearance curve (22). Subsequently, the intracarotid Xe method has been replaced with the less invasive Xe^{133}inhalation method and Xe-enhanced CT. Compared with Xe^{133} technique, the Xe-enhanced technique avoids extracerebral contamination, has higher spatial resolution, and it has been used in both human and animals post-resuscitation as early as 8 h after resuscitation (9, 23). Xe-CT scan is portable and has relatively safe profile, however, the inhalation of Xe at higher concentration has the potential risk of respiratory depression and increased ICP (24). In addition, only a few pediatric intensive care units worldwide have Xe-CT available for use, and to our knowledge Xe-CT is currently used strictly for research purposes.

Near-Infrared Spectroscopy (NIRS)

Near-infrared spectroscopy measures the oxygen saturation in tissues using the differences of near-infrared (700–1,000 nm) light absorption between oxygenated and deoxygenated hemoglobin.

The intensity changes between the transmitted and received NIR light are detected by a sensor and used to determine the tissue oxygen saturation (25). NIRS can be used to assess relative brain oxygenation and is considered a surrogate of CBF (26); it is relatively easy to use and it does not interfere with clinical care. Its limitations thus include significant attenuation at the extracerebral tissue, limited depth penetrance with measurement limited to the cortex, and lack of absolute measurement values that can be compared directly across subjects and conditions (25). Longitudinal assessment of NIRS post-resuscitation might signal changes consistent with clinical deterioration or might direct clinical care by establishing an optimal blood pressure for cerebral perfusion (27). NIRS can also be used to correlate changes in cerebral oxygenation with blood pressure to assess blood pressure autoregulation (27, 28).

In summary, multiple methods for assessment of CBF and cerebral perfusion are available in animals, and with the recent addition of novel methods such as optical imaging detailed assessment of the effect of critical care interventions and clinically relevant therapies on CBF in animal models is possible. Detailed characterization of regional CBF post-resuscitation has been ascertained from animal models, yet only limited data on post-resuscitation CBF is available for humans, due to the availability of only a few methods for clinical assessment of CBF. Partnering with engineering teams to design devices for bedside cerebral monitoring after cardiac arrest is necessary for assessment of cerebral function and perfusion, and ultimately to conduct cerebral resuscitation.

ALTERATIONS IN CBF AFTER CARDIAC ARREST: ANIMAL MODELS

Cardiac arrest produces a global cerebral ischemic injury. Early animal models of global cerebral ischemia included, among others, aortic balloon occlusion (29) and neck tourniquet insults (30). Clinically relevant models of cardiac arrest were developed more recently, and CBF was thoroughly assessed using these models. These models include: ventricular fibrillation cardiac arrest (VF) (31), asphyxial cardiac arrest (10, 31), and KCl-induced cardiac arrest (32). CBF has been characterized after cardiac arrest in pediatric and adult age groups in rats, pigs, cats, and rabbits. Animal models offer the advantage of serial and regional assessment of CBF providing a temporal frame of the cerebrovascular changes in the four phases of post-cardiac arrest syndrome: immediate (0–20 min), early (20 min to 6–12 h), intermediate (6–12 to72 h), and recovery (>72 h) (33). Another benefit of the animal models is the ability to assess CBF after cardiac arrest of progressive durations, which provides important clinical insight for alterations of CBF in insults of moderate duration (in-hospital cardiac arrest model) vs. prolonged durations (out-of-hospital cardiac arrest model). Finally, the ability to correlate CBF and CBF-related interventions with functional outcome and histology is another important aspect of experimental cardiac arrest models.

Classically, three stages of CBF alterations have been described after resuscitation from cardiac arrest. During cardiac arrest and CPR, there is initially absence of flow during cardiac arrest and subsequently either no-flow or low-flow perfusion during CPR. After return of spontaneous circulation, the initial post-resuscitation CBF stage is known as cerebral hyperemia, and occurs between 5 and 30 min after resuscitation. Following hyperemia, cerebral hypoperfusion occurs from 30 min to 6 h after resuscitation. Finally, either resolution of CBF, continued hypoperfusion, global hyperemia, or cessation of flow and brain death occurs during the days post-cardiac arrest (34). More recent studies, however, reveal that cerebral perfusion during each stage is different in various brain regions: subcortical areas generally display early hyperemia, whereas cortical areas generally display hypoperfusion. Additionally, cerebral perfusion is dependent on insult duration: hyperemia is less frequently observed in prolonged insults, whereas hypoperfusion is more pronounced in prolonged insults. Finally, the age of the animal and the type of cardiac arrest also influence post-resuscitation CBF. Immature animals have different hemodynamic response to stimuli due to ongoing neurogenesis, synaptic pruning, and changes in the vascular architecture of the brain (35, 36).

Significant data have been gathered on CBF changes in animal models during each of the four phases of the post-cardiac arrest syndrome. We present their highlights below.

CBF in the Immediate Phase of the Post-Cardiac Arrest Syndrome (0–20 min)

In the immediate phase post-resuscitation, CBF disturbances have traditionally been characterized by hyperemia; however, recent studies show that the alterations are brain-region specific depend on three factors: age (pediatric vs. adult model), pathophysiological mechanism of cardiac arrest (VF vs. asphyxia), and insult duration (mild, moderate vs. severe insults).

In the adult experimental cardiac arrest, hyperemia is repeatedly noted in various models. Blomqvist and Wieloch (37) reported hyperemia of different intensities in 17 regions early after VF cardiac arrest in rats. Similarly, early hyperemia was also found in adult rats and dogs with longer duration (10–13 min) of VF cardiac arrest (38, 39). Hyperemia after asphyxial cardiac arrest was also described by Xu et al. in the thalamus and cortex (40). The regional distribution of hyperemia was also recognized in a dog model of VF cardiac arrest: the brain stem and basal ganglia had longer duration of hyperemia compared with the cortex (41). A comprehensive comparison of CBF in VF cardiac arrest vs. asphyxial cardiac arrest in adult rats revealed that after asphyxial cardiac arrest marked early hyperemia is observed in all regions, whereas after VF cardiac arrest early hyperemia was limited to the cortex, whereas subcortical regions had baseline levels of CBF (31). The influence of insult duration on CBF has not been completely characterized in adult models of cardiac arrest. To date, no studies provided a parallel assessment of regional CBF in insults of progressive durations in models of adult cardiac arrest.

In pediatric asphyxial cardiac arrest in rats, CBF is markedly dependent on the brain region (cortical vs. subcortical) and insult duration (moderate vs. severe insult) (**Figure 1**) (10). In contrast with earlier studies in adult animal models showing universal early hyperemia, in immature rats hyperemia is limited

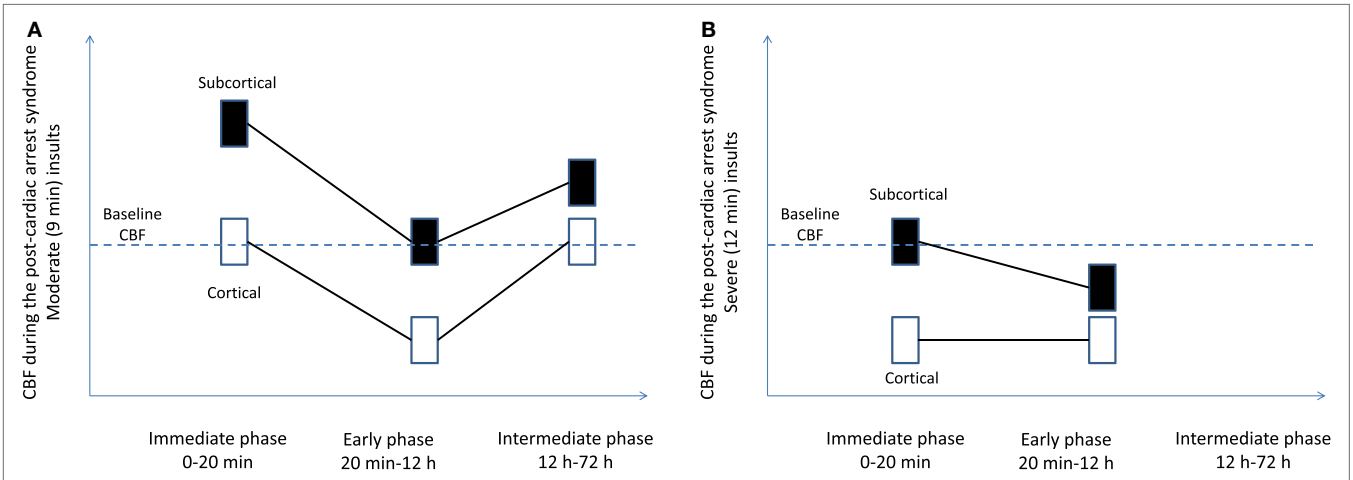

FIGURE 1 | Regional cerebral blood flow (CBF) after pediatric asphyxial cardiac arrest after moderate **(A)** and prolonged **(B)** insults. Figure is a graphic representation of a compilation of two studies from our laboratory (10, 55).

to the subcortical areas, whereas cortical areas have normal or even decreased CBF. Specifically, in insults of moderate duration (9-min asphyxia) subcortical areas are characterized by marked early hyperemia. However, after insults of prolonged duration (12 min) subcortical areas have baseline CBF levels without evidence of hyperemia (**Figure 1**) (10). Cortical CBF is markedly different than subcortical CBF. Cortical CBF returns to baseline level immediately after resuscitation in insults of moderate duration, whereas after cardiac arrest in insults of prolonged duration cortical hypoperfusion occurs immediately post-resuscitation (**Figure 1**) (10). Measurement of brain tissue oxygen level in these insults revealed that brain tissue oxygen mirrored the CBF changes: subcortical hyperoxia occurred in insults of moderate duration, while cortical hypoxia occurred in insults of severe duration (42). These studies in pediatric models of cardiac arrest showed that alterations in CBF are accompanied by alterations of tissue oxygenation post-resuscitation.

The significance of early hyperemia is still being elucidated. Some studies suggest that hyperemia is an indication of coupling of CBF and metabolism, and thus is an indication of increased local metabolic rates. Others suggest that hyperemia is detrimental as it intensifies the reperfusion syndrome, and propose that a more gradual reperfusion might be beneficial. Thalamic areas, where early hyperemia is observed after pediatric cardiac arrest, is characterized by extensive degeneration of neurites and activation of microglia, suggesting an association between early hyperemia and neurodegeneration (43). Therapies targeting the early hyperemic phase to improve neurological outcome included antioxidants such as superoxide dismutase and polynitroxyl albumin, which decreased the early hyperemia of the subcortical areas and improved outcome (10, 44).

CBF in the Early Phase of Post-Cardiac Arrest Syndrome (20 min–12 h)

After the initial period post-resuscitation, CBF is generally characterized by a longer hypoperfusion stage, which appears to occur more uniformly across species, age groups, and models (34, 37–39, 41, 45–47). Hypoperfusion is observed anywhere from 15 to 60 min post-resuscitation and can persists for hours or even days.

In adult cardiac arrest models, both asphyxial and VF, hypoperfusion has been observed in all regions, cortical and subcortical (31). Gray matter appeared to be more vulnerable to hypoperfusion than the white matter (48).

In pediatric asphyxial cardiac arrest in immature rats the hypoperfusion is more evident in the cortex and is more pronounced in longer durations of cardiac arrest (10, 49). In the subcortical areas such as thalamus, hypoperfusion was seen only with prolonged durations of cardiac arrest (10) (**Figure 1**).

Cerebral blood flow and metabolism are likely uncoupled during the delayed hypoperfusion period, suggested by the cortical hypoxia observed after pediatric asphyxial cardiac arrest (42), and suggesting that the brain suffers a secondary ischemic event during this period. Multiple mechanisms are implicated in the development of delayed hypoperfusion, including damage at the level of the endothelial cells, unbalance of local vasodilator and vasoconstrictors, as well as impaired autoregulation in the setting of decreased blood pressure. Therapies targeting these mechanisms have been assessed in animal models (5, 30, 50–52).

CBF in the Intermediate Phase of the Post-Resuscitation Syndrome (12–72 h)

Cerebral blood flow at greater than 12 h after experimental cardiac arrest has not been extensively studied. In severe cardiac arrest models, the animals need intensive care and might not survive if extubated and returned to their cages. CBF was assessed at 24 h after moderate durations of pediatric cardiac arrest (9 min, **Figure 1**). CBF returned to normal values in the delayed period in all regions except for the thalamus. Thalamic areas have increased CBF at 24 h after CA (53). The function of thalamic circuitry is impaired after pediatric cardiac arrest, as demonstrated by increased firing rates in thalamocortical neurons at 48–72 h after

cardiac arrest and associated with histologic evidence of injury in the thalamic nuclei.

Cerebral Perfusion at the Microvascular Level: No-Reflow Phenomenon after Cardiac Arrest

During the immediate and early periods after cardiac arrest there are microcirculatory disturbances, resulting in localized areas of no flow, interspersed with areas of low flow and increased flow. This phenomenon was initially described by Ames et al. in a model of global ischemia in rabbits in 1968 as incomplete filling of the cortical capillary bed upon perfusion with contrast agent and is known as the no-reflow phenomenon (54). The perfusion deficits increased with increased duration of ischemia and the no-reflow phenomenon has been observed in various models of cardiac arrest (55, 56).

Multiple mechanisms have been proposed to be responsible for the no-reflow phenomenon, including post-resuscitation hypotension, increase in blood viscosity, and fibrin clots (34, 57–59). Therapies targeting these mechanisms have shown beneficial effect in animal models. For example, blood flow promotion therapy with hypertension and hemodilution immediately after cardiac arrest has been shown to normalize the CBF pattern and improve outcome in dogs (46, 60). Thrombolytic therapies with plasminogen activator and heparin reduced no-reflow phenomenon seen after cardiac arrest and produced more homogeneous perfusion (61). The no-reflow phenomenon likely contributes to the hypoperfusion observed post-resuscitation and likely causes a secondary ischemic injury.

In summary, valuable data regarding alterations of CBF post-resuscitation is obtained from animal models of cardiac arrest. These models have the advantage of allowing serial, regional assessment of CBF, and comparison of CBF alterations in insults of progressive durations, simultaneous assessment of CBF, brain oxygenation, metabolism, and electrical activity (62), assessment of microvascular alterations, and development of novel CBF and neuronal targeted therapies.

CBF DYSREGULATION AFTER CARDIAC ARREST IN CHILDREN AND ADULTS

Data on CBF from animal models provide us with an appreciation of post-cardiac arrest perfusion variability for different types of cardiac arrest (asphyxial vs. VF), and progressively longer insults in pediatric and adult models. CBF data from humans are generally compiled from various insult types (VF, asphyxia, and often unknown), and various and unknown insult durations. Thus, human CBF data post-cardiac arrest are more variable. The vast majority of CBF data after cardiac arrest have been ascertained from adults and have been obtained at delayed time points post-resuscitation. A prevailing pattern of CBF post- resuscitation is the protracted hypoperfusion followed by hyperemia in the days following cardiac arrest. The current CBF data demonstrate the presence of perfusion abnormalities after cardiac arrest and underscore the need for cerebral monitoring post-resuscitation.

Cerebral perfusion in children varies greatly with age paralleling cerebral maturation during development, and thus combining data from different age groups in the pediatric population may be a confounding factor (63). Highlighting the dynamic nature of brain development in infancy, childhood, and adolescence, global CBF values average 16 ml/100 g/min in the neonate, increase to 39 ml/100 g/min in infancy, further increase to 100 ml/100 g/min by 6–8 years of age, and finally decrease to 60 ml/100 g/min in males and 75 ml/100 g/min in females by age 18 (63–67). Within each age group, some individual variation exists and regional differences in CBF at each age group are noted. The basal ganglia and the thalamus have the highest perfusion values, and the gray matter has lower perfusion values (67). Because of individual and age-related variations, age-matching is imperative in studies related to cerebral hemodynamics. Comparing mean CBF values at one time point post- resuscitation between groups of children of wide age ranges is unlikely to lead to interpretable results. Ideally, although difficult, repeated longitudinal assessment of perfusion in the same subject and correlation with metabolism and tissue oxygenation would be performed.

We will present below the current knowledge on CBF post-cardiac arrest in adult and pediatric patients assessed by TCD, ASL-MRI, Xe-CT, and CBF autoregulation after cardiac arrest (**Table 2**).

Cerebral Perfusion Assessment in Adults and Children Using TCD

Transcranial Doppler was used in several studies after cardiac arrest. These studies confirmed that cerebral hemodynamics are altered during the post-cardiac arrest syndrome and evolve during the first 24–72 h after cardiac arrest.

During the first 12 h after cardiac arrest several small studies in adults demonstrate the presence of hypoperfusion and high vascular resistance, evidenced by low mean flow velocity and high PI (68–70). This diffuse hypodynamic TCD pattern suggests microangiopathy secondary to vasoconstriction and no-reflow in the microcirculation, and is associated with poor neurological outcome (18).

After 24 h post- resuscitation, a diffuse hyperdynamic pattern is observed, evidenced by high mean flow velocity and low PI, suggesting hyperemia or vasospasm (68–70). This pattern was also associated with poor prognosis, progression to brain death, and increased ICP (18). These changes were associated with increased endothelin levels, decreased nitric oxide levels, and increased cGMP levels, suggesting that an imbalance between local vasodilators and vasoconstrictors plays a role in the cerebral vasoconstriction and hypoperfusion phase (70).

Underscoring the importance of serial assessment of CBF post-cardiac arrest, one study showed that the initial hypodynamic pattern observed during the first 12 h after resuscitation was followed by normalization of mean flow velocity and PI for 24 h, and then by increased mean flow velocity and low PI for 48–72 h (69). Therefore, a single measurement cannot be used for prognostication without taking into account the CBF trajectory for the respective patient. Possibly related to the time of measurement of CBF post-resuscitation, a recent study failed

TABLE 2 | Summary of studies assessing cerebral blood flow (CBF) post-resuscitation.

Reference	Method	Age	Time point	Highlights
Iida et al. (68)	Transcranial Doppler (TCD)	Adults	0–12 h	Low mean flow velocity, high pulsatility index (PI). Suggestive of microangiopathy, vasoconstriction, and no reflow
Lemiale et al. (69), Buunk et al. (70)	TCD	Adults	12–24 h	Low mean flow velocity, high PI. Suggestive of microangiopathy, vasoconstriction, and no reflow
Doepp Connolly et al. (71)	TCD	Adults	0–48 h, 3–5 days, 7–10 days post-resuscitation	No correlation of TCD and outcome
Lin et al. (72)	TCD	Children	Before, during, and after hypothermia	Undetectable flow was associated with death. Markers for good prognosis: normal flow velocity during rewarming and normal PI during rewarming or hypothermia
Manchester et al. (21)	Arterial spin labeling magnetic resonance imaging (ASL-MRI)	Children	>24 h post-resuscitation	No CBF difference between patients with favorable and unfavorable outcomes. MRI was performed at 6 ± 4 days after cardiac arrest
Pollock et al. (73)	ASL-MRI	Adults and children	1–13 days post-resuscitation	Global hyperperfusion pattern identified. Most patients had poor prognosis
Beckstead et al. (75)	^{133}Xenon Washout	Adults	2–6 and >6 h post-resuscitation	Decreased CBF and decreased oxygen metabolism at 2–6 h, followed by increased CBF with relative hyperemia at >6 h
Cohan et al. (76)	Xenon inhalation	Adults	18–36 h post-resuscitation	Increased CBF was associated with coma, isoelectric encephalogram, and death. Normal CBF was associated with regaining consciousness
Brodersen (77)	Xenon inhalation	Adults	1–12 days post-resuscitation	Most patients had relative hyperemia. CBF was variable and paralleled the oxygen metabolism
Sundgreen et al. (78)	TCD	Adults	0–24 h post-resuscitation	Cerebral autoregulation was either absent or right-shifted
Nishizawa and Kudoh (79)	CBF index	Adults	3 days post-resuscitation	All patients were comatose. Impaired cerebral autoregulation was detected

to show a correlation between TCD parameters and outcome. In this particular study, the first CBF measurement was obtained within 48 h after cardiac arrest, and subsequent measurements were obtained at days 3–5 and 7–10 post-resuscitation (71).

Transcranial Doppler was successfully assessed in 17 children after cardiac arrest at three points: during the pre-hypothermia, hypothermia, and rewarming phases. All patients with undetectable flow during any phase died. Patients with normal mean flow velocity during the rewarming phase had better prognosis vs. patients with low mean flow velocity. Patients with normal pulsatility indices during the hypothermia and rewarming phases had better outcomes compared with the ones with high pulsatility indices (72).

CBF Assessment in Adults and Children Using ASL-MRI

MRI assessment of CBF early after cardiac arrest is difficult to perform, due to the patients' clinical instability. In a prospective observational study, pediatric patients underwent MRI to assess CBF and ADC maps after cardiac arrest (21). This study was the first pilot study in the pediatric patients to assess CBF after cardiac arrest and identified both the opportunities and current challenges of ASL-MRI after cardiac arrest. The patients were transported to the MRI suite when the clinical team was comfortable that the patient was stable for transport and seizure-free. The brain MRI was performed at 6 ± 4 days after cardiac arrest (IQR 2.7–8.7 days).

Cerebral blood flow was 76.8 + 32.5 vs. 91.6 + 38.9 ml/100 g/min for patients with favorable vs. unfavorable outcome, with no significant difference between patients with favorable vs. unfavorable outcomes. Importantly, children with unfavorable outcome had decreased apparent diffusion coefficient compared with children with favorable outcome, suggesting cytotoxic edema. Brain regions with abnormalities in diffusion consistent with cerebral edema had also increased CBF. The assessment of CBF at only one time point after cardiac arrest and the necessity to analyze data after cardiac arrest among patients of different ages could have contributed to the limited conclusions that could be drawn regarding CBF from this study. Another study of 14 adults and 2 children that underwent ASL-MRI at a range of 1 and 13 days after cardiac arrest showed a universal global hyperperfusion pattern. A majority of patients in this latter study died (10/14 adults, and 2/2 children) (73).

CBF Assessment in Adults Using Inhalation of Xe^{133} and the Ketty-Schmidt Technique

Before the advent of MRI, CBF was measured in human subjects for decades using the Xe^{133} washout technique. Xe^{133} was administered by inhalation, and CBF was calculated using a compartment method (74). With this technique, human CBF and metabolism were assessed in eight adult patients post-resuscitation with inhalation of Xe^{133} and concomitant measurement of $CMRO_2$ using the jugular venous oxygen tension measurement technique. From

2 to 6 h post-cardiac arrest, CBF was decreased to 50% along with a decrease in oxygen metabolism. After 6 h, CBF was increased toward baseline, while the metabolism also started recovering, albeit disproportionately in comparison to CBF, such that a relative hyperemia developed. This "luxury perfusion" was also seen at 24–60 h after cardiac arrest. This study suggested that CBF at delayed time points after cardiac arrest is uncoupled from metabolism (75).

Similarly, in 13 patients resuscitated from cardiac arrest, CBF was assessed using Xe inhalation. Seven (54%) patients who regained consciousness had normal CBF values, while six (46%) patients who did not regained consciousness had increased CBF between 18 and 36 h. In these comatose patients, decreased CBF after the period of hyperemia was associated with isoelectric encephalogram and death (76). In another similar study, a majority of patients had relative hyperemia; however, CBF showed great variability between patients (77).

Assessment of CBF Autoregulation and CO_2 Reactivity after CA

Cerebral blood flow autoregulation is a physiological phenomenon that maintains a relatively constant CBF for blood pressures in the range of 50–150 mmHg, through vasodilatory and vasoconstrictor mechanisms.

After cardiac arrest, CBF autoregulation was found to be compromised in 13 of 18 adult patients in the first 24 h after resuscitation. For assessment of autoregulation, the blood pressure was increased with 30 mmHg using intravenous infusion of norepinephrine. The autoregulation was absent in some patients, while the lower limit of autoregulation was shifted toward a higher pressure in others. Five patients (28%) had normal autoregulation, eight patients (45%) had loss of autoregulation, and another five patients (28%) had preserved but right-shifted autoregulation, with the lower limit of autoregulation increased to a median of 114 mmHg (range 80–120), a derivation from a median of 76 mmHg (range 41–105) in the healthy individuals studied (78). Cerebral autoregulation was also found to be impaired in eight adult patients that were comatose 3 days after cardiac arrest. The patients had internal jugular vein cannulation, and CBF index was indirectly calculated using the arterial-jugular bulb venous oxygen content difference (79).

More recently, NIRS was validated as a tool for measuring cerebrovascular autoregulation (80). Correlating changes in oxygen saturation with fluctuations of arterial blood pressure over time can detect an impairment in the CBF autoregulation. Several studies correlated impaired autoregulation with worse neurological outcome after cardiac arrest. In a study in adults a combined measure of tissue oxygenation and blood pressure was performed daily for the first 3 days after CA. Impaired autoregulation on days 1–3 after cardiac arrest was associated with increased mortality at 3 months (81). In another study, impaired autoregulation was found in 35% patients during the first 24 h after cardiac arrest and was correlated with worse outcomes (82). Since hypotension after cardiac arrest was shown to be deleterious and higher blood pressure after cardiac arrest were associated with favorable outcomes (83, 84), it is important to maintain the blood pressure in an optimum range for cerebral perfusion. Important studies by Lee et al. generated an index of vasomotor reactivity by correlating relative tissue hemoglobin with mean arterial pressure (MAP), and based on this index, the optimal MAP range with most robust autoregulation can be identified (28, 85). In a landmark pilot study in 35 pediatric patients monitored with NIRS after cardiac arrest, patients who spent more time with MAP below the optimal autoregulatory range during the first 48 h after cardiac arrest had worse outcomes (27). Thus, combining real-time NIRS with continuous blood pressure monitoring might not only be used as a tool for prognostication early after cardiac arrest, and may serve as a measure of goal-directed blood pressure management after cardiac arrest.

The cerebrovascular reactivity to changes in arterial carbon dioxide tension (CO_2 reactivity), accountable for a 3% decrease in CBF in response to a 1 mmHg decrease in pCO_2 (86), appears to be maintained after cardiac arrest (70). Thus, hyperventilation after cardiac arrest might induce cerebral vasoconstriction and a secondary ischemic insult and should, therefore, be avoided.

In summary, there are relatively few studies assessing CBF post-resuscitation in adults, and even fewer studies in children. CBF varies greatly from infancy to adolescence, and thus pediatric studies of CBF should group data for each age group (neonate, infant, toddler, school age, and adolescent) to allow for meaningful interpretation of results. The limiting factor for assessing CBF after cardiac arrest is a reliable non-invasive device that can be used at the bedside and allow for serial measurements of cerebral perfusion. TCD could offer non-invasive repeated measures of cerebral perfusion, and is largely underutilized after cardiac arrest. There are good data to support that decreases in CBF correlate with decreases in cerebral oxygenation (1, 42) and thus NIRS could provide some guidance post-resuscitation especially to guide maintenance of blood pressure within the range with most robust autoregulation (27).

In conclusion, we reviewed here CBF changes in animal models and in adult and pediatric patients after cardiac arrest. There are many challenges to the assessment of perfusion after cardiac arrest. Multidisciplinary and multi-institutional collaborations are necessary to fully evaluate CBF dysregulation in pediatrics, as CBF varies vastly in an age-dependent manner. Understanding cerebral perfusion after cardiac arrest would be beneficial in guiding current therapies, assessing novel vasoactive therapies, and prognostication.

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Conception and design; critical revision of the article for important intellectual content; final approval of the article: MM, BI, LL, and RC. Drafting of the article: LL, BI, and MM.

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Lost in Transition: A Systematic Review of Neonatal Electroencephalography in the Delivery Room—Are We Forgetting an Important Biomarker for Newborn Brain Health?

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Background: Electroencephalography (EEG) monitoring is routine in neonatal intensive care units (NICUs) for detection of seizures, neurological monitoring of infants following perinatal asphyxia, and increasingly, following preterm delivery. EEG monitoring is not routinely commenced in the delivery room (DR).

Objectives: To determine the feasibility of recording neonatal EEG in the DR, and to assess its usefulness as a marker of neurological well-being during immediate newborn transition.

Methods: We performed a systematic stepwise search of PubMed using the following terms: infant, newborns, neonate, DR, afterbirth, transition, and EEG. Only human studies describing EEG monitoring in the first 15 min following delivery were included. Infants of all gestational ages were included.

Results: Two original studies were identified that described EEG monitoring of newborn infants within the DR. Both prospective observational studies used amplitude-integrated EEG (aEEG) monitoring and found it feasible in infants >34 weeks' gestation; however, technical challenges made it difficult to obtain continuous reliable data. Different EEG patterns were identified in uncompromised newborns and those requiring resuscitation.

Conclusion: EEG monitoring is possible in the DR and may provide an objective baseline measure of neurological function. Further feasibility studies are required to overcome technical challenges in the DR, but these challenges are not insurmountable with modern technology.

Keywords: newborn, electroencephalography, neuro-monitoring, delivery room, hypoxic–ischemic encephalopathy, prematurity

INTRODUCTION

Electroencephalography (EEG) has become a routine component of neurological monitoring in the neonatal intensive care unit (NICU) (1, 2). It has well-documented benefits in monitoring newborn infants with perinatal asphyxia (3–6) and seizures (7–13) and in predicting long-term outcome (14–21). Five to ten percent of newborn infants require some measure of stabilization in

the delivery room (DR) (22). The majority of infants who require complex stabilization are either extremely premature or have sustained birth asphyxia. In recent decades, the survival rates for both preterm and asphyxiated infants have improved, but neurodevelopmental morbidity has not decreased in corresponding order (23, 24). An increased focus on the early identification and prevention of brain injury in newborn infants is now a major focus of newborn care in the setting of the NICU. However, neurological monitoring is not routine during newborn stabilizations in the DR, nor is it recommended in recent international guidelines (25, 26). First, we will discuss the current methods for assessing brain health in the DR, and then we outline our rationale for considering EEG as a very useful biomarker of brain health in the DR. **Table 1** summaries the different assessment tools discussed.

CURRENT METHODS FOR ASSESSING BRAIN HEALTH IN THE DR

At present, neonatal stabilization teams rely on clinical parameters to assess a newborn infant's neurological status during immediate newborn transition. Assessments of muscle tone and reflex irritability are incorporated into the Apgar score, which is routinely assigned to infants after 1 and 5 min (27, 28). However, Apgar scores are subjective and inter-rater variability is high (29). Neonatal objective hemodynamic monitoring with reliable, continuous, non-invasive measurements of physiological parameters such as heart rate and pre-ductal oxygen saturations (with pulse oximetry) is now routine in the DR (29–32). However, neonatal stabilization teams do not have objective information available about neurological function during resuscitation. The availability of accurate and objective baseline neurological information may help guide resuscitation and plan appropriate early interventions for neonates that may not have tolerated the stresses of labor so well.

Studies that have previously sought to introduce neurological monitoring into the DR initially focused on cerebral blood flow using Doppler measurements of cerebral or carotid arteries (33–38). More recently, studies have concentrated on near infrared spectroscopy (NIRS), which provides non-invasive monitoring of cerebral tissue oxygenation in the DR (39–46). Guidelines for the use of NIRS monitoring and EEG in NICUs overlap, and it is advised that they should be used simultaneously (6).

RATIONALE FOR PROPOSING EEG AS A BIOMARKER OF NEWBORN BRAIN HEALTH IN THE DR

Electroencephalography is not a new technique, but its application in neonatology in the past has been hampered by a lack of appropriate technology for recording and analysis. This has changed dramatically in the last decade, and there are now high quality digital amplifiers available that can record excellent EEG signals even in very noisy environments. The time is now right to reexplore the use of EEG as a valuable biomarker of neurological function in the DR; an environment where previously, it was just not possible.

The signal measured by the EEG is of the order of microvolts and represents a direct measure of postsynaptic neuronal activity in the cortex. Research has shown that the EEG of fetal sheep can be recorded during labor (47–49). Thaler and colleagues performed intrapartum EEG on fourteen women with uncomplicated pregnancies (50), and a clinical trial of EEG monitoring during labor is currently underway (https://clinicaltrials.gov/ct2/show/NCT03013569). During normal labor, the fetus is exposed to brief but repeated episodes of hypoxia, which are balanced by the fetus's striking ability to adapt to these episodes (51). Fetal EEG monitoring in both human and animal studies during labor has shown that these episodes are associated with rapid EEG amplitude reduction and also with fast amplitude recovery as soon as the uterine contraction ends (48, 52). The EEG is exquisitely sensitive to any impairment in oxygen delivery to the brain. A reduction in oxygen leads to an immediate suppression of synaptic transmission with a reduction (often complete

TABLE 1 | Current and possible future tools for assessing neonatal brain health in the delivery room (DR).

	Method	Strengths	Limitations
Clinical assessment	Muscle tone and reflex irritability as part of the APGAR score	Immediate score	Subject to inter- and intra-rater variability
Cerebral blood flow	Ultrasound Doppler of cerebral or carotid artery	Immediate assessment of cerebral blood flow	Technically challenging and continuous data acquisition not feasible
Near infrared spectroscopy (NIRS)	Non-invasive monitoring of cerebral tissue oxygenation by application of NIRS pad to frontal area	Feasible to obtain continuous reliable data in the DR Normative values established	Wide range for normative values
Fetal electroencephalography (EEG)	Application of >1 EEG electrodes to fetal scalp during labor	Would allow for real time assessment of fetal brain health	Technically challenging Can only be applied during late stages of labor Not established as method for assessing fetal health Paucity of normative data
EEG	Application of >1 EEG electrodes to neonatal scalp after delivery	Would allow for real time assessment of neonatal brain health Established method for monitoring neonatal brain health in neonatal care	Technically challenging Paucity of normative data

suppression) in EEG amplitude (48, 53). This adaptive response, believed to be mediated by multiple inhibitory neuromodulators including adenosine, to hypoxia may be protective by decreasing energy consumed by the generation of synaptic potentials (54). If cerebral hypoxia is sustained, however, EEG amplitudes remain severely reduced and membrane failure will eventually occur accompanied by energy depletion and cell damage (52). Thus, sustained changes in the EEG signal a risk of impending brain injury.

In neonates with hypoxic–ischemic encephalopathy (HIE), an EEG showing sustained suppression for hours after birth has long been associated with a very poor outcome (5, 15, 55, 56). Neonatal EEG monitoring is recommended for all infants with moderate and severe HIE, and neonatal teams are now familiar with its application in NICUs. Fetal EEG monitoring has clear benefits for the early recognition of HI injury but requires considerable research before it is adopted as a routine tool for fetal surveillance. Immediate EEG acquisition in the DR on the other hand is much more feasible and may quickly identify those neonates that have not tolerated labor and delivery very well, which will be seen as disrupted patterning on the EEG.

An early EEG in the DR of an infant requiring resuscitation will indicate if EEG activity is present or not or if EEG activity returns following this stabilization process. As we know that EEG activity should recover immediately following restoration of oxygen delivery to the brain, if EEG activity does not return immediately post resuscitation or activity is severely disrupted, this indicates that the infant is at risk of hypoxic–ischemic brain injury. This could provide a clear indication for immediate passive cooling prior to transfer to the NICU. This early indication of cerebral function is very important as Thoresen et al. have shown that infants cooled within 3 h of birth have better neurodevelopmental outcomes when compared to infants whose cooling commenced between 3 and 6 h (57). Further improvements in outcome are highly likely to arise from earlier improved identification of affected infants that would allow earlier initiation of treatment after resuscitation.

Therefore, early EEG monitoring could provide neonatal stabilization teams with valuable, much needed, information about the neurological status of the newborn infant immediately after birth. Thus, we set out to assess whether any studies had already attempted to measure the human EEG in the DR by conducting a systematic review of available literature. We also aimed to establish the feasibility of EEG monitoring in the DR, and determine whether valuable information has been acquired from its application thus far.

METHODS

Search Strategy

We performed a systematic stepwise search of PubMed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (58). Articles up to and including February 2017 were included. Studies had to involve EEG monitoring in the DR. Search terms included the following: infant, newborns, neonate, DR, afterbirth, transition, and EEG. Only human studies were included, and this was incorporated into the initial search. Additional published reports identified in review articles or referenced in articles screened were also included. Publication bias was not assessed.

Study Selection

Articles identified by our search strategy were screened for inclusion by one author (DF). Titles and abstracts were initially screened. Articles had to pertain to EEG monitoring immediately after birth. Studies that focused on infants post birth asphyxiation or infants who had intracranial pathology were excluded as the subjects were, by nature, recruited post-delivery and not relevant to our search. Studies that specified a time frame for initial EEG monitoring outside of the first 15 min of life, or initial recruitment outside of the DR were also excluded. Where uncertainty remained regarding eligibility for inclusion the full text was reviewed. Studies that were not available in English were excluded.

RESULTS

Our initial search identified 215 articles (see Appendix 1 in Supplementary Material). After assessment of these articles, two original studies were identified that described EEG monitoring of the newborn infant within the DR (**Figure 1**). One study also contributed to a review article identified by our search, which was excluded from our study to avoid duplication (59). **Table 2** summarizes the two studies identified.

Pichler et al. performed a prospective observational study of infants born by elective cesarean section over 34 weeks gestational age (60). Infants at lower gestational ages were excluded due to concerns about their small head size, and the feasibility in applying EEG leads and NIRS to a small surface area. Four gold electrodes (two frontal and two parietal) were applied with contact gel, along with an NIRS pad to the left forehead, and overlying elastic bandages for support. Amplitude-integrated EEG (aEEG), a rectified, filtered, and compressed form of EEG, was acquired and stored. Overall, they found that aEEG monitoring of the newborn infant in the DR is feasible, but it is difficult to obtain continuous reliable data. Of a total number of 63 infants, 17 (27%) were excluded due to unreliable data. Of the remaining 46 infants, no data were recorded prior to 3 min of delivery, 25% had data available at 3 min, and just over 50% were available at 5 min. aEEG data were analyzed for mean minimum and mean maximum voltages every minute, and then correlated with cerebral oxygenation, heart rate and pre-ductal oxygen saturations. Findings were then compared between infants who were uncompromised at birth ($n = 31$) and infants who required neonatal resuscitation ($n = 16$).

Different cerebral activity patterns were identified between uncompromised newborns and those requiring resuscitation. They reported that infants in the uncompromised transition group started with initially high voltages on aEEG, followed by a significant decrease to baseline voltages at 4–5 min. In contrast, infants in the group requiring respiratory support did not show this pattern. However, there were no significant differences between minimum and maximum voltages when the two groups

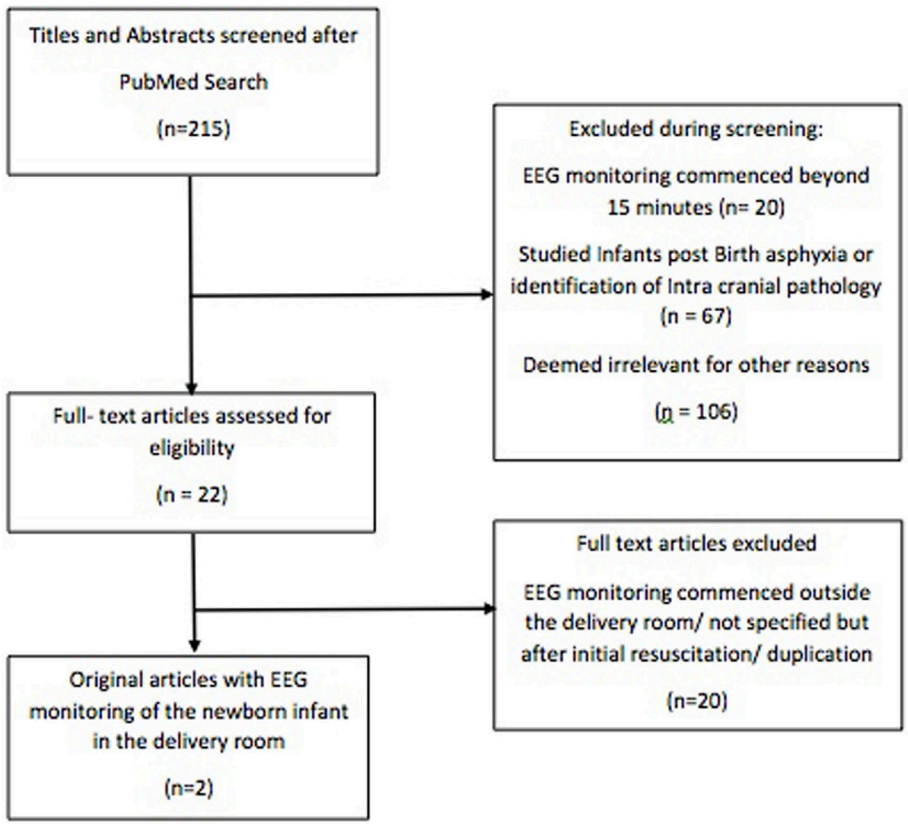

FIGURE 1 | Flow diagram of literature search.

TABLE 2 | Summary of electroencephalography (EEG) studies in the delivery room.

Reference	Neonates	Number recruited and monitored	Design	Number included in analysis	Observation
Pichler et al. (42, 60)	>34 weeks	46	Observational Amplitude-integrated EEG (aEEG) analysed for minimum and maximum voltages Near infrared spectroscopy (NIRS)	*N* = 46 31 uncompromised 15 required respiratory support	No significant differences between minimum and maximum voltages when the 2 groups are compared Uncompromised infants had higher V max in minute 3 and 4 compared with minute 10
Tamussino et al. (61)	Term	244	Observational aEEG analysed for minimum and maximum voltages Infants with initial low voltages which normalized were compared to infants with normal voltages throughout NIRS	*N* = 59 9 met inclusion criteria 50 control studies	Neonates with initially low cerebral activity during immediate transition after birth displayed lower cerebral saturations (<10th percentile) on NIRS, but increased cerebral oxygen extraction (cFTOE >90th percentile)

were compared, which the authors attribute to low numbers in the respiratory support group.

Tamussino et al. recorded simultaneous aEEG and NIRS in 244 term neonates during the first 15 min after delivery (61). Similar to the study of Pichler et al., aEEG data were analyzed for mean minimum and mean maximum voltages every minute, and then correlated with cerebral oxygenation, heart rate, and pre-ductal oxygen saturations. Neonates with initial low voltages, which normalized during transition, were compared to neonates with normal aEEG values throughout the monitoring period. Nine neonates had low initial aEEG voltages and were compared to 50 neonates with normal aEEG voltages throughout. Therefore, of 244 infants recruited, 59 aEEG recordings were included in the analysis. Neonates with initially low cerebral activity during immediate transition after birth displayed lower cerebral saturations (<10th percentile) on NIRS, but increased cerebral oxygen

extraction (cFTOE >90th percentile). The authors concluded that neuro-monitoring with aEEG and NIRS might provide useful information on the neonates' condition during immediate transition.

DISCUSSION

Neonatal mortality has decreased significantly in recent decades (24). As more infants survive following preterm delivery and birth asphyxia, achieving the best possible neurological outcomes for survivors is paramount. Whilst EEG has an essential role within the NICU in newborn neurological monitoring following birth asphyxia, and in monitoring preterm infants, it is not routinely initiated in the DR, and at present has no role during newborn stabilizations. We set out to determine if first it was feasible to perform newborn EEG in the DR, second to assess what information it provides about newborn brain activity in the immediate postnatal period and most importantly, to determine if this early objective information about brain activity would be useful. We found two studies that had performed aEEG during the first 15 min of birth. They found aEEG to be feasible in infants >34 weeks, but technically difficult to obtain continuous reliable data. Patterns of brain activity differed between infants that required newborn stabilization measures and infants that transitioned from the fetal to neonatal period without the need for medical intervention (60). Also, newborn infants with initially low cerebral activity during immediate transition after birth displayed lower cerebral saturations and increased cerebral oxygen extraction, compared with normal voltages throughout (61). The authors proposed a number of possible explanations for the differences between groups. They postulated that apnea, respiratory distress, and bradycardia in the immediate newborn may result in a lower cardiac output and resultant lower brain activity in compromised infants (60). For uncompromised infants who had initially high levels of activity, they suggested that catecholamine release may be responsible (62).

The brain is the most vulnerable organ in newborn infants. A non-invasive, continuous method to measure cerebral activity (EEG) is already available but it has not transitioned to the DR. Initial research focused on cerebral blood flow measurements but they were found to be technically difficult and did not provide continuous data (59). NIRS has shown great promise in providing continuous data on cerebral tissue oxygenation values. It utilizes the transparency of biological tissue to light in the near infrared spectrum to measure cerebral tissue oxygenation (63). A number of studies have examined cerebral oxygenation using NIRS in the DR (59), and recently, normative values for infants not requiring resuscitation have been published (42).

As the importance of the early instigation of neuroprotective strategies for term newborns with perinatal asphyxia has become evident, EEG monitoring (usually aEEG) has become more common in NICUs (1, 7). In contrast to cerebral blood flow and NIRS, EEG has well documented applications in the clinical management of newborn infants. It is the gold standard method for the accurate detection of all neonatal seizures in term and preterm infants (6, 9). It has well-proven efficacy in predicting outcomes following perinatal asphyxia, based on patterns of poor background activity and the timing of sleep wake cycling reestablishment (14, 15, 64, 65). Prediction of outcome following preterm delivery is more complicated, but investigations are ongoing (20). Several studies have shown that early background EEG suppression correlates with severity of periventricular hemorrhage (66–68). Also, continuous displays of inter-burst interval duration, which differs with gestational age, may become a useful prognostic measure in preterm infants in the near future (69, 70).

Despite its importance in monitoring the newborn brain in the NICU, EEG monitoring in the DR is currently not recommended. Stabilization of newborn infants in the DR, including infants with perinatal asphyxia, occurs without any objective measure of brain activity, and we found only two studies that have assessed the feasibility of obtaining a newborn EEG recording in the DR. Both studies used the aEEG trend and both found it possible to obtain aEEG tracings within 3 min in some cases, but obtaining continuous reliable data was generally difficult (60). Within these limitations the authors describe different patterns in brain activity for infants that required respiratory support and infants that transitioned independently. Also, aEEG was correlated with different cerebral oxygenation patterns. These findings are important as they pave the way for future studies.

Both studies analyzed brain activity by interrogating the aEEG mean minimum and mean maximum voltages. However, the aEEG trend alone is a high level summary measure of the EEG with poor time resolution due to compression in the aEEG algorithm, and it does not display the second by second activity of the brain; as a result, it is not optimal for application in the DR. Digital aEEG machines obtain one or two channels of EEG signal, which is then amplified and passed through an asymmetric bandpass filter that strongly attenuates activity less than 2 Hz and more than 15 Hz, to minimize artifacts. Additional processing includes semilogarithmic amplitude compression, rectification, and time compression (13). Heavy signal processing used in the aEEG algorithm eliminates much of the detail (e.g. frequency band content) available in the EEG, and many clinically important features are lost. Furthermore, there is no clear definition for aEEG, and most EEG machines implement different versions of the aEEG algorithm (71). The mean and maximum of the aEEG voltage need to be plotted and displayed for a number of minutes before any assessment of the overall baseline EEG activity can be made. In addition, it is well known that interpretation of the background aEEG pattern can be problematic due to baseline drift and other artifacts (72, 73). This is not optimal for DR EEG recording when real-time second by second information would be advantageous. For example, a recording of approximately 30 s duration alone using standard EEG would be enough to establish the presence of continuous EEG activity in a term newborn. This information would be hugely beneficial in the DR to help guide resuscitation and to determine the need for immediate passive cooling. Thoresen et al. coined the phrase "time is brain" in relation to the timing of cooling for neuroprotection (57), and we strongly believe that EEG in the DR could help identify those infants who would benefit most from early neuroprotective strategies.

Whether EEG could play a role in prognostication for infants requiring TH in the immediate newborn period is less clear. From clinical and preclinical studies, we know that recovery of

EEG activity during the first 24 h after hypoxia ischemia, after a period of prolonged (several hours) suppression, can be associated with normal outcome (74, 75), and little to no histological injury (76). However, we now know that infants with even mild HIE can have cognitive delays at 5 years (14). The prolonged suppression is an actively mediated response, at least partially mediated by neurosteroids such as pregnanes and adenosine, which are upregulated for hours after the insult (77, 78). Previous papers that reported normal outcomes in infants with an initial flat EEG trace that recovered quickly and had normal outcome were limited by small numbers and follow-up continued until 2 years of age (75). The authors even admit this themselves as they say that "a normal score in the early years cannot preclude later neurological, perceptual-motor, or cognitive abnormalities" (75). Therefore, we continue to recommend multichannel continuous EEG monitoring for such infants for the duration of TH.

Electroencephalography in its raw format (not a modified aEEG) can be assessed both qualitatively and quantitatively. Qualitative EEG analysis is mainly used for clinical purposes. It is based on visual interpretation of the EEG signal and describes background features such as amplitude, frequency, and continuity of the EEG, symmetry, synchrony, and sleep–wake cycling. Quantitative EEG analysis is a method predominantly used in research and includes time and frequency domain analysis. Neither study identified in our review analyzed the EEG in its raw format, either for qualitative or quantitative purposes.

However, we still have a way to go before EEG monitoring is routine in the DR. Signal interpretation is difficult, but huge advances have already been made in quantitative analysis of the neonatal EEG and we now have algorithms that can accurately grade the EEG in term and preterm newborns (70, 79–84). The feasibility of EEG recording is constantly improving and newer amplifiers with high common mode rejection ratios are now available that make EEG recording more possible and less susceptible to noise and other artifacts. We have seen that excellent quality EEGs are now possible for even extremely preterm infants in the NICU, as long as there is adequate setup and preparation (85). Multiple channels of EEG are not required to assess the grade of EEG baseline activity in the DR, one channel of good quality EEG is perfectly acceptable to assess amplitude, continuity, and frequency of the EEG. EEG sensors are constantly evolving, and newer disposable single application sensors are now available also making EEG electrode acquisition more feasible.

Electroencephalography has long been considered just too difficult to deploy in environments like the DR and NICU. There have been major recent advances to the adoption of EEG in the NICU primarily due to advances in technology (2). Modern machine learning techniques are also advancing rapidly and will soon be able to provide non-EEG experts with the help needed to assist in the interpretation of EEG patterns on a 24/7/365 basis. These difficulties should no longer be a barrier to the adoption of EEG in the DR.

In conclusion, the time is now right to advance the objective monitoring of neurological function of newborn infants in the DR, and urgent research is clearly warranted. More EEG studies from healthy term and preterm newborns in the DR to establish feasibility and normative reference ranges are clearly a priority. Advances in automated analysis of the baseline EEG will be hugely beneficial in this effort particularly if outputs are incorporated into standard patient monitors. We look forward to further studies in this area.

AUTHOR CONTRIBUTIONS

GB and ED conceived and designed the review. DF performed the literature search and drafted the initial manuscript. All the authors (DF, ED, and GB) critically revised the manuscript for important intellectual content, agreed on the final manuscript, and approved its submission for publication.

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SUPPLEMENTARY MATERIAL

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CORRECTION
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Corrigendum: Monitoring Cerebral Oxygenation in Neonates: An Update

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Keywords: near-infrared spectroscopy, cerebral oxygenation, neonates, neonatal intensive care, neonatal neurology

A Corrigendum on

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Cerebral Oxygenation and the Patent Ductus Arteriosus

The hemodynamically significant patent ductus arteriosus (PDA) remains a controversial topic. Clinicians and researchers are still debating whether or not it should be treated, what the best treatment strategy is and when would be the best time to intervene (48–51).

Reference 48–51 are:

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However, these references are supposed to be:

– Perez KM, Laughon MM. What is new for patent ductus arteriosus management in premature infants in 2015? *Curr Opin Pediatr* (2015) 27(2):158–64. doi:10.1097/MOP.0000000000000200
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– Ibrahim TK, Haium AA, Chandran S, Rajadurai VS. Current controversies in the management of patent ductus arteriosus in preterm infants. *Indian Pediatr* (2014) 51(4):289–94. doi:10.1007/s13312-014-0403-2 PMID:24825266

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way.

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REVIEW
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Epinephrine Use during Newborn Resuscitation

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Epinephrine use in the delivery room for resuscitation of the newborn is associated with significant morbidity and mortality. Evidence for optimal dose, timing, and route of administration of epinephrine during neonatal resuscitation comes largely from extrapolated adult or animal literature. In this review, we provide the current recommendations for use of epinephrine during neonatal resuscitation and also the evidence behind these recommendations. In addition, we review the current proposed mechanism of action of epinephrine during neonatal resuscitation, review its adverse effects, and identify gaps in knowledge requiring urgent research.

Keywords: epinephrine, neonatal resuscitation, asphyxia, newborn, delivery room, infants

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INTRODUCTION

Approximately 10% of newborns require some assistance to begin breathing at birth (1). Majority of these newborns improve without the need for cardiac compression or epinephrine if skillful positive-pressure ventilation is initiated in a timely manner. Less than 0.1% of all newborns require epinephrine, making epinephrine use in delivery room neonatal resuscitation an uncommon event (2, 3). Newborns who do require extensive cardiopulmonary resuscitation (CPR) including epinephrine have a high incidence of mortality. Those who survive frequently suffer from poor long-term neurodevelopmental outcomes (4–7).

The majority of recommendations regarding indication, dose, and route of administration of epinephrine in the delivery room are based on extrapolations from adult and animal studies. The infrequent use of epinephrine in the delivery room and ethical dilemmas in designing a clinical trial for examining the role of epinephrine during neonatal resuscitations make it very difficult to obtain high levels of evidence for recommendations regarding epinephrine use during neonatal resuscitation. Many of the animal and adult data come from a non-perfusion ventricular fibrillation arrest, which is not the pathophysiology of a newborn in the delivery room who suffers from an asphyxial arrest. Another major limitation of extrapolation from these studies is that newborns in the delivery room have unique transitional physiology including fluid-filled alveoli, an open ductus arteriosus, and high pulmonary pressures with limited pulmonary blood flow. Newly born infants must transition from fetal to newborn circulation. In the era of evidence-based medicine, due to lack of rigorous scientific evidence, proper use of epinephrine including dose and route of administration remains controversial. Even though epinephrine is not commonly needed in neonatal resuscitation, its association with death and poor prognosis raises questions as to whether optimization of epinephrine use and dosing, specifically tailored to the unique circumstances of the newly born infant, could improve outcomes.

This review aims to describe current recommendations for epinephrine use in neonatal resuscitation, the evidence behind such recommendations, and the critical knowledge gaps.

HISTORY OF EPINEPHRINE USE IN NEONATAL RESUSCITATION

Epinephrine is the only medication recommended during neonatal resuscitation in the delivery room (8, 9). Naloxone, sodium bicarbonate, and other vasopressors are currently not considered a part of acute resuscitation but can be used postresuscitation for special circumstances (9–11).

Management of the airway and assisted ventilation of the newborn baby can be found in ancient texts dating back to the Old Testament of the Bible, the Talmud, and Hippocrates (12, 13). However, reports of medication use in neonatal resuscitation can only be found after the early 1950s with the evolution of modern neonatology (13, 14). George Oliver and Edward Schaffer in 1893 first showed that adrenal glands contained a substance with distinct pharmacological properties (14, 15). It is a naturally occurring catecholamine produced by chromaffin cells at the adrenal medulla and stored in chromaffin granules. In 1897, John Abel in the United States prepared crude adrenal extracts and called them epinephrine (16). Epinephrine was used first time in pulseless patients in around 1906 by Crile and Dolley (17). Its resuscitative properties were further investigated by Wiggers in the 1930s and Redding and Pearson in the 1960s (18, 19).

HEMODYNAMIC EFFECTS OF EPINEPHRINE

Epinephrine stimulates all four adrenergic receptors (α_1, α_2, β_1, and $ß_2$) *in vivo*. When looked at in isolation, stimulation of the different adrenergic receptors by epinephrine results in different and sometimes opposing effects. It causes peripheral vasoconstriction *via* stimulation of α_1 receptors in vascular smooth muscle cells. By stimulating β1 receptors in the myocardium, it causes chronotropy (increased heart rate), inotropy (increased contractility), dromotropy (increase conduction velocity), and lusitropy (increased rate of myocardial relaxation) (10, 20–22). Stimulation of α_2 receptors leads to presynaptic inhibition of nor-epinephrine release in the central nervous system and vasoconstriction of coronary arteries. Through β_2 receptor stimulation, it causes vascular smooth muscle relaxation and increased myocardial contractility, but these effects are usually minor. *In vivo* effects of epinephrine depend on the dose of epinephrine, number of receptors available on target tissues, the affinity of these receptors, and local target tissue environments (23).

MECHANISM OF ACTION DURING CPR

Initially it was believed that epinephrine causes return of spontaneous circulation (ROSC) in cardiac arrest *via* its myocardial stimulant effects (β adrenergic effects: chronotropic and inotropic) (10). In the 1960s, Redding demonstrated in dogs that the pure α-agonist, methoxamine, was as effective as epinephrine in achieving ROSC during CPR, whereas the pure β-agonist, isoproterenol, was no more effective than CPR alone (19). Otto et al. who used pretreatment with α-adrenergic blockade (phenoxybenzamine) and β-adrenergic blockade (propranolol) before infusing epinephrine confirmed that α-adrenergic stimulation is the most important action of epinephrine for ROSC in CPR (24).

It is now established that the most reliable method for determining the effectiveness of CPR is to measure aortic diastolic blood pressure or coronary perfusion pressure (25). When heart muscles do not receive adequate blood flow and/or oxygen, their energy substrate is depleted. In turn, heart muscles stop contracting and the heart stops pumping. To restart the cardiac pump, it is critical that myocardial perfusion with oxygenated blood is reestablished. In acidotic asphyxiated neonates, there is loss of peripheral vascular tone, i.e., maximum vasodilation. When chest compressions are performed, blood from the cardiac chambers takes the path of least resistance and thus preferentially flows through aorta and into peripheral circulation rather than into narrow more constricted coronary arteries that have high resistance (**Figure 1**). The use of epinephrine in this situation results in intense peripheral vasoconstriction. This elevates the aortic to right atrial pressure gradient during the relaxation phase

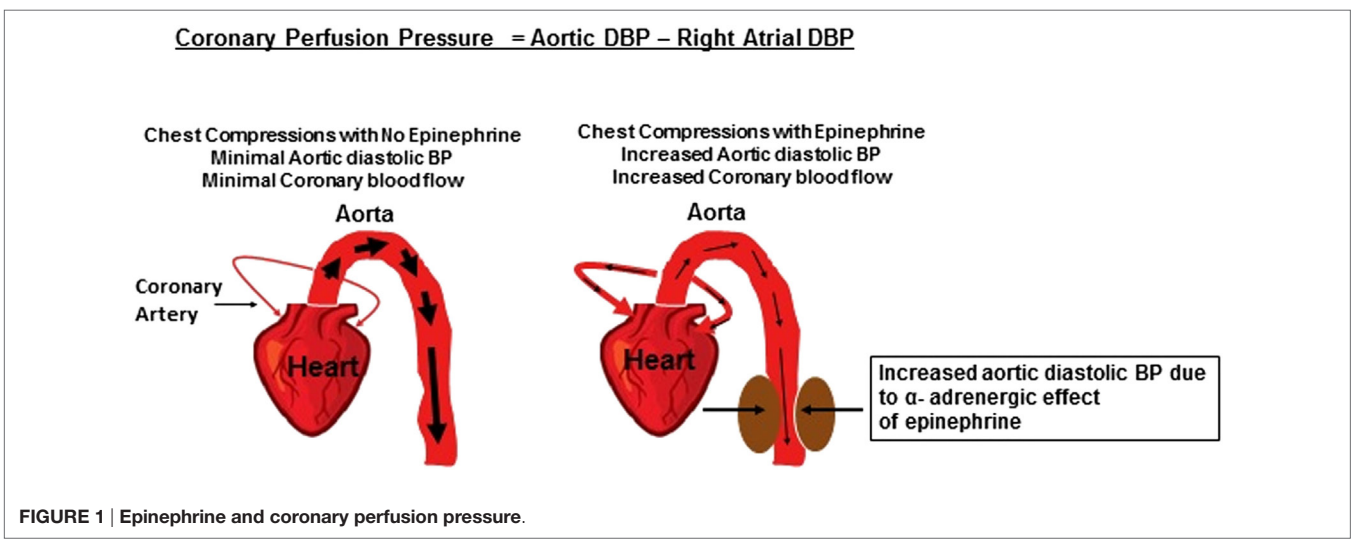

FIGURE 1 | **Epinephrine and coronary perfusion pressure**.

of CPR (26–29). Due to this pressure gradient, blood during chest compressions enters the coronary arteries and myocardial blood flow increases. Hence, this pressure gradient is called the coronary perfusion pressure. As oxygenated blood enters the coronary circulation, it facilitates resynthesis of adenosine triphosphate within myocardial mitochondria improving myocardial contractility and viability. In animal models and humans, coronary perfusion pressure correlates directly with myocardial blood flow, which is a good predictor of ROSC.

Although minor, β2 receptor-mediated coronary vasodilation may contribute to improved coronary perfusion following epinephrine administration (10, 21, 30). Cerebral electrographic activity and cerebral oxygen uptake improves following epinephrine administration during CPR as cerebral blood flow increases due to epinephrine-induced peripheral vasoconstriction (28, 29). Through its α receptor stimulation, epinephrine may counteract carotid artery collapse induced by elevated intrathoracic pressures due to CPR and further optimize blood flow (28).

Studies utilizing posttransition asphyxia animal model have demonstrated the importance of epinephrine, where after asphyxia cardiac arrest, chest compressions alone were ineffective, but majority of animals reached the critical diastolic blood pressure (rising aortic to right atrial pressure gradient) and ROSC after epinephrine administration (31–33). It is important to note that these studies also showed that interruptions in chest compression lead to lowering of diastolic blood pressure, thus highlighting the importance of minimizing interruptions in cardiac compressions during CPR (31–33).

The majority of the above information was obtained from adult animal studies, posttransitioned neonatal animal studies, or human adult studies. No studies in term or preterm newborns or animal models with newborn transition physiology have investigated the mechanism of action of epinephrine during CPR. The distribution and maturation of α and β receptors in term and preterm newborns remain unknown (23).

CURRENT INDICATION FOR EPINEPHRINE DURING NEONATAL CPR

Bradycardia in newly born infants is usually the result of inadequate aeration of lungs and ventilation or profound hypoxemia and acidosis from prior poor placental perfusion. Hence, effective ventilation is the top priority during delivery room resuscitation of the bradycardic newborn. Current resuscitation guidelines recommend that epinephrine should be used if the newborn remains bradycardic with heart rate <60 bpm after 30 s of what appears to be effective ventilation with chest rise, followed by 30 s of coordinated chest compressions and ventilations (1, 8, 9).

OPTIMAL DOSE AND ROUTE OF ADMINISTRATION OF EPINEPHRINE DURING CPR

Epinephrine during neonatal CPR in the delivery room can be given by three routes: intravenous, endotracheal (ET), and intraosseous (**Table 1**).

TABLE 1 | Epinephrine use during newborn resuscitation: route, dose, and summary of evidence.

Route	Dose	Summary of evidence
Intravenous	0.01–0.03 mg/kg	• Preferred route and appear to be more efficacious than other routes • Dose extrapolated from adult experience • High-dose epinephrine offers no advantage and is associated with increased postresuscitation adverse effects and increased mortality • Dose escalation studies in neonatal animal model with transition physiology are urgently needed
Endotracheal (ET)	0.05–1 mg/kg	• Less effective than IV route • Achieved plasma concentration is less and it peaks slower with ET epinephrine compared to IV epinephrine • Can be used until IV access is available
Intraosseous	0.01–0.03 mg/kg	• Limited evidence compared to IV route • Providers frequently involved in newborn resuscitation feel more comfortable with rapid UVC insertion compared to IO route
Intramuscular	Not recommended	• Very limited evidence • Significant tissue damage at local site

Intravenous Epinephrine

This is the preferred route of administration during neonatal CPR in the delivery room as it appears to be more efficacious compared to other routes (1, 8, 9). The umbilical vein is a rapidly accessible, direct intravenous route. If epinephrine use is anticipated based on risk factors and no response to optimized positive-pressure ventilation (preferably *via* a secured airway), one team member should prepare to place an umbilical venous catheter, while the others continue to provide ventilation and chest compression. Chest compressions should be provided from head of the bed to allow adequate access to place the umbilical venous catheter (1).

The optimal dose of intravenous epinephrine has been the subject of much debate. In animal ventricular fibrillation models, Redding and Pearson demonstrated that intravenous epinephrine of 1 mg (0.1 mg/kg in 10 kg dogs) increased ROSC when combined with ventilation and chest compressions alone (19). Human studies following this study did not take into account the weight difference between the 10-kg dogs that were studied and the average adult weight, which is 7- to 10-fold more. Surprisingly, even with such low doses, epinephrine was reported to be effective in achieving ROSC in adult CPR (34). As there are no neonatal epinephrine dosing studies, the recommended dose was extrapolated from the adult experience with a suggested dosing range of 0.01–0.03 mg/kg. Given the overlooked weight difference between dogs in the study by Redding and Pearson (19) and humans, studies were conducted to see if higher dose epinephrine would be more efficacious. Initially, studies in ventricular fibrillation adult animal model showed increased ROSC and improved cerebral and coronary blood flow with escalating doses of epinephrine (35). Based on these data, adult and pediatric resuscitation guidelines started recommending using 0.1 mg/kg high dose of epinephrine if no response was seen with standard dose epinephrine (36).

Clinical studies conducted later found that high-dose epinephrine (0.1 mg/kg) is not more effective and may be harmful (35, 37, 38).

Animal Data

Berg et al. in a pediatric asphyxia swine model demonstrated that high-dose epinephrine did not result in increased ROSC, and in fact, there was higher postresuscitation mortality (39). Burchfield et al. in a neonatal lamb model demonstrated that high-dose epinephrine reduced stroke volume and cardiac output (40). McCaul et al. demonstrated dose-related adverse outcomes with higher tachycardia, hypertension, mortality, and increased troponin with high-dose epinephrine in a rat model (41). Observation of hypertension following hypotension with high-dose epinephrine is especially important for preterm newborns who are vulnerable to development of intraventricular hemorrhage with fluctuations in blood pressure (42, 43).

Adult Data

Meta-analysis of randomized control trials in adult cardiac arrest patients demonstrated increased ROSC with high-dose epinephrine but no improvement in survival to hospital discharge (35).

Older Children

Perondi et al. randomized 68 children (mean age of 6 years) to either 0.1 versus 0.01 mg/kg for the second dose of epinephrine after failure of standard first dose (0.01 mg/kg) (38). This study demonstrated that ROSC rates were similar between both groups. Alarmingly, no child survived in the high-dose epinephrine group compared to 21% survival in the standard epinephrine group. Patterson et al. confirmed these findings that high-dose epinephrine did not confer any benefits but reduced survival when arrest was precipitated by asphyxia (37).

Neonatal Data

There is a stark absence of any neonatal studies including randomized controlled trials studying any dose of epinephrine. Halling et al. described in an observational study of 20% success rate with single standard dose of IV epinephrine. Multiple doses were needed by large number of newborns (3).

In summary, these data suggest that there is no advantage with high-dose epinephrine, and it is associated with postresuscitation hypertension, tachycardia, and increased mortality especially following cardiac arrest from asphyxia. Neonatal data remain sparse, and dose escalation studies in appropriate neonatal models with transition physiology are urgently needed.

ET Epinephrine

Although the ET route is readily available and less time consuming than establishing an intravenous or intraosseous access, it appears to be less effective (36, 44, 45). However, until intravenous access is available, some clinicians may choose to give epinephrine ET (1, 9). Currently, the recommended dose is 0.05–0.1 mg/kg, which is much higher than the recommended intravenous epinephrine dose (1, 9).

Adult Animal Data

Redding et al. were the first to suggest the use of ET epinephrine during cardiac arrest (46). In a ventricular fibrillation pig model, Crespo et al. compared 0.01 versus 0.1 mg/kg ET epinephrine doses (47). The study demonstrated that higher dose was able to achieve higher plasma concentrations of the drug but that did not translate to higher blood pressure. Roberts et al. also investigated different ET epinephrine doses and compared them with equivalent intravenous epinephrine doses (48). The study demonstrated that the peak concentration of epinephrine was found in 15 s after either route of administration, but with ET epinephrine, blood concentrations were more sustained. Importantly maximum plasma concentration achieved by ET epinephrine was one-tenth of the plasma concentration achieved by the intravenous route. Vali and Lakshminrusimha conducted a study of ET versus intravenous epinephrine in a fetal lamb model of asphyxia where animals had not yet transitioned to newborn circulation (49). They demonstrated that plasma epinephrine peaks much faster and higher compared to ET epinephrine although no difference in rates of ROSC was observed between either group.

Human Adult Data

Many retrospective adult case series have noted ET epinephrine to be less effective than IV epinephrine in achieving ROSC during CPR (36, 44, 45).

Neonatal Data

Four case series in neonates noted some evidence of absorption or cardiovascular improvement following ET epinephrine administration, but doses were 10 times higher than typical intravenous doses, and the majority of newborns had bradycardia, not asystole (50–52). Barber and Wyckoff reported on a retrospective review of all neonates who received epinephrine in the delivery room during the study period (2). The study demonstrated that the majority of infants received their first dose as ET epinephrine. They found that ET epinephrine dose of 0.01–0.03 mg/kg failed to re-establish HR > 60 bpm two-thirds of time. In the neonates who failed to respond to ET epinephrine, 77% of them responded to subsequent intravenous epinephrine. ET epinephrine efficacy may be limited in the newly born due to dilution by non-mobilized lung fluid. Elevated pulmonary arterial pressure in the presence of patent ductus arteriosus could result in right-sided cardiac output bypassing the lungs and thus limiting epinephrine absorption from the lung (23, 25). Based on this evidence, guidelines recommended an increase in ET epinephrine dosing from 0.01 to 0.03 to 0.05 to 0.1 mg/kg (1, 9). Halling et al. presented a retrospective review comparing the dosing from 0.03 to 0.05 mg/kg (3). They found no improvement in rates or time of ROSC with the higher ET epinephrine dose. It is possible that there may not be an optimal ET epinephrine dose. Current guidelines stress the importance of education, practice, and preparation to rapidly establish IV access in delivery room for newborns who need epinephrine during delivery room resuscitation (9).

Intraosseous Epinephrine

Simulation studies have shown that for inexperienced personnel, establishment of an intraosseous line was faster and easier than the placement of umbilical catheters (53). In a neonatal case series of 27 neonates who received intraosseous epinephrine for resuscitation, no short-term complications were demonstrated

(54). Also many critical clinical outcomes were not described. Given the comfort level that can be achieved by neonatal providers for rapid placement of umbilical catheters and limited evidence regarding IO placement in delivery room, IV epinephrine is preferred (1).

Intramuscular Epinephrine

Mauch et al. demonstrated that 0.1 mg/kg of IM epinephrine resulted in similar ROSC and survival in infant piglet cardiac arrest model (55). Case reports indicate that intramuscular epinephrine of 0.02 mg/kg causes significant tissue damage at injection site (56). Currently, intramuscular epinephrine is not recommended for neonatal CPR.

ADVERSE EFFECTS OF USE OF EPINEPHRINE DURING CPR

Epinephrine especially with repeated doses or with high doses can cause postresuscitation hypertension and tachycardia (39, 57). This can result in injury to various organ systems especially in preterm neonates. Excess epinephrine due to its vasoconstrictive properties can impair blood flow to various organs such as kidneys and intestines. Epinephrine can also result in elevation of pulmonary arterial pressures and increase myocardial oxygen consumption and demand through its β adrenergic effects (58, 59). This may be detrimental especially in situations where hypoxia persists and oxygen delivery is impaired. It has also been associated with imbalance of various neurotransmitters such as gamma-aminobutyric acid, dopamine, serotonin, acetylcholine (60–63). It can impair blood–brain barrier and possibly decrease the threshold for seizures (62, 64).

ALTERNATIVES TO EPINEPHRINE IN DR

Given the limitations of epinephrine in neonatal CPR, there is a great interest in finding other vasoconstrictors that have fewer detrimental side effects. Vasopressin has been studied in the adult literature as an alternative. Endogenous vasopressin levels were found to be higher in successfully resuscitated adults compared to those who died. Vasopressin through V1 receptors is a potent vasoconstrictor of blood vessels in the skin, skeletal muscle, and mesenteric blood vessels (10, 65, 66). It does not have any stimulant effect on the myocardium, and at low doses, it can vasodilate coronary, pulmonary, and cerebral vessels. Even though it has these theoretical benefits over epinephrine, in randomized control trials in adults, vasopressin has not found to be more effective than epinephrine (67). A cohort study on pediatric in-hospital cardiac arrest vasopressin was found to be less effective and associated with higher mortality (68). In neonatal piglet posttransition asphyxia model, McNamara et al. showed that vasopressin resulted in improved survival, lower postresuscitation troponin, and less hemodynamic compromise compared to epinephrine (69). No human neonatal data exist regarding vasopressin in CPR. Studies with neonatal animal models with transition physiology are urgently needed.

OTHER CONSIDERATIONS FOR EPINEPHRINE IN THE DELIVERY ROOM

Interval between Doses

The current recommendation is to repeat the dose of IV epinephrine every 3–5 min if the heart rate remains less than 60 bpm (1, 9). Vali and Lakshminrusimha in a fetal lamb asphyxia model demonstrated an incremental increase in plasma epinephrine concentration with repeated IV epinephrine doses every 3–5 min (49). Warren et al. performed retrospective review of in-hospital cardiac arrest in adults and found the optimal interval to repeat dose to be 9–10 min instead of 3–5 min (70). Linner et al. gave epinephrine before chest compressions to bradycardic and severely asphyxiated newborn piglets and demonstrated that this strategy did not improve ROSC or cerebral circulation (71). More studies are needed to find out optimal interval between doses, but current evidence would suggest that more frequent or early epinephrine does not seem to be more beneficial.

Flush Volume after IV Epinephrine Dose through Low UVC

Currently recommended flush volume after IV epinephrine dose is 0.5–1 ml (1). Vali and Lakshminrusimha showed higher incidence of ROSC and faster ROSC with right atrial epinephrine compared to low UVC epinephrine in fetal lamb asphyxia model (49). It is possible that the currently recommended flush volume will deposit the epinephrine in umbilical vein but might not be enough to reach the heart. It is unclear if current flush volume is adequate and if higher flush volume may result in faster rise and higher epinephrine plasma concentrations. Studies are underway to answer this question.

OUTCOMES IN NEWBORNS WHO REQUIRE EPINEPHRINE IN THE DELIVERY ROOM

Cohort study data suggest that epinephrine is needed in <0.1% of all liver born deliveries (2, 3) although there is a large variation among different centers. Severe fetal acidemia, malpositioned ET tubes, and ineffective ventilator support contribute to the higher use of delivery room epinephrine (72, 73). Thus, it remains critical that neonatal providers focus on optimizing positive-pressure ventilation including placement of an alternate airway as a part of their ventilation corrective measures if a newborn is not responding to initial positive-pressure ventilation. Provision of effective ventilation that moves the chest should eliminate or reduce unnecessary intensive CPR. Term infants who require intensive CPR including multiple epinephrine doses and those whose Apgar score remain low at 10 min of life suffer from high incidence of death or poor neurodevelopmental outcomes (4, 5). In preterm infants due to lack of good evidence for use of epinephrine and its adverse effects of epinephrine especially postresuscitation hypertension, outcome data become even more important. Multiple retrospective observational studies have noted that preterm neonates requiring CPR and epinephrine have significantly lower

survival, higher incidence of early onset sepsis, NEC, grade 3–4 intraventricular hemorrhage, cystic periventricular leukomalacia, bronchopulmonary dysplasia, and neurodevelopmental impairment (7, 74–76). These studies frequently suffer from small numbers and selection bias as the most compromised and sicker preterm neonates may require CPR but all studies point toward worse outcomes associated with extensive delivery room CPR. These data suggest that optimization of CPR and epinephrine use in delivery room has potential to impact outcomes significantly.

CONCLUSION

Epinephrine use in delivery room remains uncommon especially when neonatal providers focus on effective positive-pressure ventilation. Epinephrine use in delivery room is associated with high mortality and poor long-term outcomes. Recommendations regarding epinephrine use including dose and route are based mostly on extrapolation of data from animals or adult literature. Even the majority of available animal data come from ventricular fibrillation cardiac arrest models and posttransition models that have little in common with newborns in the delivery room. There is a scarcity of human neonatal term and preterm epinephrine data even in the form of observational studies. Based on the limited available literature, intravenous epinephrine is preferred to ET epinephrine. Clinical and animal studies in transition neonatal models are urgently needed to identify optimal indication, timing, dose, route, and alternatives to epinephrine in neonatal CPR.

AUTHOR CONTRIBUTIONS

VK performed the literature review, created first draft of the article, revised the draft, and created and approved the final draft of the article. MW critically reviewed the first draft, revised the draft, approved the final draft of the article, and contributed substantially to this manuscript.

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Diffusion Tensor Imaging Colour Mapping Threshold for Identification of Ventilation-Induced Brain Injury after Intrauterine Inflammation in Preterm Lambs

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Purpose: The aim of this study is to examine whether advanced magnetic resonance imaging (MRI) techniques can detect early brain injury caused by intrauterine inflammation and inappropriate initial respiratory support in preterm lambs.

Hypothesis: Neuropathology caused by intrauterine inflammation is exacerbated by mechanical ventilation at birth and is detectable with advanced MRI techniques.

Methods: Pregnant ewes received intra-amniotic lipopolysaccharide (LPS) 7 days prior to delivery at ~125 days of gestation (85% of gestation), whereupon lambs were delivered and randomised to receive an injurious (LPS + INJ, $n = 6$) or protective (LPS + PROT, $n = 6$) ventilation strategy. MRI of the brain was conducted 90 min after preterm delivery, using structural, diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS) techniques. A colour map threshold technique was utilised to compare distributions of low diffusivity voxels in the brains of LPS-exposed lambs with those not exposed to LPS (PROT, $n = 7$ PROT and INJ, $n = 10$).

Results: No overt cerebral injury was identified on structural MRI images of any lamb. However, on DTI, axial diffusivity, radial diffusivity, and mean diffusivity values were lower and significantly more heterogeneous in specific brain regions of lambs in the LPS + INJ group compared to the LPS + PROT group. Colour mapping revealed lower diffusivity

Abbreviations: AD, axial diffusivity; DTI, diffusion tensor imaging; FA, fractional anisotropy; IA, intra-amniotic; INJ, injurious ventilation; LPS, lipopolysaccharide; MD, mean diffusivity; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, *N*-acetylaspartate; PROT, protective ventilation; RD, radial diffusivity; RF, radio frequency; SWI, susceptibility-weighted imaging; T_1, spin–lattice relaxation time; T_2, spin–spin relaxation time.

in the thalamus, periventricular white matter, internal capsule, and frontal white matter in the LPS + INJ group compared to LPS + PROT group. The MRS peak area ratios of lactate, relative to those for the metabolites creatine, choline, and *N*-acetylaspartate, were not different between LPS-exposed groups. Lambs exposed to LPS had lower diffusivity within the white matter regions assessed than non-LPS-treated control lambs.

Conclusion: DTI colour map threshold techniques detected early brain injury in preterm lambs exposed to intrauterine inflammation and detected differences between injurious and protective ventilation strategies. DTI mapping approaches are potentially useful for early detection of subtle brain injury in premature infants.

Keywords: brain, delivery room, diffusion tensor imaging, magnetic resonance imaging, neonate

INTRODUCTION

Infants born preterm are at a high risk of brain injury, with the rate of neurodevelopmental disability exceeding 50%, and cerebral palsy rates at ~10% (1, 2). Further, preterm infants are born prior to adequate maturation of both breathing control and pulmonary morphology; they have a reduced respiratory surface area, a thickened air–blood gas barrier, and poor production of surfactant (3). Consequently, preterm infants often require respiratory support immediately after delivery to support lung aeration, promote pulmonary gas exchange, and facilitate the transition of the circulation from the fetal to the infant phenotype (4). However, if poorly controlled, the initiation of respiratory support can lead to brain injury by two main mechanisms: adverse fluctuations in cerebral blood flow and the initiation of a systemic inflammatory cascade resulting in an inflammatory response within the brain (5–7). Ventilation-induced brain injury can be detected within 90 min of delivery using magnetic resonance imaging (MRI) techniques, in particular, diffusion tensor imaging (DTI) (6).

Intrauterine inflammation, clinically defined as chorioamnionitis, is a common antecedent of preterm birth (8, 9) and affects ~3–10% of all pregnancies (10). We have previously demonstrated that acute (2 days) exposure to intra-amniotic (IA) lipopolysaccharide (LPS) increases the incidence and severity of ventilation-induced brain injury in preterm lambs (11). Furthermore, a protective ventilation strategy did not reduce the severity of brain injury, assessed histologically, after IA LPS (12) compared to control lambs (5). These results support clinical findings that intrauterine inflammation increases the risk and severity of postnatal white matter injury (13), periventricular leukomalacia, and periventricular/intraventricular haemorrhages (14–17). Thus, preterm infants exposed to chorioamnionitis are at a high risk of long-term neurodevelopmental impairment including cerebral palsy (13, 18, 19).

MRI is commonly used in neonatology as a diagnostic and prognostic tool and is usually conducted several days to weeks after birth (20, 21). Given that the only clinically implemented treatment for newborn brain injury, hypothermia for hypoxic–ischemic encephalopathy, needs to be initiated within the first hours after birth (22), it is critical to establish new tools for early detection of brain injury to guide current and future clinical interventions.

We have previously demonstrated the utility of DTI in detecting early brain injury using a region of interest (ROI) analysis (6). An alternative to the ROI approach is to analyse DTI data for the whole brain volume, which can detect more subtle brain injury (23). Previous studies that applied whole brain statistical analysis for DTI parameters in preterm infants demonstrated a reduction in DTI measures, thought to reflect alternations in brain microstructure (24, 25). However, this approach has not yet been applied to early detection of ventilation-induced brain injury in neonates after preterm delivery.

The objective of this study was to develop new techniques to detect early brain injury using diffusion-weighted MRI that have the potential to improve future diagnostic strategies for identifying abnormalities in white matter. In particular, we aimed to examine whether non-invasive MRI techniques can differentially detect brain injury caused by injurious or protective ventilation in preterm lambs exposed to intrauterine inflammation, factors known to cause early brain injury. Although we have demonstrated that both protective (PROT) and injurious (INJ) ventilation strategies increased brain inflammation and oxidative stress, and more so in the INJ group (5), it has not been established if DTI analyses are sensitive enough to detect the exacerbation of brain injury caused by a double hit. In our initial studies, we examined the acute response of the preterm brain to ventilation injury (5, 6). In this study, we examined the effects of ventilation injury superimposed on chronic inflammation (double hit) with MRI and magnetic resonance spectroscopy (MRS) techniques. We hypothesised that high tidal volume (V_T) ventilation after chronic intrauterine inflammation exacerbates brain injury compared to protective ventilation and is detectable using DTI on a clinical MR scanner.

MATERIALS AND METHODS

The experimental protocol was approved by Monash Medical Centre animal ethics committee at Monash University and conducted in accordance with guidelines established by the National Health and Medical Research Council (NH&MRC) of Australia.

LPS Treatment of the Fetus, Preterm Delivery, and Stabilisation

Ultrasound-guided IA injections of LPS (10 mg; from *Escherichia coli* 055; Sigma-Aldrich, Australia) were administered to one

amniotic sac of twin-bearing ewes (Border Leicester; $n = 12$) at 118 ± 2 days of gestation (mean ± SD). Lambs were delivered by caesarean section 7 days later, dried, and a transcutaneous oxygen saturation probe was placed around a forelimb (SpO_2; Masimo, CA, USA). The lambs were intubated and then randomised to receive either a protective ventilation strategy (LPS + PROT, $n = 6$) or injurious ventilation strategy (LPS + INJ; $n = 6$), as described previously (5). Briefly, lambs in the LPS + INJ group underwent immediate cord clamping followed by 15 min of high V_T ventilation (targeting 12–15 mL/kg) using a neonatal positive-pressure ventilator (Babylog 8000+, Dräger, Lübeck, Germany). After 15 min, LPS + INJ lambs received surfactant (100 mg/kg, Curosurf®, Chiesi Pharma, Italy), followed by tidal ventilation targeting V_T of 7 mL/kg. LPS + PROT lambs received prophylactic surfactant, a single 30-s sustained inflation at peak inspiration pressure (PIP) 35 cmH_2O (Neopuff Fisher & Paykel Healthcare, Auckland, New Zealand), followed by tidal ventilation (7 mL/kg) for 3 min prior to umbilical cord clamping (26). V_T targeted 7 mL/kg for the protective strategy for the duration of the experiment.

Monitoring and Care

After delivery, umbilical arterial and venous catheters were inserted for measurement of blood pressure, arterial blood gas sampling, and invasive real-time monitoring of heart rate (HR) (Powerlab: ADInstruments, Castle Hill, Australia). Anaesthesia was maintained *via* intravenous infusion of Alfaxan (10 mg/kg/h in 5% glucose, Jurox, Auckland, New Zealand). Samples of arterial blood were collected every 5 min for the initial 15 min and at 15-min intervals thereafter for measurement of the partial pressure of arterial carbon dioxide ($PaCO_2$), oxygen (PaO_2), oxygen saturation (SaO_2), and pH (ABL30, Radiometer, Copenhagen, Denmark). Ventilation and oxygen delivery were altered to target $PaCO_2$ of 45–55 mmHg and an oxygen saturation of 90–95%. Ewes were killed humanely (sodium pentobarbitone 100 mg/kg i.v.) immediately after delivery of the lambs, while still under general anaesthesia. Lambs were killed humanely (sodium pentobarbitone 100 mg/kg i.v.) after the MRI.

Magnetic Resonance Imaging

The lambs were transferred to the MR scanner 1 h after delivery. The radiographers and team involved in supporting lambs during MRI acquisition were blinded to group assignment of each lamb. Lambs were scanned in a supine position, and ventilation was maintained using a BabyPAC portable and MR compatible ventilator (Pneupac, Smiths Medical, UK). HR and SpO_2 were continuously monitored to guide anaesthesia maintenance, and blood gas parameters were recorded at 15-min intervals to monitor lamb well-being and guide mechanical ventilation. Scans were performed on a 3T MR scanner (Siemens Skyra, Erlangen, Germany) at Monash Biomedical Imaging, Monash University (Clayton, Australia), with a 15-channel radio frequency (RF) coil for both RF transmission and reception. The MRI protocol comprised structural imaging sequences (T1, T2, and DTI), susceptibility-weighted imaging (SWI), and a single-voxel MRS (6). The total acquisition time was about 40 min.

A 3D MPRAGE sequence was applied to achieve T1-weighted images, 102.5 mm thick, for whole brain coverage. The repetition time (TR) was 1,440 ms, with echo time (TE) of 3.92 ms, an inversion time of 900 ms, and a flip angle of 9°. The data matrix was 256 × 256 × 128, collected from a field of view (FOV) of 200 mm × 200 mm, giving a voxel size of 0.78 mm × 0.78 mm × 0.8 mm.

T2-weighted images with a 3D SPACE sequence, 44 mm thick, were also obtained to provide whole brain coverage (TR = 1,000 ms, TE = 132 ms, flip angle = 120°, and averages = 2). The matrix size was 384 × 384 × 88, collected from a FOV of 192 mm × 192 mm, giving a voxel size = 0.5 mm × 0.5 mm × 0.5 mm.

A standard 3D gradient echo sequence was used to acquire SWI for the whole brain with a slab thickness of 72 mm (TR = 28 ms, TE = 20 ms, and flip angle = 15°). The matrix size was 288 × 216 × 60, collected from a FOV of 176 mm × 132 mm, giving voxel size = 0.6 mm × 0.6 mm × 1.2 mm. The second phase encoding direction for 1.2-mm voxel was acquired in a parallel direction to the main magnetic field to optimise the susceptibility effect.

Diffusion tensor imaging with a spin-echo echo planar imaging sequence in the axial plane was obtained with 50 contiguous 1.2-mm slices (TR = 11,400 ms, TE = 99 ms). The data matrix was 128 × 128, collected from a FOV of 154 mm × 154 mm, giving a voxel size of 1.2 mm × 1.2 mm × 1.2 mm; for five *b*0. Diffusion encoding gradients were acquired in 30 directions with a *b* value of 1,000 s/mm^2. The diffusion-weighted imaging was performed twice, and five $b = 0$ volumes were acquired.

A single-voxel spin-echo sequence was used to acquire MRS, localised on the supratentorial deep grey matter and central white matter (TR = 2,000 ms, TE = 270 ms) with a voxel size of 15 mm × 15 mm × 20 mm.

MRI Data Analysis

MRI examination, image processing and analysis, and interpretation of the structural MR images were performed completely blind. Once ROI was drawn, the group allocation of each lamb was revealed for the final statistical analysis. The colour mapping approach was then completed, but not performed in a blinded fashion. Images acquired from T1, T2, and SWI scans were used to determine the presence of gross brain injury including infarcts and haemorrhages. DTI images were converted into NIFTI format, and then a brain mask was manually placed over the image using the FMRIB Software Library [FSL, FMRIB, Oxford, UK (27)]. DTI data were corrected for eddy-current distortion and then DTI parametric maps: fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) were created with the Diffusion Toolbox of FMRIB. AD was used as the largest eigenvalue of the tensor, and RD was used as the average of the second and third eigenvalues of the tensor. All maps were then coregistered with high-resolution T2 images of the brains using Linear Image Registration Tool [FLIRT (28)]. The *b*0 image was used as the reference for the coregistration.

ROI were defined manually on high-resolution T2 images and then exported to the FA, AD, MD, and RD maps to calculate the region mean values for each lamb. ROIs were placed in specific regions including the thalamus (Th),

periventricular white matter (PVWM), internal capsule (IC), frontal white matter (FWM), and the cerebellum (CB) vermis, targeting the stalk and midline white matter (**Figure 1**). The Sheep Brain Atlas from Michigan State University (Brain Biodiversity Bank, National Science Foundation) was used to facilitate accurate identification of the anatomical structures.

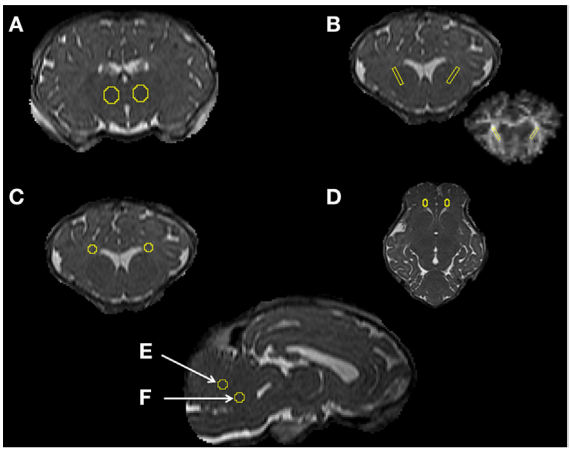

FIGURE 1 | Magnetic resonance imaging data analysis [regions of interest (ROIs)]. Examples of ROIs in specific regions of the thalamus **(A)**, internal capsule **(B)**, periventricular white matter **(C)**, frontal white matter **(D)**, and the cerebellum vermis, targeting the midline and stalk white matter **(E,F)** for DTI analysis.

The mean value of the adjacent four to five slices that defined a given ROI volume was calculated for each of the ROIs to test between-animal variability in diffusivity for both groups. MATLAB R2013a (MathWorks, MA, USA) was then used to calculate the SD for the ROIs of each region of the lamb brains to test within-animal variability (heterogeneity in DTI).

MRS data were processed using TARQUIN software to implement spectral fitting in the time domain (6). Peak area ratios for lactate (Lac) relative to *N*-acetylaspartate (NAA) (total of NAA and *N*-acetylaspartylglutamate), creatine (Cr; total of phosphocreatine and free creatine), and choline (Cho; total of glycerophosphocholine and phosphocholine) were calculated. In addition, we calculated peak area ratios for NAA/Cho, NAA/Cr, and Cho/Cr.

DTI data from the ROIs appeared to show more heterogeneity in the injured lamb brains. To further examine this variability, we utilised a colour map threshold technique to determine where the low diffusivity voxels were distributed in the DTI volumes. ImageJ (version 1.48, NIH, USA) was used to create a histogram of the distribution of the MR image pixel intensities at each position. For the purposes of comparison between animals, the histograms from all lambs in the two groups were normalised. The total pixel intensity distribution (histograms) for each lamb brain was compared between the minimum and maximum intensities within the brain for 256 bins in all DTI images. Histograms of the diffusivities for the whole brains of individual lambs in the two groups exposed to LPS were determined (**Figure 2**). Histograms were also

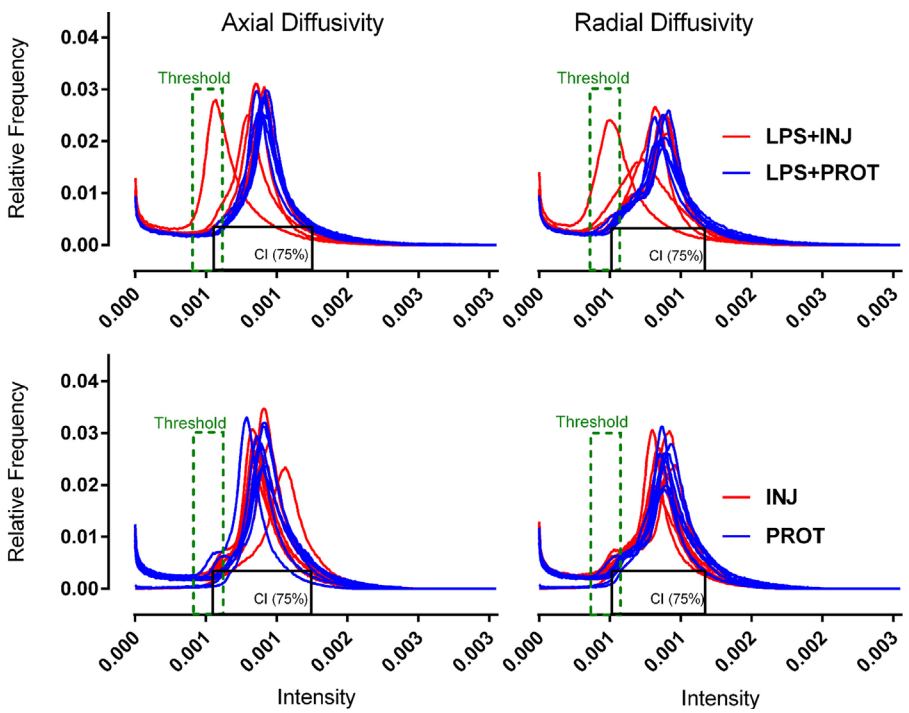

FIGURE 2 | Diffusion tensor imaging–histogram distributions. Histogram distribution plots of axial diffusivity and radial diffusivity for the whole brains from each group. The red lines represent the injurious ventilation groups (LPS + INJ and INJ), while the blue lines represent the protective ventilation groups for both data sets (LPS + PROT and PROT). Black box represents the 75% CI of all voxel intensities observed in the distribution in protective lamb brains. Threshold (green dashed line) applied to the mapped intensities in the overlay in both groups. LPS, lipopolysaccharide; CI, confidence interval.

plotted for the whole brains in the two groups of lambs that were not exposed to LPS in our previous study (6), as shown in (**Figure 2**). The histograms demonstrate the frequency distribution of MR image voxel intensity levels at each position. In the histograms, the black box represents 75% confidence interval (CI) of all voxel intensities observed in the distribution in protective lamb brains. The lower limit of this box was the lowest 10% of observed intensities. We then applied a threshold to the mapped intensities in the overlay in both groups (width ~10%). The upper threshold limit (**Figure 2**, green dashed line) was manually set at an intensity where voxels were almost completely absent across the whole brain in protective ventilation groups of lambs. However, coloured voxels were still evident at the edges of the brain mask in protective lambs. We found that the upper threshold of the colour mapping was consistent with the 90th percentile of intensities in the protective lambs, with 3–5% overlap in observed pixel intensities between protective and injurious ventilation groups (**Figure 2**). This process permitted mapping and quantification of the number of voxels of low diffusivity for AD, RD, and MD colour map images, using ImageJ.

Statistical Analyses

Physiological data were compared using a two-way repeated measure ANOVA and Holm–Sidak *post hoc* analyses to determine significant interactions (Sigmaplot, Systat Software Inc.). The LPS + INJ group was compared to the LPS + PROT group to assess between-group differences in DTI and MRS parameters. The mean and SEM of voxel intensities within the predefined ROIs were calculated, and independent *t*-tests were used to compare treatment groups with the significance level set at $P < 0.05$. Data from the ROIs are presented as mean (box 5-95% CI of mean) with maximum − minimum error bars. Further, we calculated the SD for the ROIs in each lamb's brain to test within-animal variability and to test the heterogeneity of DTI diffusivities for differences between groups using MATLAB (MathWorks Inc., MA, USA) software.

RESULTS

Baseline Characteristics

LPS was successfully injected into the amniotic sac as confirmed by electrolyte analysis of amniotic fluid aspirated at the time of injection and the presence of thickened fetal membranes characteristic of this experimental intervention observed at delivery (12).

Mean gestational age (125 ± 2 days), body weights (LPS + PROT: 3.4 ± 0.6 kg; LPS + INJ: 3.6 ± 0.2 kg), and sex distributions of the lambs (LPS + PROT: 3 males and 3 females; LPS + INJ: 2 males and 4 females) were not different between groups.

Physiological Parameters

Physiological parameters were recorded for the initial 60 min, prior to transfer of the lamb into the MRI scanner. Peak inflation pressure (**Figure 3A**) was significantly higher in the LPS + INJ group than the LPS + PROT group during the first 15 min ($P < 0.001$), resulting in a significantly higher V_T during the initial 15 min than the LPS + PROT group ($P < 0.001$; **Figure 3B**). However, PIP was lower in LPS + INJ lambs once protective ventilation was initiated, likely due to the delivery of surfactant at 15 min in these lambs. Consistent with this contention, the LPS + INJ group demonstrated significantly increased lung compliance at 20, 30, and 45 min of ventilation ($P = 0.02$, $P = 0.04$, and $P = 0.05$, respectively; **Figure 3F**). PaO_2, $PaCO_2$, and pH were not different between groups ($P = 0.38$, $P = 0.7$, and $P = 0.9$, respectively; **Figures 3C–E**) nor was FiO_2 (LPS + INJ; mean 0.41 ± 0.07 vs. LPS + PROT; mean 0.31 ± 0.06, $P = 0.20$). Oxygen saturation (SaO_2) did not differ significantly between groups after the first 5 min of ventilation ($P = 0.5$; **Figure 3G**).

Carotid blood flow was variable within groups and between groups, but overall there was no significant differences observed ($P = 0.8$; **Figure 3H**). Mean HR tended to be lower at all time points in the LPS + INJ compared to LPS + PROT group ($P = 0.09$; data not shown).

Structural MRI and MR Spectroscopy

No overt cerebral injury was seen on T1, T2, or SWI images in either group. The MRS peak area ratios of Lac to other metabolites (Cr, Cho, and NAA) (**Figure 4**) as well as NAA/Cho, NAA/Cr, and Cho/Cr were not different between groups.

DTI of ROI-Based Analysis

While mean AD, RD, and MD values were lower in the LPS + INJ lambs compared to the LPS + PROT lambs in many of the ROIs (**Figure 5**), no statistically significant differences were found. However, lambs in the LPS + INJ group showed significantly increased heterogeneity of diffusivity in multiple regions [Th, PVWM, and CB (middle)] compared to the LPS + PROT group (Figure S1 in Supplementary Material), indicating more animals with increased heterogeneity in their diffusivities within the ROIs. Given the greater variability in injury in the LPS + INJ group, we applied a colour map threshold technique to better distinguish between the two ventilation groups.

Colour Mapping Threshold of Whole Brain Analysis

Colour map techniques were used to describe the tensor orientation in relation to the white matter tract direction (29). Histograms of AD and RD for the whole brains of individual lambs in the two groups exposed to LPS and two groups without LPS treatment (6) are plotted in **Figure 2**. The threshold range that highlighted lower diffusivity voxels (**Figure 2**, green dashed line) was manually set below the 90th percentile of intensities in the protective lambs and hence corresponded to the red shading in the injured lambs as shown in the examples of **Figures 6** and **7**.

In the low diffusivity maps obtained from the lambs exposed to LPS during the perinatal period, the red shading (threshold range) was more visible in the Th of AD and RD maps (Figure S2 in Supplementary Material) in three LPS + INJ lambs, while the lowest diffusivity values were almost absent in the same region in the LPS + PROT group. Further, there were low AD and RD values in the amygdala of one LPS + INJ lamb (Figure

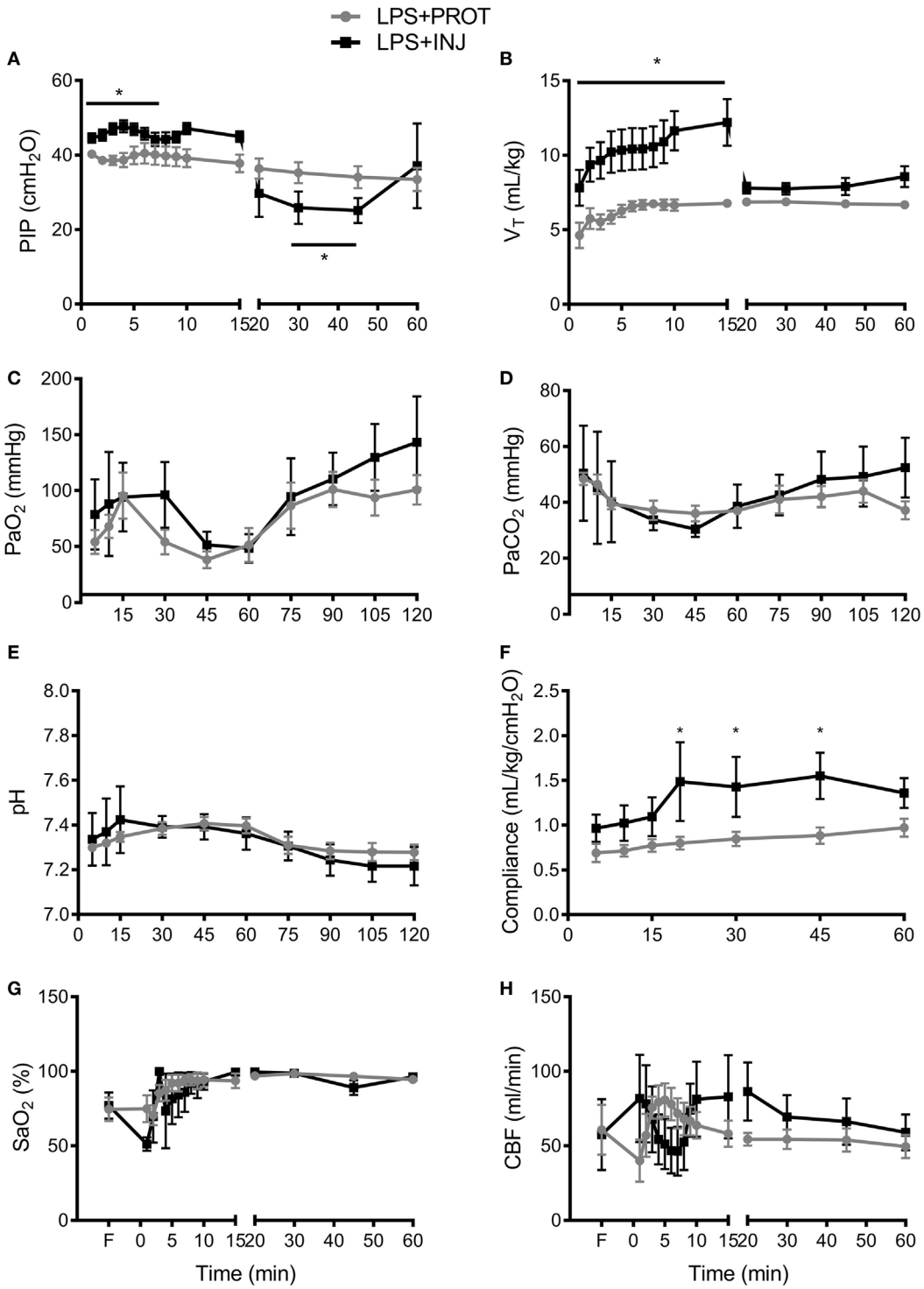

FIGURE 3 | **Physiological parameters**. **(A)** Peak inspiration pressure (PIP) delivered to LPS + PROT lambs (closed circle) and LPS + INJ lambs (closed squares). **(B)** Tidal volume (V_T). **(C)** Partial pressure of arterial oxygen (PaO_2) and **(D)** carbon dioxide ($PaCO_2$). **(E)** pH values. **(F)** Lung compliance. **(G)** Arterial oxygen saturation (SaO_2). **(H)** Total carotid blood flow (CBF). *$P < 0.01$.

S2 in Supplementary Material). In the FWM, there were three LPS + INJ lamb brains that showed lower AD values compared to those in the LPS + PROT group (Figure S3 in Supplementary Material). Further, low RD values appeared in the FWM of two LPS + INJ lambs compared to the LPS + PROT group lambs (Figure S3 in Supplementary Material). We also found exceptionally low AD and RD voxel values, as shown in red and black (below the threshold range), in the IC, putamen,

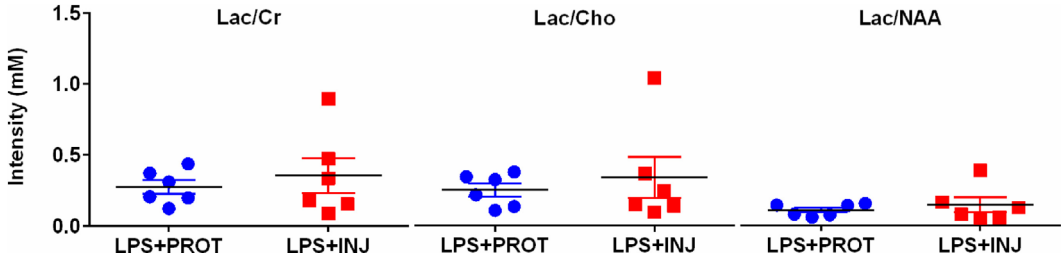

FIGURE 4 | **Peak area MRS lactate ratios**. Individual MRS peak area ratios utilising a single-voxel encompassing supratentorial central white matter and deep grey matter in the LPS + PROT group (blue circles) and the LPS + INJ group (red squares). Lac, lactate; Cr, creatine; Cho, choline; NAA, *N*-acetylaspartate; MRS, magnetic resonance spectroscopy.

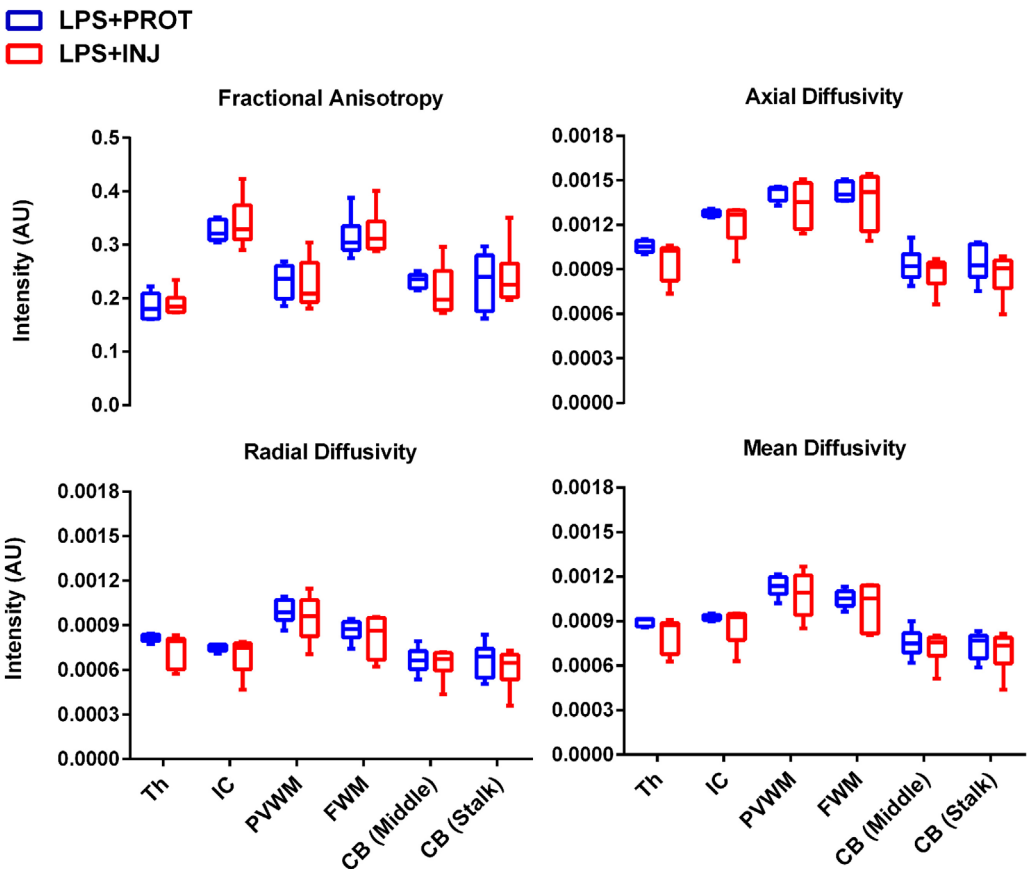

FIGURE 5 | **Mean of diffusion tensor imaging measurements**. The mean fractional anisotropy, axial diffusivity, radial diffusivity, and mean diffusivity measurements for each region of interest (ROI) in the LPS + INJ and LPS + PROT groups. The ROIs shown in **Figure 1** were located in the thalamus (Th), internal capsule (IC), periventricular white matter (PVWM), frontal white matter (FWM), cerebellum (CB) middle, and cerebellum (CB) stalk.

caudate, and septum of lambs in the LPS + INJ group, but rarely in the LPS + PROT group (**Figures 6** and **7**). In the PVWM, low AD and RD voxel diffusivities were found in the LPS + INJ group when compared to LPS + PROT group lambs in addition to grey matter regions of the cerebellum, which were lower in diffusivity than white matter (Figure S4 in Supplementary Material). In all ROIs, the calculated MD maps had similar patterns of distribution of low diffusivity as shown in the AD and RD maps (Figures S4 and S5 in Supplementary Material). Therefore, the colour maps revealed that the low-intensity voxels for AD, RD, and MD closely correlated with white matter regions in most of the cerebral anatomical structures that were chosen.

Colour Mapping Threshold Comparison with Control Lambs

As a control reference, we applied the colour map technique to lambs that underwent the same ventilator and MRI protocols

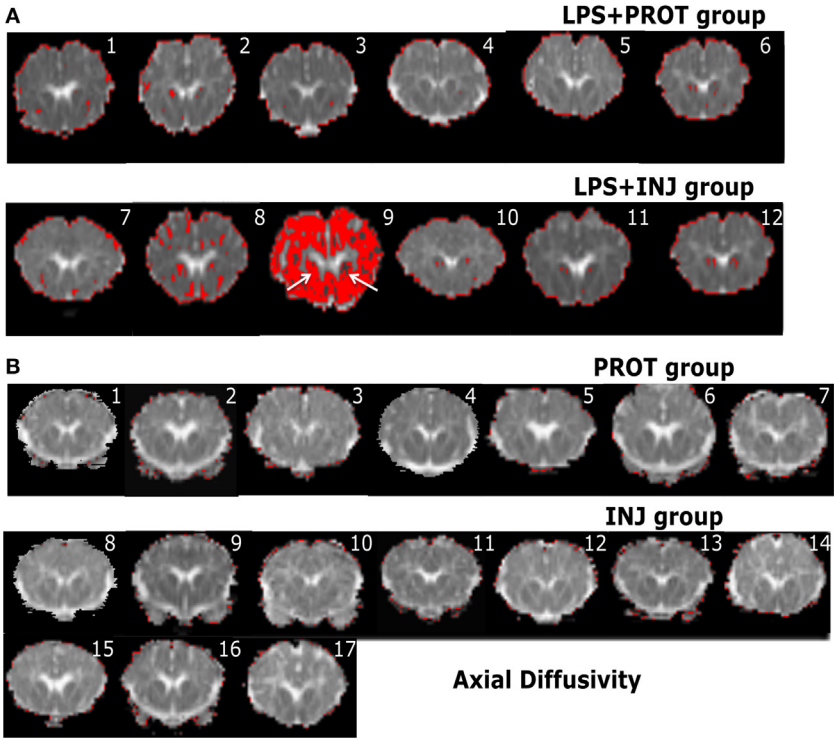

FIGURE 6 | **Example whole brain diffusion tensor imaging-colour maps of the internal capsule (IC) and axial diffusivity (AD)**. Voxel diffusivity intensities falling below the low threshold are shown as red for AD measurements for all lambs exposed to intrauterine inflammation [lipopolysaccharide (LPS) **(A)**] and control lambs not exposed to LPS **(B)**. In the LPS + INJ, all low-diffusion maps are overlaid on diffusion images for a slice passing through the IC. While the red colour indicates lower values in the range of the threshold, the black colour indicates lower values below the threshold shown in **Figure 2**. In the control groups, INJ and PROT, no lamb had low AD values in the IC, putamen, caudate, and septum in either group. Numerals in images indicate the ID for individual lambs.

but were not exposed to LPS (PROT and INJ control lambs); the physiology and other MRI data have been reported previously (6). Lambs from our previous study did not differ in body weight, blood gas parameters, or HR at the time of intubation and cord clamping (time 0; **Table 1**) with the lambs from this study. We found no low AD values in the FWM, IC, putamen, caudate, septum, and PVWM for either PROT or INJ groups, while low RD values appeared in some regions of white matter of INJ lambs when compared to PROT group (Figures S6 and S7 in Supplementary Material). Finally, quantifying the number of voxels found to have low diffusivity within each ROI, we compared counts between LPS and control lambs (**Figure 8**). There were frequently lower AD, RD, and MD intensities in the Th, IC, PVWM, and FWM in a subgroup of LPS + INJ lambs compared to LPS + PROT, as well as when compared to controls when compared to controls that were not exposed to LPS.

DISCUSSION

Preterm neonates exposed to intrauterine inflammation are at an increased risk of ventilation-induced brain inflammation and injury (11). In this study, we aimed to detect subtle brain injury in lambs associated with intrauterine inflammation and different ventilation strategies within the first 90 min after birth, using clinical 3T MRI. We found that conventional MRI techniques were unable to detect subtle differences in brain injury between LPS groups. However, colour mapping demonstrated that there were more regions of low diffusivity in a subgroup of LPS + INJ lambs compared to LPS + PROT lambs, indicative of increased brain injury. Further, exposure to LPS resulted in consistently increased regions of low diffusivity than control lambs, suggesting that early detection of brain injury in infants exposed to chorioamnionitis may be possible.

Advanced MRI methods such as DTI and MRS provide useful information about structural connectivity and altered brain chemistry, allowing improved detection of newborn brain injury over conventional MRI (30–33). However, these strategies have limited ability to detect brain injury early enough whereupon it can guide clinical intervention within a therapeutic window (24, 25). This contention is confirmed by our finding that conventional MRI sequences revealed no evidence of brain injury in the preterm lambs that had received LPS with or without injurious ventilation, despite histological studies demonstrating that injury is normally present (11). Therefore, there is an urgent need to develop advanced MRI strategies that can detect subtle brain injury early after birth. Further, clinicians need to be confident that brain injury is developing, or already present, prior to administration of any therapy.

Several other research groups have presented evidence of DTI changes due to brain injury in lambs utilising *ex vivo* MRI analyses that were strongly correlated with histopathological evidence of injury (34–36). The colour map threshold approach

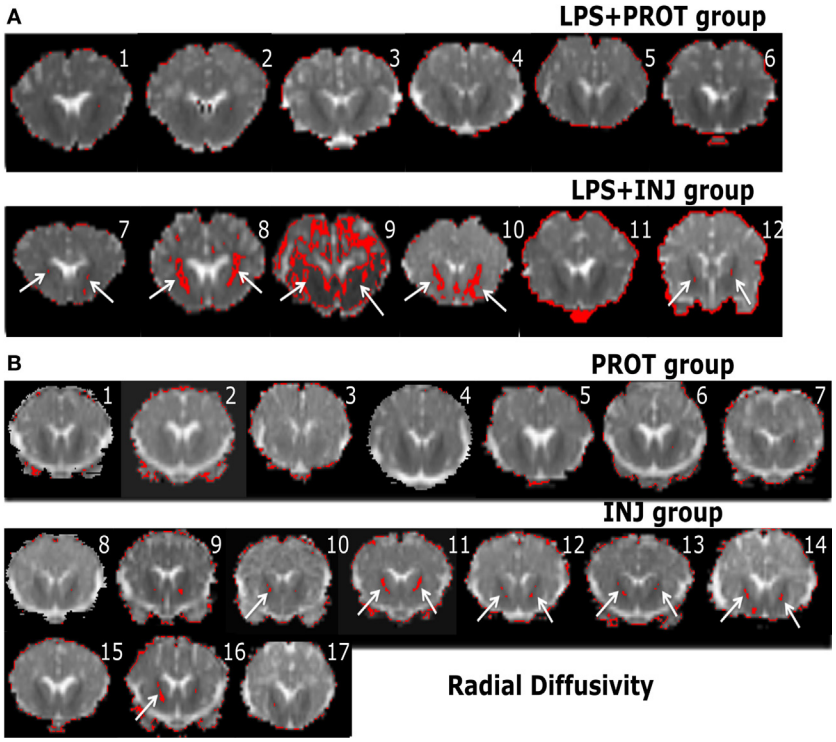

FIGURE 7 | Example whole brain diffusion tensor imaging-colour maps of the internal capsule (IC) and radial diffusivity (RD). Voxel diffusivity intensities falling below the low threshold are shown as red for RD measurements for all lambs exposed to intrauterine inflammation [lipopolysaccharide (LPS) **(A)**] and control lambs not exposed to LPS **(B)**. In the LPS + INJ, all low-diffusion maps are overlaid on diffusion images for a slice passing through the IC. While the red colour (IC indicated by white arrows) indicates lower values in the range of the threshold, the black colour indicates lower values below the threshold shown in **Figure 2**. In the control groups, INJ and PROT, the colour images display low diffusivity in the IC for some INJ lambs, while there were no low RD values found in the PROT group. Numerals in images indicate the ID for individual lambs.

TABLE 1 | Comparison of blood gas parameters at the time of delivery between the lambs that were exposed to intrauterine inflammation (LPS) and controls lambs that were not exposed to LPS at the delivery time.

Variable	PROT	INJ	LPS + PROT	LPS + INJ	*P* value
Sex (M/F)	4/3	4/6	3/3	2/4	–
Gestational age (days)	126 ± 1	126 ± 1	125 ± 2	125 ± 2	0.9
Body weight (kg)	3.3 ± 0.2	3.2 ± 0.2	3.4 ± 0.4	3.6 ± 0.3	0.09
SpO_2 (%)	71.7 ± 4.2	79.3 ± 11.6	75.3 ± 22.8	61 ± 26.9	0.5
Heart rate (bpm)	158.7 ± 24.5	130.0 ± 3.5	128.7 ± 10.7	145.8 ± 33.8	0.3
pH	7.3 ± 0.7	7.2 ± 0.7	7.3 ± 0.5	7.2 ± 0.6	0.2
$PaCO_2$ (mmHg)	51.4 ± 11.1	64.5 ± 0.8	57.2 ± 15.5	54.2 ± 15.4	0.4
PaO_2 (mmHg)	62.4 ± 17.7	23.5 ± 0.8	42 ± 28.9	48.2 ± 54.3	0.2

Characteristics of the PROT and INJ lambs from the study by Skiold et al. (6) and LPS + PROT and LPS + INJ lambs in this study and their fetal blood gases at the time of intubation and cord clamping are presented as mean ± SD. Variables were compared using one-way ANOVA with a Holm-Sidak's multiple comparisons tests relative to the PROT group. P < 0.05 was considered statistically significant.
PROT, protective ventilation; INJ, injurious ventilation; LPS, lipopolysaccharide.

was used in this *in vivo* study to measure the distribution of diffusivity values in specific brain regions that have been identified as being vulnerable to injury. The advantage of colour mapping is that it enables the analysis of thousands of voxels compared with very small numbers of voxels when using small defined ROIs (37). We used lambs from a previous study, which received protective ventilation after preterm delivery to determine the ~10% threshold, as these lambs were most likely to have very little brain injury (6). By using this new technique, we found that lower AD, RD, and MD intensities are more frequently seen in the Th, FWM, IC, and PVWM of LPS + INJ lambs compared to LPS + PROT lambs. We then compared these data with that of lambs from our previous study (6), which were not exposed to LPS. We observed that lambs exposed to chronic intrauterine inflammation more frequently had low diffusivity in the Th, FWM, IC, and PVWM regions when compared with lambs

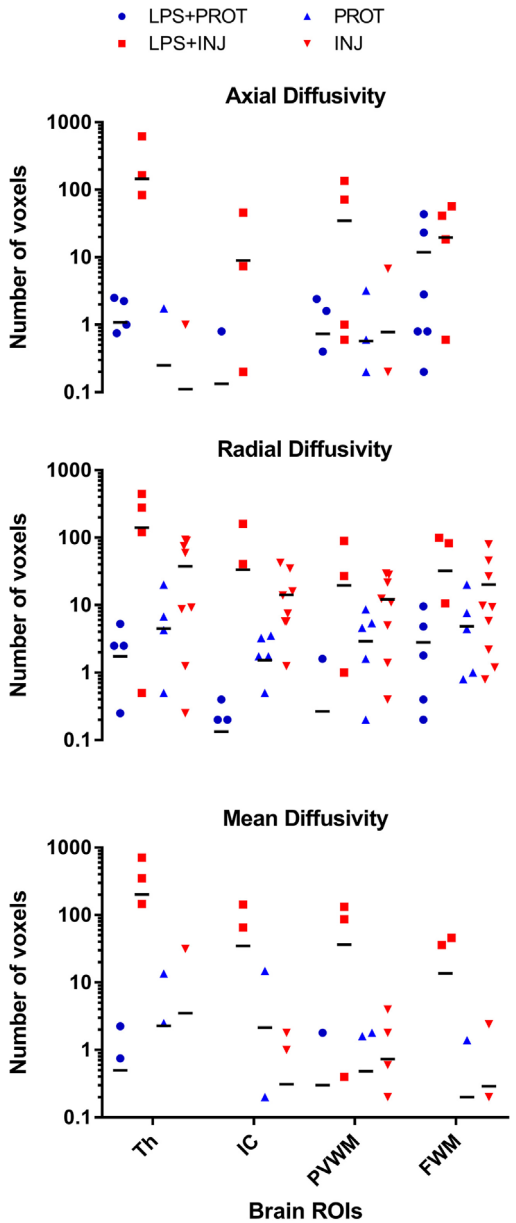

FIGURE 8 | **Comparison of voxel-based colour map image**. The comparison of voxel-based colour images for axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) measurements for each region of interest (ROI) in the lamb brains for both data sets. The ROIs shown in **Figure 1** were located in the thalamus (Th), internal capsule (IC), periventricular white matter (PVWM), and frontal white matter (FWM). There were widespread low RD intensity voxels in all white matter regions in both groups of lambs exposed to intrauterine inflammation [lipopolysaccharide (LPS)], but low AD and MD intensity voxels were more frequent in the LPS + INJ group only. In contrast, lambs that were not exposed to intrauterine inflammation (LPS) were found to have few low RD intensity voxels in white matter regions, and no change was found in the AD and MD intensities.

not exposed to intrauterine inflammation. Therefore, threshold mapping of DTI is a more sensitive approach to assess the microstructural changes associated with preterm brain injury as early as 90 min after birth.

The colour map technique identified decreased AD, RD, and MD in LPS + INJ lambs, suggestive of microstructural alterations in many ROIs. The decrease in AD indicates a decrease in water diffusion parallel to white matter fibre tracts, suggesting that there is a breakdown of axon integrity within these ROIs (38). The reduction in RD, reflecting the degree of water diffusion perpendicular to white matter fibre tracts in anatomical brain structures, also suggests that myelin might be affected (38). This observation is consistent with a previous observation that LPS exposure decreased myelination in fetal sheep (39). Nonetheless, a limitation of the colour mapping approach is that it was not sensitive enough to detect significant differences between the groups in the cerebellum. This may be attributed to fibre tracts being less organised and only partially myelinated (40). For this reason, the cerebellum may be less sensitive to the effects of inflammation. Further, the water content in the premature brain is more uniform than later on in development (41), diminishing the MR contrast between the white matter and grey matter in some regions, such as the cerebellum (42).

In this study of chronic intrauterine inflammation, a subgroup of LPS + INJ lambs had brain injury of greater extent than the LPS + PROT group. In contrast, our previous study utilising a protective ventilation strategy did not find a reduction in the degree or severity of white matter injury in preterm lambs exposed to 2 days of LPS (12). It is most likely that this disparity reflects differences in the methods of assessment of brain injury utilised in the two studies. However, other studies suggest that part of the difference between the past study (12) and this study is likely to be also due to the longer time (7 days) of LPS exposure, which may increase the susceptibility of the brain to ventilation-induced injury. Previously we found increased incidence and severity of white matter injury in ventilated preterm lambs receiving LPS 4 days prior to delivery compared to 2 days (11). Importantly, our evidence that changes in brain diffusion was greater in LPS-exposed lambs than controls supports both our findings (5) and clinical studies (13) demonstrating an increased risk of postnatal brain injury after intrauterine inflammation.

We did not find differences in MRS peak area ratios for Lac relative to other metabolites (Cr, Cho, and NAA) between PROT and INJ groups following LPS administration. These ratios are indicative of brain metabolism and correlate with neonatal brain injury (43) and subsequent outcome (44). We do not know why we were unable to detect differences using MRS, but the prior exposure to LPS may alter the response of the metabolites to ventilation.

There are some limitations to this study. We did not correlate our quantitative DTI findings with histological assessment to conclusively demonstrate that these alterations truly represent microstructural changes exacerbated by multiple risk factors such as injurious ventilation and chronic inflammation. Further, conducting longer term studies is required to investigate whether the early injury markers manifest as disability later in life. Moreover, we concede that the greatest limitation of the application of this imaging and analysis approach to very preterm and very low-birth-weight neonates in the NICU is that it is difficult to image ventilated babies

in an MR scanner within hours of birth, and this would be discouraged by the general policy of minimal handling of such neonates. However, if we can develop robust strategies that can accurately determine brain injury, then the potential benefit of early identification and treatment would likely outweigh the minimal handling policies of such units. The use of new MRI-compatible cribs might make such early diagnosis easier to implement.

In conclusion, the use of colour mapping demonstrated that injurious ventilation after LPS was associated with low AD, RD, and MD in the cerebral white matter of preterm lambs, which was not detected using standard MRI techniques. Colour mapping also demonstrated greater alterations in water diffusivity, and therefore neural function, in LPS lambs compared to controls. The colour map technique might be a sensitive way to detect early white matter injury and may lead to improved detection of preterm brain injury within a suitable time frame for clinical intervention.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work; revised drafts; and approved the final version to be published.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fped.2017.00070/full#supplementary-material.

FIGURE S1 | **SD of diffusion tensor imaging measurements**. The SD of the distribution of voxel intensities within each region of interest (ROI) for each animal was calculated for fractional anisotropy, axial diffusivity, radial diffusivity, and mean diffusivity measurements in the LPS + INJ and LPS + PROT groups. The means of the SDs were tested for differences between the two groups of lambs. The ROI (see **Figure 1**) were located in the thalamus (Th), internal capsule (IC), periventricular white matter (PVWM), frontal white matter (FWM), cerebellum (CB) middle, and cerebellum (CB) stalk. $^{*}P < 0.01$ and $^{**}P < 0.001$.

FIGURE S2 | **Diffusion tensor imaging-colour maps of the thalamus; lipopolysaccharide (LPS) groups**. Voxel diffusivity intensities falling below the low threshold are shown as red for axial diffusivity (AD) and radial diffusivity (RD) measurements for all lambs exposed to intrauterine inflammation (LPS). All low-diffusion maps are overlaid on diffusion images for a slice passing through the thalamus. The red overlay (threshold range) was more visible in the thalamus of AD and RD maps in three LPS + INJ lambs (#7–9), while the lowest diffusivity values were almost absent in the same region in the LPS + PROT group. Further, there were low AD and RD values in the amygdala of one LPS + INJ lamb (#9). Numerals in images indicate the ID for individual lambs.

FIGURE S3 | **Diffusion tensor imaging-colour maps of the frontal white matter (FWM); lipopolysaccharide (LPS) groups**. Voxel diffusivity intensities falling below the low threshold are shown as red for axial diffusivity (AD) and radial diffusivity (RD) measurements for all lambs exposed to intrauterine inflammation (LPS). All low-diffusion maps are overlaid on diffusion images for a slice passing through the FWM. While the red colour indicates lower values in the range of the threshold (arrows indicating FWM), the black colour indicates voxel intensity below the threshold range shown in **Figure 2**. There were three LPS + INJ lamb brains (#7–9) that showed lower AD values in the FWM compared to those in the LPS + PROT group. Further, low RD values appeared in the FWM of two LPS + INJ lambs (#8 and 9) compared to the LPS + PROT group lambs. Numerals in images indicate the ID for individual lambs.

FIGURE S4 | **Diffusion tensor imaging-colour maps of the periventricular white matter (PVWM); lipopolysaccharide (LPS) groups**. Voxel diffusivity intensities falling below the low threshold are shown as red for axial diffusivity, radial diffusivity, and mean diffusivity measurements for all lambs exposed to intrauterine inflammation (LPS). All low-diffusion maps are overlaid on diffusion images for a slice passing through the PVWM. The red shows the lower diffusivities values in the range of the threshold, while the black colour indicates diffusivities values below the threshold (**Figure 2**). While noting the red colour in the grey matter regions, which have lower diffusivity than white matter, there are two. LPS + INJ lambs (#8 and 9) with widespread lower diffusivity values in the PVWM when compared to LPS + PROT group lambs. Numerals in images indicate the ID for individual lambs.

FIGURE S5 | **Diffusion tensor imaging-colour maps of the mean diffusivity (MD) in the thalamus; lipopolysaccharide (LPS) groups**. Voxel diffusivity intensities falling below the low threshold are shown as red for MD, measurements for all lambs exposed to intrauterine inflammation (LPS). All low-diffusion maps are overlaid on diffusion images for a slice passing through the thalamus. The red colour in the images shows low MD that is more visible in the thalamus of three injured lambs (LPS + INJ) (#7–9), while the MD images of the LPS + PROT group show very few red voxels. There were reduced MD values in amygdala of one injured lamb as well (#9). Numerals in images indicate the ID for individual lambs.

FIGURE S6 | **Diffusion tensor imaging-colour maps of the frontal white matter (FWM); control groups**. Voxel diffusivity intensities falling below the low threshold are shown as red for axial diffusivity (AD) and radial diffusivity (RD) measurements for all control lambs not exposed to intrauterine inflammation (lipopolysaccharide). All low-diffusion maps are overlaid on diffusion images for a slice passing through the FWM. None of the lambs in either group had low AD values in the FWM, but the red colour is evident in the grey matter in some animal of both groups. In contrast, low RD values appeared in the FWM of three INJ lambs (#9, 11, and 12). Numerals in images indicate the ID for individual lambs.

FIGURE S7 | **Diffusion tensor imaging-colour maps of the periventricular white matter (PVWM); control groups**. Voxel diffusivity intensities falling below the low threshold are shown as red for axial diffusivity (AD) and radial diffusivity (RD) measurements for all control lambs not exposed to intrauterine inflammation (lipopolysaccharide). All low-diffusion maps are overlaid on diffusion images for a slice passing through the PVWM. There were no low AD diffusivity voxels concentrated in the PVWM in either group of lambs, but there were four INJ lambs (#9, 11, 13, and 16) with widespread low RD voxels in the PVWM when compared to PROT group lambs. Numerals in images indicate the ID for individual lambs.

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REVIEW
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Cerebral Autoregulation, Brain Injury, and the Transitioning Premature Infant

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Improvements in clinical management of the preterm infant have reduced the rates of the two most common forms of brain injury, such as severe intraventricular hemorrhage and white matter injury, both of which are contributory factors in the development of cerebral palsy. Nonetheless, they remain a persistent challenge and are associated with a significant increase in the risk of adverse neurodevelopment outcomes. Repeated episodes of ischemia–reperfusion represent a common pathway for both forms of injury, arising from discordance between systemic blood flow and the innate regulation of cerebral blood flow in the germinal matrix and periventricular white matter. Nevertheless, establishing firm hemodynamic boundaries, as a part of neuroprotective strategy, has challenged researchers. Existing measures either demonstrate inconsistent relationships with injury, as in the case of mean arterial blood pressure, or are not feasible for long-term monitoring, such as cardiac output estimated by echocardiography. These challenges have led some researchers to focus on the mechanisms that control blood flow to the brain, known as cerebrovascular autoregulation. Historically, the function of the cerebrovascular autoregulatory system has been difficult to quantify; however, the evolution of bedside monitoring devices, particularly near-infrared spectroscopy, has enabled new insights into these mechanisms and how impairment of blood flow regulation may contribute to catastrophic injury. In this review, we first seek to examine how technological advancement has changed the assessment of cerebrovascular autoregulation in premature infants. Next, we explore how clinical factors, including hypotension, vasoactive medications, acute and chronic hypoxia, and ventilation, alter the hemodynamic state of the preterm infant. Additionally, we examine how developmentally linked or acquired dysfunction in cerebral autoregulation contributes to preterm brain injury. In conclusion, we address exciting new approaches to the measurement of autoregulation and discuss the feasibility of translation to the bedside.

Keywords: autoregulation, near-infrared spectroscopy, intraventricular hemorrhage, white matter injury, brain injury, prematurity

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INTRODUCTION

Premature infants weighing less than 1,500 g at birth are frequently affected by two specific forms of brain injury, such as intraventricular hemorrhage (IVH) and white matter injury (WMI). In the last 30 years, the incidence of IVH has fallen from nearly 50% (1) to 25% (2) as a result of antenatal steroid

administration, improved ventilator strategies, and improved obstetrical practices. In contrast, the incidence of WMI has remained essentially unchanged, affecting approximately 10% of infants less than 1,500 g (3). Both forms of injury are linked to the development life-long neurodevelopmental impairment, including cerebral palsy (4, 5).

Although there long have been defined associations between clinical factors (e.g., pneumothorax, need for cardiopulmonary resuscitation, sepsis, and necrotizing enterocolitis) and both forms of brain injury (5), the precise underlying mechanisms have remained less clear, despite the efficacy of some neuroprotective strategies. Given histologic evidence (6) suggesting the injury arises from discordance between systemic and cerebral blood flow (CBF) in the germinal matrix and periventricular white matter, a primary target for understanding the mechanism of brain injury, should be based in the investigation of perfusion. Current methods for assessing the adequacy of cardiac output to support proper organ system are typically imprecise, difficult to perform, are not feasible for longitudinal monitoring, or lack specificity to cerebral circulation.

Heart rate and capillary refill time remain key parts of the primary hemodynamic assessment. As neonates lack the ability to alter stroke volume, tachycardia is the primary means for increasing cardiac output, yet frequent confounding factors such as pain/agitation and caffeine citrate administration can confound the heart-rate assessment (7). Capillary refill can also be a very specific indicator of hemodynamic compromise; however, it lacks sensitivity (approximately 35%) needed for consistent assessment (8). Echocardiography remains the "gold standard" of evaluating volume status and vascular tone (preload and afterload), essential for estimate of cardiac output; however, it requires the skills of a cardiac sonographer and an expert interpreter and is impractical for longitudinal monitoring. Blood flow through the superior vena cava, a measure of volume status, can also be measured by echocardiography (9) but again faces the challenge of longitudinal data capture. A similar measure of right ventricular filling can be evaluated by measurement of the central venous pressure *via* an umbilical venous catheter; however, there are significant challenges in interpretation of these values as there is a broad range of normal values, hampering discrimination between normal and pathologic states (10).

Over the last 10 years, investigation has shifted from examination of systemic blood flow to detailed investigation of patterns of CBF. This shift has been enabled by new technology, driving deeper investigation into the regulation of CBF in preterm infants, finding significant impairment of autoregulation as a major contributing factor to the development of IVH. Additionally, new strategies for identifying and classifying WMI on MRI have changed our views of the link between WMI and neurodevelopmental outcome (11). Cutting-edge techniques to identify WMI using simple, bedside monitoring provide an opportunity for earlier diagnosis and counseling of the family.

Taken together, technological advancements now provide a window, for the first time, into the detailed interplay of cerebrovascular regulation, ischemia–reperfusion, and the development of brain injury in preterm infants. These advances offer the potential for early detection of impending brain injury, allowing the opportunity for intervention with the aim of prevention or minimization of injury.

In this review, we seek to discuss advances in the field of brain monitoring, with a focus on hemodynamics, as related to the development of preterm brain injury. We explore new knowledge about the role clinical factors and management play in providing additional neuroprotection or contributing to worsened injury. Finally, we discuss future developments in the field including the potential for new clinical management strategies, which incorporate real-time, multimodality bedside monitoring in the NICU.

MECHANISMS OF INJURY—IVH

During fetal development, neurons and glial cells arise from the germinal matrix and, sub-ventricular zone and migrate outwards toward the cortex. This process requires rich vascular support from a dense capillary bed within the germinal matrix. Unlike mature blood vessels, those of the germinal matrix are thin-walled, lack pericytes and have limited glial fibers, making them extremely fragile. This capillary bed drains into the terminal vein before entering the internal cerebral vein (5).

Two postulations have emerged as to the pathogenesis of IVH. In one theory, significant fluctuations in arterial blood pressure, the result of sepsis, noxious stimuli, fluid boluses, or inotrope drugs, overwhelm the fragile capillary bed and lead to the bursting of the vessels. Alternatively, obstruction of the venous system, whether by pneumothorax impeding venous return, ventilator asynchrony or simply a change in head position caused an increase in hydrostatic pressure, again leads to the rupture of vessels in the capillary bed (5).

Both mechanisms likely provide contributory components, with cycles of ischemia and reperfusion further weakening the vascular structures until the blood vessels can no longer tolerate the fluctuations and burst.

MECHANISMS OF INJURY—WMI

Investigation into the underlying pathophysiology of WMI has revealed a link between three predisposing factors (disturbances in cerebral oxygenation, infection, and inflammation) and a developmental vulnerability of the white matter between 23 and 32 weeks of development (5, 12). Premyelinating oligodendrocyte progenitor cells (pre-OL), a subtype of glial cells that proliferate in waves during the second trimester, are found in high densities in the white matter and exhibit a maturation-dependent vulnerability to oxidative stress (5, 13). This vulnerability can be intrinsic, caused by excessive glutathione depletion from oxidative stress or extrinsic, caused by glutamate receptor-mediated toxicity, the result of glutamate release by adjacent dying cells (14). Either mechanism sets up a cascade of events, leading to loss of pre-OLs and damage to surrounding white matter (15–17).

The premature brain is vulnerable to oxidative stress from hypoxic–ischemic injury as a result of the confluence of three key risk factors: heart-rate dependent cardiac output, the immature vascular supply, and disturbances in vascular autoregulation. First, continued adequate cardiac output in premature infants

is tenuous; given that stroke volume is relatively fixed, cardiac output is dependent on heart rate (13). Any disturbance in the heart rate [e.g., apnea of prematurity, with resulting bradycardia (18)] sets up the possibility of ischemia. Second, the white matter, particularly in the periventricular zone, is supplied by the long penetrating arteries, which first arise around 24 weeks of gestation but maintain remarkably low levels of blood flow, with minimal collateralization, until 30–32 weeks of gestation (6, 19). Finally, there is evidence of an impaired cerebrovascular autoregulatory system, suggesting that the preterm brain has limited capacity to regulate blood flow when oxygen saturation or cardiac output is reduced (20, 21). Repeated ischemic episodes associated with any of these mechanisms will generate an inflammatory response, thus increasing the metabolic demand, utilizing a greater fraction of delivered oxygen, and potentiating further injury during the next ischemic episode.

REVIEW OF CEREBROVASCULAR AUTOREGULATORY SYSTEM

The cerebrovascular autoregulatory system is a physiologic mechanism, which functions to maintain constant and stable CBF. The classic depiction of this system is a sigmoidal curve (**Figure 1**) with stable CBF over a range of normal blood pressures and unstable CBF when the blood pressure is outside of this range. The work of Lou (22) and Ment (23) demonstrated the failure of the preterm cerebral vasculature to maintain uniform cerebral perfusion over a range of systemic blood pressures, a phenomena termed "pressure-passive circulation."

A complementary view of blood flow regulation was initially proposed in the nineteenth century by Siegmund Mayer when he observed spontaneous rhythmic oscillations in blood vessel diameter, with a periodicity of 10 s (0.1 Hz), in the wings of bats. Recent computational techniques have allowed greater exploration of this dynamic model, with data suggesting that the autoregulatory system attenuates the effect of low-frequency fluctuations in blood pressure, effectively functioning as a high-pass filter (24, 25). These oscillations, now called "Mayer waves," arise from changes in the vasomotor tone of arterial blood vessels throughout the body and are likely driven by the autonomic nervous system.

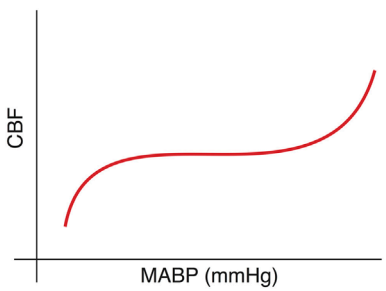

FIGURE 1 | Cerebral blood flow (CBF) is conceptualized as a sigmoidal curve with stable blood flow across a range of "normal" blood pressure and impairment at either extreme.

Oscillations in blood pressure can divided into three categories based on their periodicity—high frequency (HF, >0.5 Hz), low frequency (LF, 0.05–0.5 Hz), and very-low frequency (VLF, <0.05 Hz). HF fluctuations are driven by the respiratory cycle (and thus are relatively fixed). LF and VLF variability represent the composite influence of autonomic (26), myogenic (27, 28), and cellular (29) control mechanisms. Crucially, the intensity of response of these control mechanisms is modulated by circulating catecholamines (30), vasoactive intestinal peptides (31), nitric oxide (26, 32, 33), hypovolemia (34), and the renin–angiotensin system (35). Cerebrovascular autoregulatory system failure results in unstable CBF, generating the cycle of ischemia–reperfusion, which drives the mechanisms of preterm brain injury.

OVERVIEW OF METHODS FOR QUANTIFYING THE AUTOREGULATORY SYSTEM

Methods for quantifying the state of the autoregulatory system have evolved over time in conjunction with advances in technology. Reliably testing the function of the cerebral autoregulatory system in the preterm population, however, has proven to be a difficult task, largely due to the broad diversity in neurophysiologic development, technical challenges associated with capturing data, the lack of a clear definition for hypotension (36), and lack of a standardized analysis methodology. The earliest approaches that used PET, transcranial Doppler ultrasound, or ^{133}Xe clearance provide a dynamic view of the cerebral vasculature. While effective, they are not feasible for longitudinal monitoring due to concerns about radiation exposure, increased temperature in the target tissue (37), and the use of invasive delivery of radioactive isotopes, respectively. Furthermore, they provide only semiquantitative information about autoregulation.

The use of near-infrared spectroscopy (NIRS) to quantify cerebral flow represents a revolutionary step in obtaining longitudinal hemodynamic information and comes with a dramatically improved safety profile in the vulnerable preterm neonate. The mixed-venous oxygen saturation of hemoglobin in a tissue can be estimated using NIRS, a technique that uses the difference in absorption of near-infrared light by oxy- and deoxyhemoglobin to detect the relative concentrations of each compound (**Figure 2**). Given that only 30% of blood is intra-arterial at any given time, the measured values represent a 30/70 arterial/venous-weighted estimate of oxygen saturation. NIRS has been used extensively in the neonatal population, with recent publication of a reference dataset in a cohort of nearly 1,000 infants, suggesting a typical cerebral saturation value of approximately 65% (95% CI 55–75) (38).

Venous oxygenation is influenced by many parameters, including cardiac output, blood pressure, oxygen content of the blood, pH, and metabolic demand by tissues. These properties are highly advantageous to the study of regional tissue oxygenation, as these measurements reflect the amount of oxygen available to and consumed by the target of interest. This stands in contrast to arterial saturation measured by pulse oximetry (SpO_2), which initially may remain at or near 100% despite significant ischemia in regions of the body. Although NIRS directly measures tissue

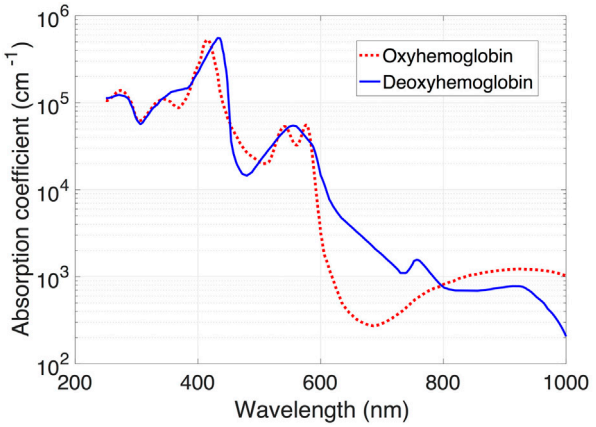

FIGURE 2 | Absorption spectra of light for oxy- and deoxyhemoglobin. Note the decreased absorption by oxyhemoglobin in the infrared band (approximately 700 nm).

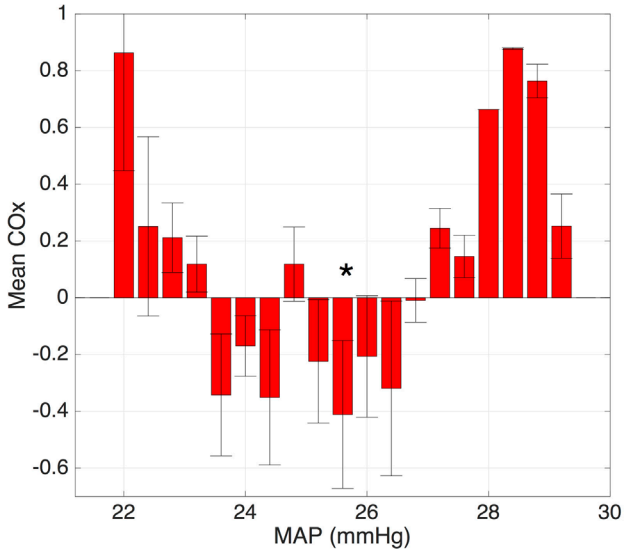

FIGURE 3 | Plot of the average correlation between the blood pressure and cerebral oxygenation. Note the lack of correlation over the range of "normal" blood pressure and increased correlation at the extreme values, representing loss of autoregulation. The optimal MAP is denoted with an asterisk.

oxygenation, it is highly correlated with measures of blood flow made by other measures (39), making it an attractive proxy for more invasive alternatives.

While other factors, such as method of respiratory support (non-invasive, invasive, and high-frequency oscillatory ventilation), do not directly affect cerebral oxygenation, NIRS measurements have been used in a variety of studies to optimize respiratory support including prediction of extubation failure (40), an alternative to pulse oximetry for titration of supplemental oxygen (41), or early detection of hypercapnia (42).

Even with advancing technology, the function of the autoregulatory system cannot be measured directly. Instead, techniques have evolved, which derive function by measuring how an input signal (arterial blood pressure) is shaped and altered into the output (CBF). Optimal autoregulation would maintain steady-state CBF, despite changes in systemic blood pressure, while impaired autoregulation would be manifested by a high degree of correlation between changes in the blood pressure and changes in CBF. Two different approaches to utilizing NIRS data to quantify the autoregulatory system have emerged in the literature.

One approach utilizes *time-domain analysis*, examining the correlation between the measured values of blood pressure and cerebral saturations. This approach has been extensively studied and optimized by Lee et al. (43–50). In this approach, the correlation between short segments of blood pressure and NIRS data is continuously calculated. The mean correlation value is then calculated for each possible blood pressure value and sorted into "bins." The resulting output (**Figure 3**) is reminiscent of the autoregulation curve shown in **Figure 2** with high correlation values at extremes of blood pressure and 0 or negative correlation values in the "normal" range of blood pressure (**Figure 3**).

An alternate approach utilizes *frequency-domain analysis*, examining the correlation between low-frequency oscillations in the blood pressure and those in CBF. Several different research groups have utilized spectral coherence, a statistical method for comparing the relationship between two signals (20, 51, 52) with resulting values between 0 (no coherence) and 1 (perfect coherence). By setting a threshold of 0.5, researchers were able to calculate the proportion of time that infants were "pressure-passive." This approach is advantageous in that it is able to measure autoregulation as a dynamic system; however, the nature of frequency-domain analysis demands a high degree of precision in time synchronization of data capture (53). This pressure-passive pattern has been documented to occur in 10–20% of measured epochs in VPT infants, and there is a suggestion that it is found in association with brain injury (20, 22, 54).

Another frequency-domain approach utilizes *transfer function analysis*, which derives the function of the autoregulatory system by examining how well the autoregulatory system is able to dampen oscillations in systemic blood pressure. Rather than using pre-defined thresholds, this technique utilizes natural low-frequency fluctuations in both the blood pressure and CBF. The resulting output resembles a band pass filter (**Figure 4**), with dampening of low-frequency oscillations around the Mayer wave frequency (0.1 Hz). There is also a developmentally linked component to this dampening, with increased dampening found in infants of increasing gestational age (21).

LINK BETWEEN DYSFUNCTION IN AUTOREGULATION AND BRAIN INJURY

There are many interconnected modulators of vascular tone, governed by a mix of local and central mechanisms, each of which contributes to the overall function of autoregulation. The most potent endogenous factors include the partial pressures of carbon dioxide and oxygen, and the autonomic nervous system. CO_2 exerts a direct vasodilatory effect, leading to excessive oxygenation, even without supplemental oxygen delivery, if left

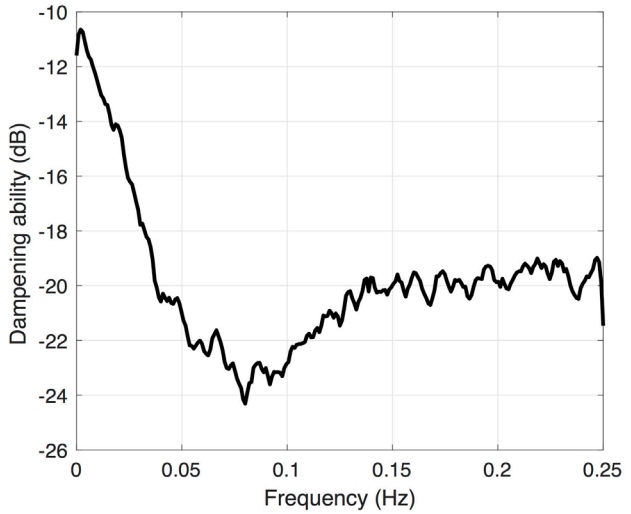

FIGURE 4 | Transfer function gain coefficient calculated between the mean arterial blood pressure and cerebral oxygenation. Note the increased dampening (more negative value) around 0.1 Hz.

unchecked (41) with small increases in CO_2 leading to profound increases in CBF. Oxygen, or more specifically hypoxia, provides a similar response; the degree of vasodilation is inversely correlated with the partial pressure of oxygen. Acute hypoxia can lead to dramatic increasing in vasodilation, and thus CBF (55). The autonomic nervous also plays an important role, with counterbalancing release of nitric oxide and catecholamines in response to sympathetic and parasympathetic stimulation (56).

As a result of this constellation of factors, maintenance of stable CBF in the vulnerable preterm infant is tenuous. Many complicating clinical factors have been linked to causing or worsening the dysfunction of the autoregulatory system including hypotension (20), hypoxic-ischemia (57, 58), seizures (59), inotropic medications (60), and possibly even IVH itself (21).

Brain injury, in the form of hypoxia–ischemia–reperfusion, is the common end result of the failure of the autoregulatory system, regardless of the contributing factors. Early in the course of hospitalization, repeated episodes of ischemia and reperfusion likely lead to weakening and then rupture of the fragile germinal matrix vessels. Indeed, impaired autoregulation has been clearly identified in infants with IVH (20, 21). This mechanism is also a likely contributing factor to WMI, where repeated episodes of ischemia, from a mismatch of perfusion and metabolic demand, accumulate in the periventricular white matter, a region with relatively limited vascular supply at this stage of development. Repeated events undoubtedly lead to neuronal death and start the cascade of events leading to gliosis and fiber loss. The threshold at which either form of brain injury occurs is not known at this time.

THE NEXT STEP—TRANSLATION TO THE BEDSIDE

While much has been learned about the function of the cerebrovascular autoregulatory system in premature infants and its role in the pathogenesis of brain injury, there are a number of key factors in translation which remain to be solved before a bedside "autoregulation monitor" can be implemented.

Primary among them is developing a consensus on the approach to quantification. Although each of the described approaches converges on essentially the same results, the approaches are quite disparate. The ideal system would be readily reproducible across patient populations and clinical confounders. It is possible that the best approach is, in fact, a hybrid of above methods, each contributing an important component of knowledge.

Another key factor is the source of data for quantification. All of the current approaches require the use of NIRS and invasive arterial blood pressure monitoring. These sources of information allow one to readily model the input and output sides of autoregulation, but obtaining these data is costly and may not be feasible or practical. Future investigation should focus on other sources of data (e.g., ECG and pulse oximetry), which may provide some of the same data, without the need for separate, invasive equipment.

In addition to the hemodynamic data provided by the approaches outlined above, a complete brain monitoring system should also include functional measures. This could most easily be accomplished by the use of amplitude integrated EEG (aEEG), which is able to provide information about the general background activity of the brain as well as detection of seizures, a well-described methodology in the neonatal population (61). This information would allow real-time feedback as the effects of impaired autoregulation and may help to better discriminate between transient asymptomatic aberrations or more consequential ones (62).

Finally, and most crucially, techniques for manipulating the autoregulatory system through hemodynamic intervention (e.g., the targeted use of inotrope medications) while guided by instantaneous measurement will allow for the advancement of neuroprotective strategies. To date, studies have focused on *ex post facto* examination of recorded data. Developing a real-time autoregulation monitor, along with methods for responding to the readout, will be essential for this to be part of a successful neuroprotection strategy (63).

CONCLUSION

In conclusion, the incidence of the two most common forms of brain injury in preterm infants, such as IVH and white matter, remains distressingly high, and current strategies for neuroprotection do not extend beyond acknowledgment of static demographic risk factors. One potential target is augmenting the function of the cardiovascular system through anti-hypotensive therapies, including inotropes and fluid resuscitation, yet there is a lack of consistent data as to the lower limit of arterial blood pressure, which confers an increased risk of brain injury. A bedside monitor capable of demonstrating the function (dysfunction) of the autoregulatory system, aided with integration of a secondary source of information such as aEEG, will allow for personalized blood pressure management, avoiding overtreatment of "hypotension" in infants with intact autoregulation and enhancing recognition

of poor cerebrovascular health in infants with "normal" blood pressures.

AUTHOR CONTRIBUTIONS

ZV participated in the conceptualization of the manuscript, wrote the initial draft, and approved the final version as submitted. AM participated in the conceptualization of the manuscript, provided a critical review of the manuscript, and approved the final version as submitted.

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REVIEW
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Monitoring Cerebral Oxygenation in Neonates: An Update

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Cerebral oxygenation is not always reflected by systemic arterial oxygenation. Therefore, regional cerebral oxygen saturation ($rScO_2$) monitoring with near-infrared spectroscopy (NIRS) is of added value in neonatal intensive care. $rScO_2$ represents oxygen supply to the brain, while cerebral fractional tissue oxygen extraction, which is the ratio between $rScO_2$ and systemic arterial oxygen saturation, reflects cerebral oxygen utilization. The balance between oxygen supply and utilization provides insight in neonatal cerebral (patho-)physiology. This review highlights the potential and limitations of cerebral oxygenation monitoring with NIRS in the neonatal intensive care unit.

Keywords: near-infrared spectroscopy, cerebral oxygenation, neonates, neonatal intensive care, neonatal neurology

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INTRODUCTION

It has been nearly 8 years, since our research group published a review on the value and pitfalls of cerebral oxygenation monitoring with near-infrared spectroscopy (NIRS) in neonatology (1). Since then, research into cerebral NIRS has taken an impressive flight. The importance of cerebral oxygenation and perfusion monitoring has been increasingly recognized in neonatal intensive care. In this review, the development of cerebral NIRS monitoring over the past years is summarized.

Value of Cerebral Oxygenation Monitoring

Unfortunately, brain injury is still common in preterm neonates and can lead to a wide range of complications later in life, such as behavioral, attentional, cognitive, sensorimotor or language impairments, and epilepsy (2). Both the increasing number of preterm infants and improved survival rates contribute to the prevalence of neonatal brain injury (3, 4). Preterm infants are particularly susceptible to brain injury as the brain undergoes rapid development during the last trimester of pregnancy. During this period, the brain does not only increase in volume but also undergoes increasing gyri- and sulcification and myelination and improves connectivity (5). Pre-oligodendrocytes and axons mature, the transient subplate neurons appear, and the cerebellum develops and matures. Throughout this process, the brain is using substantial amounts of oxygen (2, 6, 7). Cerebral pathology can present as white matter injury, such as periventricular leukomalacia, or as periventricular–intraventricular hemorrhage (PIVH) (2). Inadequate or fluctuating cerebral perfusion and oxygenation can result in brain injury (8). Hyperoxia, hypoxia, and fluctuations in

Abbreviations: aEEG, amplitude-integrated electro-encephalography; cFTOE, cerebral fractional tissue oxygen extraction; NIRS, near-infrared spectroscopy; PDA, hemodynamically significant patent ductus arteriosus; PIVH, periventricular–intraventricular hemorrhage; RDS, respiratory distress syndrome; $rScO_2$, regional cerebral oxygen saturation; SaO_2, arterial oxygen saturation; TOI, tissue oxygenation index.

cerebral oxygenation, indicative of poor cerebral autoregulation, can adversely affect brain development (9–12).

Vital parameters such as blood pressure, heart rate, and pulse oximetry [arterial oxygen saturation (SaO_2)] are important to assess the condition of the neonate but do not directly assess brain oxygenation (13, 14). NIRS-monitored regional cerebral oxygen saturation ($rScO_2$) is a non-invasive and elegant method to monitor global brain oxygenation. $rScO_2$ monitoring can be used at bedside for extended periods of time (up to several days) without side effects. Other methods that examine the brain, such as cranial ultrasound or MRI, do not allow for continuous monitoring. NIRS can be used even in the sickest infants and requires minimal handling of the infant. The device can be used at bedside in the NICU as well as during surgery or transportation (15). NIRS can easily be combined with monitoring of cerebral electrical activity by amplitude-integrated electro-encephalography (aEEG).

NIRS Technique

The NIRS technique is based on the relative transparency of biological tissue to light. Neonatal cerebral tissue can easily be penetrated by NIR light (700–1,000 nm) due to thin overlaying layers of skin and skull. An emitter sends light of the near-infrared spectrum through cerebral tissue in a semi-curved shape to a detector, approximately 2–3 cm in depth (16). Oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin absorb the NIR light at different wavelengths, together accounting for total Hb ($THb = O_2Hb + HHb$). Differences in NIR light absorption are detected by the sensor and used to calculate the concentrations of Ohb and HHb according to the modified law of Lambert–Beer. The ratio between O_2Hb and HHb is expressed as the $rScO_2$ or tissue oxygenation index (TOI), depending on the manufacturer of the NIRS device. Previous research has shown good correlation between TOI and $rScO_2$ (17, 18). The NIR light is absorbed by HHb and O_2Hb in both arterial and venous vessels, in a 25:75% ratio, and thus NRS reflects mainly cerebral venous oxygen saturation (19). The NIR light is absorbed by both superficial tissues and the cerebral cortex. When two or more detectors are used, the deeper signal reflecting cerebral cortex oxygenation can be distinguished from the superficial signal, reducing the influence of scattering. The technical details of NIRS are beyond the scope of this review but are well described elsewhere (20–23). Most commercially available devices utilize the continuous-wave technique, which measures the attenuation (or absorption) of NIR light from a continuous light source to calculate oxygenation (24). Other NIRS techniques, such as time-resolved spectroscopy and frequency-resolved spectroscopy, are now able to assess cerebral blood volume and quantify absolute concentrations of HHb and O_2Hb, respectively. However, these techniques have not yet been proved practically useful in neonatal care (24).

Sensors and Devices

Today, there are several different NIRS devices and sensors commercially available. A number of comparative studies have shown that the overall correlation between NIRS devices is acceptable, although they differ in technique and algorithm (25–27). Smaller and more flexible sensors have been designed for neonatal use. However, these neonatal sensors measure 10% higher compared to the adult sensors (28, 29). Since the upper limit of most devices is set to 95%, high cerebral oxygenation values as measured by the neonatal sensors are shown as a flat line in which all variation is lost, as demonstrated in **Figure 1A**. NIRS device and sensor type must be taken into account when NIRS monitoring of cerebral oxygenation is applied in clinical care. Reference values for the neonatal sensor have been published (see below) (29).

Validation

Regional cerebral oxygen saturation represents a mixed saturation largely determined by the venous component (75%), which is why NIRS validation studies have often focused on venous saturation (19). However, venous saturation does not reflect mixed arterial and venous saturation as NIRS does, and there is no "gold standard" to measure venous oxygen saturation (30). A good correlation has been reported between oxygen saturation in the jugular vein and NIRS-monitored cerebral oxygenation, with a mean difference of 5%, for different manufacturers (Hamamatsu, INVOS, CAS-MED) (31–34). However, the difference between jugular venous oxygen saturation and regional cerebral oxygenation may increase during hypoxia. This is presumably caused by an increased arterial contribution to the NIRS signal due to cerebral arterial vasodilatation as a response to hypoxia (35). Cerebral fractional tissue oxygen extraction (cFTOE) has been validated against central cerebral venous saturation in newborn piglets (36). Brain perfusion assessment with NIRS has been compared to perfusion assessment with MRI, which has shown strong correlations (37, 38). Both $rScO_2$ and TOI have shown good reproducibility (39, 40).

Reference Values

Several studies have analyzed changes in $rScO_2$ with advancing postnatal age. $rScO_2$ is between approximately 40 and 56% directly after birth (irrespective of delivery mode) (41–43), increases up to 78% in the first 2 days after birth (44) and then slowly stabilizes during 3–6 weeks after birth with values between 55 and 85% (45–47). Several studies have published reference ranges immediately after birth, which show a gradual increase during the first 15 min of life (42, 46). A recent study by Alderliesten et al. provides reference values based on a large study cohort during the first 72 h of life in preterm infants [<32 weeks gestational age (GA); $n = 999$]. The data are converted into reference curves stratified for different GAs which can be used for cot side interpretation of $rScO_2$ and cFTOE values, as shown in **Figure 1B** (29). These reference values, obtained with the (small) adult sensor (SomaSensor SAFB-SM, Covidien, Mansfield, MA, USA), will facilitate clinical application of cerebral oxygenation monitoring. As stated above, it is important to realize that neonatal sensors of various NIRS manufacturers display higher values (up to 10%) as compared to adult sensors (28).

CLINICAL APPLICATION

Gaining insight into the oxygenation of the neonatal brain can be of important clinical value, as a large share of neonatal pathology is brain associated. NIRS monitoring of cerebral oxygenation can be considered in several clinical situations as outlined below.

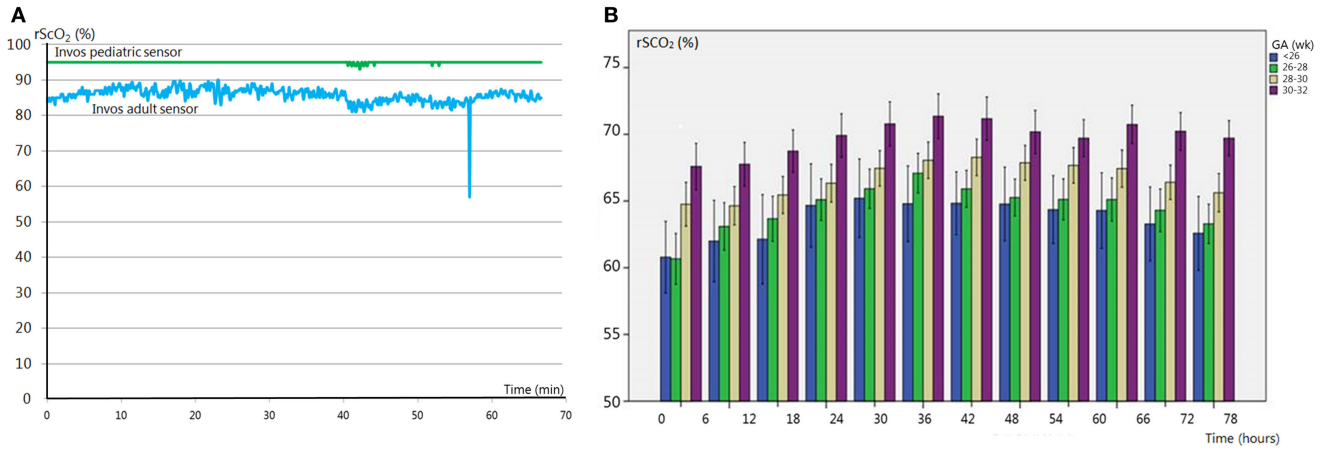

FIGURE 1 | **(A)** Regional cerebral oxygen saturation ($rScO_2$) monitored with an adult (blue line) and pediatric (green line) sensor. Hyperoxia values are untraceable with the pediatric sensor due to the cutoff value of 95%. **(B)** Reference values [stratified for gestational age (GA)] of $rScO_2$ in premature infants (GA < 32 weeks). Adapted from Ref. (29).

Cerebral Oxygenation and the Patent Ductus Arteriosus

The hemodynamically significant patent ductus arteriosus (PDA) remains a controversial topic. Clinicians and researchers are still debating whether or not it should be treated, what the best treatment strategy is and when would be the best time to intervene (48–51). Unfortunately, the brain is rarely included in this discussion. A PDA can negatively influence cerebral oxygenation. Shunting of the blood through the duct away from the brain has a profound negative effect on $rScO_2$. This effect is independent from SaO_2, which remains within normal limits during a PDA (13, 52). Cerebral oxygenation normalizes after ductal closure (13, 52). The ductal diameter is associated with cerebral oxygenation, where a larger diameter (indicating a significant left to right ductal shunt) is associated with lower $rScO_2$ (52). Infants who need surgical PDA closure are often exposed to low $rScO_2$ values for a longer period of time, as shown in **Figure 2A**, and are therefore at risk of cerebral injury (14). Additionally, a further reduction in cerebral oxygenation occurs during ductal surgery (53, 54). Weisz et al. reported an increased risk of neurodevelopmental impairment in infants after surgical ductal ligation compared to pharmaceutically treated infants (55). More specifically, underdevelopment of the cerebellar structure has been reported in infants who needed surgical closure (14). Extended episodes of low cerebral oxygenation are most likely responsible for this phenomenon (14).

Cerebral Oxygenation and Respiration

Preterm infants often require respiratory support, which can affect cerebral hemodynamics and cerebral oxygenation (56, 57). An earlier study reported NIRS-monitored changes in cerebral blood flow (CBF) during continuous positive airway pressure and artificial ventilation. CBF significantly correlated with the type of respiratory support, leading to the conclusion that ventilation can impact cerebral circulation (58). Cerebral oxygenation can also be affected by the type of ventilation support during surgery (59).

Ventilation is the main regulatory mechanism of arterial carbon dioxide pressure (pCO_2). pCO_2 can affect the brain by altering cerebral arterial vessel diameter, where hypercapnia can induce cerebral vasodilatation and hypocapnia induces vasoconstriction (60). As such, pCO_2 can affect cerebral perfusion and oxygenation, and both hyper- and hypocapnia have been associated with neuropathology (61, 62). An increase in pCO_2 is accompanied by an increase in cerebral oxygen saturation with a decrease in oxygen extraction (63, 64). Acute fluctuations in pCO_2, even within the normal range, appear to directly affect the neonatal brain perfusion (personal communication). The pCO_2-induced changes in cerebral perfusion and oxygenation can be monitored by NIRS, as shown in **Figure 2B**, in order to identify and prevent pCO_2-induced cerebral hypo- or hyperperfusion and brain damage.

Other factors related to respiration have also been shown to influence cerebral oxygenation. Apneas, for example, can affect brain oxygenation, and high mean airway pressure during artificial ventilation can also reduce cerebral oxygenation (1, 65–67). Also, infants with respiratory distress syndrome (RDS) have lower cerebral oxygenation and increased variance in $rScO_2$ and cFTOE during the first 3 days after birth (68, 69). Moreover, they often have an impaired cerebral autoregulation, which may further predispose them to cerebral injury (70). Combining arterial blood pressure and cerebral oxygenation measures can help to identify (lack of) cerebral autoregulation (see below).

Cerebral Oxygenation and Autoregulation

Cerebral autoregulation is the ability to maintain stable cerebral perfusion and oxygenation during fluctuations in blood pressure (71). Hypotension can cause a severe reduction in cerebral perfusion and impairment of cerebral autoregulation, leading to inadequate perfusion (72). Combining $rScO_2$-monitoring with arterial blood pressure monitoring enables assessment of cerebral autoregulation (73). Prematurity is a risk factor for impaired

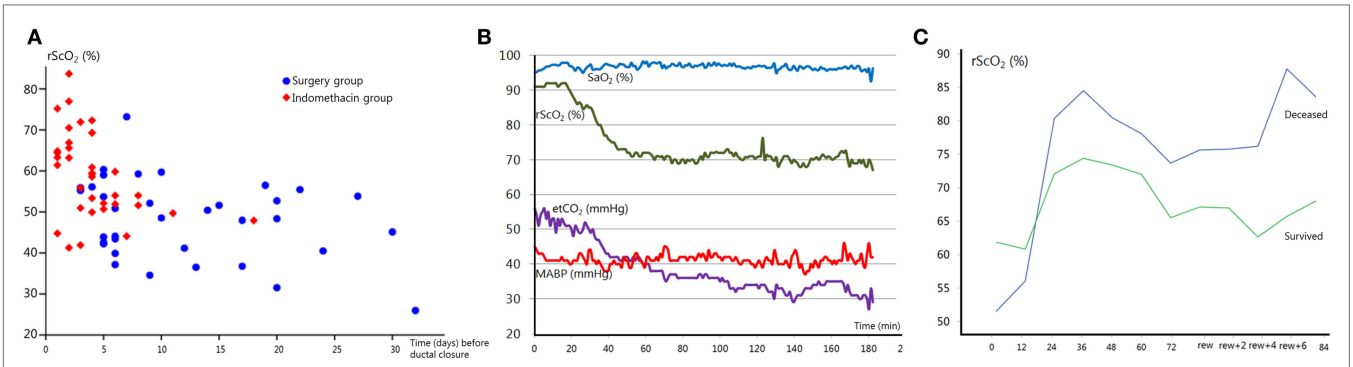

FIGURE 2 | **(A)** Regional cerebral oxygen saturation ($rScO_2$) just before ductal closure in patients treated with indomethacin (red squares) or surgery (blue circles) as a function of postnatal age in days. Note that the majority of infants requiring surgical treatment are exposed to the lowest $rScO_2$ values for a longer period. Adapted from Ref. (14). **(B)** Acute end-tidal CO_2 ($etCO_2$) decrease results in a subsequent reduction in $rScO_2$, on the contrary arterial oxygen saturation (SaO_2) remains stable. MABP, mean arterial blood pressure. **(C)** $rScO_2$ during hypothermia and after rewarming (rew) in two severely asphyxiated infants. The infant with an adverse outcome (blue line) showed higher $rScO_2$ values compared to the infant that survived (green line). Cerebral fractional tissue oxygen extraction values (not shown) mirrored $rScO_2$ values.

autoregulation, and even small variations in blood pressure can affect cerebral oxygenation in clinically sick and unstable babies (48, 74). Cerebral autoregulation can indeed be affected in several clinical situations that are commonly seen in preterm infants. Our group has previously demonstrated that RDS predisposes for lack of cerebral autoregulation (70). Autoregulation might also be impaired during surgery and high concentrations of positive inotropes such as dopamine (11, 49). Impaired autoregulation has been linked to poor neurodevelopmental outcome (50). Evaluating cerebral autoregulation at bedside can identify episodes of impaired autoregulation, and appropriate measures can be initiated to stabilize cerebral perfusion and oxygenation. Cerebral autoregulation can be computed in different ways, and software to calculate autoregulation at bedside is currently being developed (51). In summary, cerebral autoregulation may become impaired, especially in the unstable (preterm) infant, predisposing these neonates to brain injury. This underlines the importance of cerebral oxygenation an autoregulation monitoring in the early neonatal period (75).

Cerebral Oxygenation and Hypotension

Cerebral oxygenation can play an important role in assessing hypotension and whether positive inotropic therapy is indicated. There is an increasing awareness that the current definitions of *hypotension of prematurity* do not always reflect true hypotension. Permissive hypotension is increasingly accepted, unless there are (clinical) signs of hypoperfusion (76–78). As already stated above, hypotensive treatment is not without side effects and may have adverse effects on outcome (11, 79). Cerebral oxygenation plays an important role as a marker of end-organ oxygenation and can help making decisions whether or not treatment for hypotension is indicated. Other parameters such as blood gasses, urine production, and capillary refill should be taken into account. Identifying small reductions in blood pressure that do not affect cerebral oxygenation, and systemic perfusion might prevent unnecessary treatment with inotropes (78, 80). Monitoring $rScO_2$ and cerebral autoregulation during neonatal surgery is important to prevent hypotension-related injury to the immature brain (see also below) (81). Our research group is currently involved in a prospective study (the TOHOP study) to find an answer to the question at which stage hypotension treatment is warranted (TOHOP; http://ClinicalTrials.gov identifier: NCT01434251).

Cerebral Oxygenation and Small-for-Gestational-Age (SGA) Neonates

Preterm infants who are born SGA show higher cerebral oxygenation during the first postnatal days (29, 82). This is most likely related to the prenatal blood flow redistribution of the intrauterine growth restricted (IUGR) fetus, in an attempt to preserve oxygen supply to the brain (brain sparing effect) (83). However, this does not necessarily protect against cerebral injury, and infants born following IUGR are at an increased risk of neurodevelopmental impairment (84, 85). In case of a PDA, SGA infants demonstrated a significantly larger fall in cerebral oxygenation, as compared to AGA infants (86).

Cerebral Oxygenation and Neurodevelopmental Outcome

Disturbances in cerebral perfusion and oxygenation are major contributors to neonatal brain injury, increasing the risk of impaired neurodevelopmental outcome (8, 87). Infants are particularly susceptible to brain injury during the first 3 days after birth, when major hemodynamic transitional changes occur. A large international randomized controlled trial, the SafeboosC study (Safeguarding the brains of out smallest children), has investigated whether it is possible to reduce the hypoxic and/or hyperoxic burden on the immature brain with cerebral oxygenation monitoring, in order to prevent neurological damage and to improve outcome (88). The study has shown that disturbances in cerebral oxygenation could be identified with NIRS. A treatment protocol prescribed treatment steps to restore normal brain oxygenation. The burden of hypoxia (and hyperoxia), as expressed by the percentage of time spend outside the normal range of

$rScO_2$ (55–85%), was significantly lower in the group with (visible) NIRS monitoring as compared to the blinded control group (median 36.1 vs. 81.3%) (47). This difference was mainly due to a reduction in hypoxic episodes.

Impaired cerebral oxygenation below the threshold of 55% appears to affect neurodevelopmental outcome at 15 and 24 months corrected age (personal communication). Poor cerebral autoregulation, examined by the correlation between $rScO_2$ and arterial blood pressure, has been be associated with an increased risk score predictive of neonatal mortality and morbidity (CRIB II) (89).

Several studies, in newborn animals and humans, showed that $rScO_2$ values consistently below 40% (measured with adult sensors) are related to brain damage (90–92). Other clinical studies showed that low cerebral oxygen saturation immediately after birth (<15 min) is associated with PIVH (93). In accordance with these results, low cerebral oxygenation during the first 48 h after birth was associated with death or severe PIVH in a study by Cerbo et al. (94). Similarly, increased oxygen extraction cFTOE can precede development of PIVH (95, 96).

Cerebral Oxygenation and Red Blood Cell Transfusions

Several studies have shown a significant increase in cerebral oxygenation after red blood cell transfusions in anemic infants (97, 98). The infants with the lowest pre-transfusion $rScO_2$ values seem to benefit the most from transfusions (99). Similarly, high cFTOE levels (>0.4) can indicate an imbalance between cerebral oxygen supply and demand, which may underline the need for red blood cell transfusion (100). This indicates that cerebral oxygenation monitoring might be useful as a marker to identify infants with high cFTOE and/or low $rScO_2$ who might benefit from blood transfusions (100–102).

Cerebral Oxygenation and Neonatal Surgery

Infants with cardiac or non-cardiac anomalies may require major surgery in the first few months after birth (103). Exposure to neonatal surgery can put the immature brain at risk (104, 105). An increased risk of neurodevelopmental delay after neonatal surgery has indeed been reported (106, 107). Both the procedure as well as anesthetics can be harmful (108–110). Monitoring cerebral oxygenation during surgery to increase cerebral safety is therefore advised (111–116). Perioperative monitoring evaluates brain oxygenation pre- and postsurgery, while intraoperative monitoring can assist surgeons and anesthesiologists to optimize cerebral oxygenation during the procedure to protect the neonatal brain (113, 117, 118). During surgery, cerebral NIRS can detect episodes of hypoxia more reliably than arterial SaO_2 monitoring (114, 119). Introduction of cerebral oxygenation monitoring during cardiac surgery has improved intraoperative transfusion management (120). Cerebral oxygenation monitoring can also reflect changes in vital parameters during cardio-pulmonary bypass (121).

Cerebral Oxygenation and Hypoxic-Ischemic Encephalopathy (HIE)

Previous studies have demonstrated that $rScO_2$ is increased and cFTOE is decreased during the first days after severe birth asphyxia, and these findings have been correlated with an adverse outcome at 2 years of age (Griffiths Mental Developmental scales) (122, 123) (see also **Figure 2C**). NIRS monitoring combined with simultaneous assessment of aEEG background patterns has a strong prognostic value for long-term neurodevelopmental outcome. High cerebral oxygenation with an abnormal aEEG background pattern (low electrical activity) in severely asphyxiated neonates with hypothermia treatment at 12 h of age has a positive predictive value of 91%, absence of these results in a negative predictive value of 100% (123). These findings strongly suggest that NIRS monitoring of cerebral oxygenation can have an important role in the (early) prognosis of neurodevelopmental outcome. Cerebral hyperoxygenation in neonates with an adverse outcome is most likely explained by low energy metabolism after severe brain injury with low oxygen utilization, cerebral hyperperfusion, and impaired autoregulation of the cerebral vascular bed (124, 125). These findings have been confirmed in other studies, incorporating MRI (126). Cerebral oxygenation with NIRS correlates strongly with CBF as assessed by arterial spin labeled MRI in infants with severe HIE (37).

LIMITATIONS

Hair, dark skin, and interfering light from other sources such as phototherapy devices can pose a problem during NIRS monitoring (1). Subdural edema or hematoma below the sensor might also interfere with measurements (127) in small infants, placement of the electrode might be challenging if they also require simultaneous aEEG monitoring. The curvature of the skull and head circumference has been mentioned as potential limitations (24). However, Alderliesten et al. did not find a correlation between head circumference and $rScO_2$, stating that influence of head curvature seems unlikely (29). As previously discussed, type of NIRS device and sensor must be taken into account when interpreting cerebral oxygenation values (28).

CONCLUSION

Injury to the immature brain remains a major contributor to neonatal mortality and morbidity. Monitoring vital parameters provides us with critical information concerning the condition of the infant but does not offer direct information regarding brain oxygenation and perfusion. Cerebral oxygenation monitoring with NIRS, at least during the vulnerable transition period throughout the first 3 days after birth, provides the clinician with additional important information. Several clinical conditions can affect brain oxygenation, and studies have shown that systemic oxygen saturation does not always reflect cerebral oxygenation. The assessment of neonatal brain oxygenation (and perfusion) can be extremely useful in the clinical setting. It has the potential to guide clinical management in order to

prevent brain injury and to avoid unnecessary treatment. It may also provide important information regarding the infant's prognosis.

AUTHOR CONTRIBUTIONS

LD determined review subjects, collected, analyzed, and included the literature, drafted the initial manuscript, and approved the final manuscript and is accountable for all aspects of the manuscript. FvB and PL determined review subjects, interpreted the literature, reviewed and revised the manuscript, and approved the final manuscript and are accountable for all aspects of the manuscript.

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Cerebral Tissue Oxygenation during Immediate Neonatal Transition and Resuscitation

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This article provides a review of cerebral tissue oxygenation during immediate transition after birth in human neonates. Recommended routine monitoring, especially if resuscitation is needed, during this period includes arterial oxygen saturation and heart rate measured by pulse oximetry and electrocardiogram. However, there is increasing interest to monitor in addition with near-infrared spectroscopy (NIRS) the oxygenation of the brain. There is a different pattern of increase between cerebral tissue oxygenation and arterial oxygen saturation during the immediate transition, with cerebral tissue oxygenation reaching a plateau faster than arterial oxygen saturation. Differences can be explained, since cerebral tissue oxygenation is not only affected by arterial oxygen saturation but also by cerebral blood flow, hemoglobin content, and cerebral oxygen consumption. Normal values have already been established for different devices, gestational ages, and modes of delivery in neonates without any medical support. Cerebral hypoxia during immediate transition might cause brain damage. In preterm neonates with cerebral hemorrhage evolving in the first week after birth, the cerebral tissue oxygenation is already lower in the first minutes after birth compared to preterm neonates without cerebral hemorrhage. Using cerebral NIRS in combination with intervention guidelines has been shown to reduce the burden of cerebral hypoxia in preterm neonates. Cerebral tissue oxygenation during immediate transition seems to have an impact on outcome, whereby NIRS monitoring is feasible and has the advantage of continuous, non-invasive recording. The impact of NIRS monitoring and interventions on short- and long-term outcomes still need to be evaluated.

Keywords: cerebral tissue oxygenation, monitoring, neonate, transition, resuscitation

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INTRODUCTION

Transition from fetus to newborn is a complex physiological process. Monitoring this process to recognize perturbations is crucial but remains challenging. Initial assessment of neonates is usually based on visual inspection, palpation and/or auscultation, and response to stimuli. Until recently, decision to start and to guide medical support was based mainly on clinical assessment including muscle tone, reflexes, breathing, heart rate, and skin color. These parameters are summarized in the Apgar score, which was introduced by Apgar in 1952 (1). Her intention was to standardize

clinical assessment and establish an objective prognostic tool. The Apgar score is now used routinely around the world due to the easy and fast application (2, 3). Several studies tried to establish associations between low score and short- and long-term outcome. However, there is a high interobserver variability especially in preterm neonates and neonates, who are in need of medical support (4–7).

Especially in preterm neonates, minimal handling and non-invasive monitoring is preferred. Recommended routine monitoring includes therefore pulse oximetry with measuring arterial oxygen saturation and heart rate on the one hand and electrocardiography (ECG) to monitor heart rate on the other hand (8–10).

Conflicting observations on heart rate were made when pulse oximetry was used in comparison to ECG (9, 11). Differences occur especially in the first minutes after birth (11). According to recent resuscitation guidelines, both methods for heart rate monitoring can be used during resuscitation and/or continued respiratory support (10). Concerning arterial oxygen saturation monitoring, there is an ongoing discussion what target saturation should be used, if the neonate needs respiratory support and oxygen supplementation. The resuscitation guidelines recommend the 25th percentile of published normal values for target saturation at different time points during the first minutes after birth (10).

However, recommended monitoring of vital signs does not include monitoring of the brain, one of the most vulnerable organs especially to hypoxia during transition immediately after birth. At the moment, only clinical assessment of neurological behavior and examination of muscle tone and reflexes of the newly born neonate is recommended to assess status of the brain. In the last decades, different methods of monitoring during the immediate transition after birth have been tried and described.

First, there is Doppler sonography with the advantage of non-invasive monitoring the cerebral perfusion of different regions of the brain. However, this method is limited since it is affected by movement of the infant and parameters cannot be acquired continuously. Furthermore, it is technically difficult to perform during immediate transition (12).

Second, amplitude integrated electroencephalography enables measurement of cerebral activity with the advantage of continuous, non-invasive recordings and is also limited by the technical difficulties of sampling and interpretation due to artifacts (12).

Third, there is the monitoring of cerebral tissue oxygenation by means of near-infrared spectroscopy (NIRS)—a method that enables to monitor both, changes in cerebral oxygenation and perfusion. There is an increasing interest to apply NIRS during immediate transition after birth. This article provides a review of the literature (**Table 1**) on cerebral regional oxygenation measured with NIRS during the immediate transition after birth in human neonates.

TABLE 1 | Cerebral tissue oxygenation immediately after birth in human neonates.

Reference	Term/preterm	Device	Study type
Peebles et al. (13)	Term	/	Case report
Isobe et al. (14)	Term	IMUC 7000	Observational
Isobe et al. (15)	Term	IMUC 7000	Observational
Fauchère et al. (16)	Term	NIRO 300	Observational
Urlesberger et al. (17)	Term	INVOS 5100	Observational
Urlesberger et al. (22)	Term	INVOS 5100	Observational
Fuchs et al. (19)	Preterm	FORESIGHT	Observational
Kratky et al. (18)	Term	INVOS 5100	Observational
Noori et al. (26)	Term	INVOS	Observational
Fuchs et al. (20)	Preterm	FORESIGHT	Observational
Binder et al. (30)	Preterm	INVOS 5100	Observational
Urlesberger et al. (22)	Term	INVOS 5100	Observational
Pichler et al. (39)	Term	INVOS 5100	Observational
Pichler et al. (35)	Term/preterm	INVOS 5100	Observational
Almaazmi et al. (24)	Term	FORESIGHT	Observational
Hessel et al. (37)	Term	INVOS/ FORESIGHT	Observational
Karen et al. (25)	Term	NIRO 300	Observational
Li et al. (21)	Preterm	INVOS 5100	Case report
Schwaberger et al. (31)	Preterm	INVOS 5100	Observational
Baik et al. (36)	Term	NIRO 200 NX	Observational
Baik et al. (41)	Preterm	INVOS 5100	Observational
Kenosi et al. (38)	Preterm	INVOS 5100	Observational
Montaldo et al. (23)	Term	Nonin	Observational
Pocivalnik et al. (34)	Term	INVOS 5100	Observational
Schwaberger et al. (29)	Preterm	NIRO 200 NX	RCT
Schwaberger et al. (33)	Term	NIRO 200 NX	Observational
Baik et al. (28)	Preterm	INVOS 5100	Observational
Pichler et al. (42)	Preterm	INVOS 5100	RCT
Pichler et al. (32)	Preterm	INVOS 5100	Observational
Tamussino et al. (40)	Term	INVOS 5100	Observational

DISCUSSION

Peebles et al. described measurements of cerebral hemodynamics using NIRS during immediate transition after birth of a healthy term neonate in 1992 for the first time (13). The NIRS sensors were applied to the head of the neonate during labor before birth. They were able to demonstrate rapid changes in cerebral oxygenation during fetal to neonatal transition especially with onset of respiration. Unfortunately, it took a decade until first studies using cerebral NIRS immediately after birth were reported (14, 15), and another 10 years until studies were performed to monitor cerebral tissue oxygenation and hemodynamics using NIRS immediately after birth.

In the last decade, several studies have demonstrated feasibility of cerebral NIRS during immediate transition in healthy term neonates (13–18), preterm neonates (19, 20), and even during resuscitation with chest compressions (21).

Cerebral tissue oxygenation can be obtained quickly within 2 min after birth, thus enabling continuous non-invasive monitoring immediately after birth. Several studies have demonstrated that cerebral oxygenation changes differently within the first minutes after birth when compared to arterial oxygen saturation, heart rate, or even peripheral tissue oxygenation (17, 22). Cerebral tissue oxygenation reaches a plateau faster compared to arterial oxygen saturation, thus indicating that there might be a preferential oxygen delivery to the brain in the first minutes after birth (17, 23). Furthermore, changes in cerebral tissue oxygenation and arterial oxygen saturation depend on mode of delivery (15, 22, 24, 25). While arterial oxygen saturation and heart rate changes differently after cesarean section and vaginal delivery,

cerebral tissue oxygenation shows similar changes after both modes of delivery.

Cerebral tissue oxygenation is affected by arterial oxygen saturation and also by cerebral blood flow, hemoglobin content, and cerebral oxygen consumption, which may explain the differences between cerebral tissue oxygenation and arterial oxygen saturation. Cerebral blood flow depends on cardiac output, vascular resistance, and especially during immediate transition on open shunts. Noori et al. demonstrated that ductal shunting rapidly changes from balanced to left to right after birth, with a responsive increase in left ventricular stroke volume (26). Cerebral oxygen saturation increases as arterial oxygen saturation rises during the first minutes. Urlesberger et al. demonstrated that during postnatal transition term infants with left-to-right shunt via the ductus arteriosus have significantly higher cerebral tissue oxygenation values compared to infants without shunts (27). Additionally, shunting from the "foramen ovale" shunting might also have an influence on cerebral perfusion thus cerebral oxygenation. The increasing sum of ductus arteriosus and "foramen ovale" diameters were correlated negatively with cerebral oxygen saturation (28). These data suggest that all shunts have an influence on cerebral tissue oxygenation during immediate neonatal transition. In healthy newborns immediately after birth, there is a significant decrease in cerebral blood volume (29). This is most probably caused by cerebral vasoconstriction due to the steep increase in arterial oxygen tension and may be regarded as a physiological process. This suggests that a reduction in cerebral blood flow is likely due to (i) increase in arterial oxygen content, (ii) shunting via the ductus arteriosus and/or foramen ovale, or (iii) very often a combination of these mechanisms.

Any disturbances during immediate transition and necessary interventions during resuscitation might therefore influence transitional physiological cerebral oxygenation and hemodynamics. Neonates in need of respiratory support have compromised cerebral tissue oxygenation compared to neonates with undisturbed transition. Differences between neonates needing respiratory support and neonates with uncomplicated transition after birth have been observed for cerebral tissue oxygenation as well as for cerebral tissue oxygen extraction (calculated out of arterial oxygen saturation and cerebral tissue oxygen saturation). These observations indicate that decreased cerebral tissue oxygenation in neonates with respiratory support might be due to lower arterial oxygen saturation levels as well as compromised perfusion (30, 31). Delayed cord clamping is an intervention recommended by resuscitation guidelines. However, delayed cord clamping causes lower initial cerebral tissue oxygenation in spontaneous breathing preterm neonates when compared to preterm neonates with early cord clamping (32). This initial lower cerebral oxygenation might be explained by inadequate lung aeration due to delayed adequate respiratory support during delayed cord clamping. Sustained lung inflation, which remains a controversial intervention, might affect cerebral blood volume in preterm neonates during the first minutes after birth (33). Neonates receiving sustained lung inflation had no physiological decrease in cerebral blood volume during the first minutes after birth compared to neonates with conventional respiratory support. The authors of this study hypothesized that after sustained lung inflation an impaired venous return to the heart led to cerebral venous stasis and the potential hazardous differences in cerebral blood volume behavior (33). In term newborns, oropharyngeal suctioning, often routinely performed, did not compromise cerebral tissue oxygenation (34).

Reference ranges have been established in healthy term neonates after vaginal delivery and cesarean section as well as in healthy late preterm neonates after cesarean section with the INVOS 5100 (35). Median (10th–90th percentiles) cerebral regional oxygen saturation measured with INVOS 5100 was 41% (23–64) at 2 min, 68% (45–85) at 5 min, 79% (65–90) at 10 min, and 77% (63–89) at 15 min after birth. Reference ranges have also been established with the NIRO 200 in healthy term neonates (36). Median (10th–90th percentiles) "cerebral tissue oxygenation index" measured with NIRO 200 NX was 56% (39–75) at 2 min, 66% (50–78) at 5 min, 75% (62–85) at 10 min, and 73% (61–84) at 15 min after birth. However, there were differences between these two devices. Differences between NIRS devices are well known, and they are most probably related to differences in algorithms used to calculate values. A comparison of INVOS 5100 and FORESIGHT also reported differences between the two devices (37). The INVOS and FORESIGHT cerebral oxygenation estimates showed oxygenation level-dependent difference during birth transition. Published percentile should therefore only be used as reference range, when the same device, with which a percentile has been established, is used.

Reference ranges have also been published for very low birth weight preterm neonates (19, 20). However, especially in preterm neonates in need of medical support, reference ranges have to be interpreted with caution since percentiles depend on medical support given (e.g., amount of supplemental oxygen, respiratory support). For example, infants given >0.3 FiO_2 are described to have more cerebral hypoxia than infants requiring <0.3 FiO_2 but there is no difference in the degree of cerebral hyperoxia, both in the delivery suite and the NICU (38).

Both, hypoxia and bradycardia, are common events during immediate transition in preterm neonates. In particular, cerebral hypoxia–ischemia may cause perinatal brain injury, which is a major cause of mortality and long-term neurodevelopmental impairment in preterm neonates. Cerebral hypoxia during immediate transition might be associated with alteration in cerebral activity (39), whereby neonates with initially low cerebral activity at birth showed low cerebral tissue oxygenation (<10th percentile), but increased cerebral oxygen extraction (>90th percentile) (40).

Further, preterm neonates requiring respiratory support could have arterial oxygen saturation within normal ranges; however, cerebral tissue oxygenation might remain hypoxic. In a two-center prospective observational cohort study, effects of cerebral tissue oxygenation on perinatal brain injury in preterm infants <32 weeks of gestational age during the immediate neonatal transition (15 min) were examined (41). Neonates, who developed intraventricular hemorrhage during the first week after birth, showed significantly lower cerebral tissue oxygenation already within the first 15 min after birth compared to neonates

without intraventricular hemorrhage. However, no difference between groups in arterial oxygen saturation or heart rate was observed (41).

Furthermore, a prospective randomized controlled pilot study compared supplemental oxygen delivery either via cerebral tissue oxygenation monitoring in addition to arterial oxygen saturation (NIRS-visible group) to arterial oxygen saturation monitoring alone (NIRS-not-visible group) in preterm neonates <34 + 0 weeks of gestation (42). The primary outcomes were burden of cerebral hypoxia (<10th percentile) or hyperoxia (>90th percentile) measured in %minutes cerebral tissue oxygenation during the first 15 min after birth. Overall, in the NIRS-visible-group burden of cerebral hypoxia in %minutes was halved, whereby relative reduction was 55.4%. There was a trend to lower mortality and/or cerebral injury in NIRS-visible-group compared to control group (13 vs. 20%) (42).

In the last decade, several studies have addressed cerebral tissue oxygenation during the immediate transition in term and preterm neonates and have proven feasibility of measurement. Limitation of NIRS includes differences between devices, which should be considered when normative data or data of different studies are compared. Penetration depth of the mainly used devices in neonates is 15–20 mm (half of distance from light emitter to sensor); thus, NIRS mainly measures oxygenation in brain cortex and not the brain stem. Regardless, NIRS provides the advantage of continuous non-invasive measurement of cerebral tissue oxygenation with fast acquisition time (within 2 min after birth) and potentially has a role in guiding medical support and resuscitation in neonates with compromised transition. Current available data demonstrate that cerebral hypoxia can be reduced by monitoring cerebral tissue oxygenation with NIRS in combination with intervention guidelines. The next step would be a larger randomized controlled trial to investigate the effect of cerebral NIRS monitoring in combination with intervention guidelines on short- and long-term outcome in preterm neonates, which is currently underway.

AUTHOR CONTRIBUTIONS

Conception and design; critical revision of the article for important intellectual content; final approval of the article: GP, GS, and BU. Drafting of the article: GP.

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REVIEW
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Understanding the Full Spectrum of Organ Injury Following Intrapartum Asphyxia

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Birth asphyxia is a significant global health problem, responsible for ~1.2 million neonatal deaths each year worldwide. Those who survive often suffer from a range of health issues including brain damage—manifesting as cerebral palsy (CP)—respiratory insufficiency, cardiovascular collapse, and renal dysfunction, to name a few. Although the majority of research is directed toward reducing the brain injury that results from intrapartum birth asphyxia, the multi-organ injury observed in surviving neonates is of equal importance. Despite the advent of hypothermia therapy for the treatment of hypoxic–ischemic encephalopathy (HIE), treatment options following asphyxia at birth remain limited, particularly in low-resource settings where the incidence of birth asphyxia is highest. Furthermore, although cooling of the neonate results in improved neurological outcomes for a small proportion of treated infants, it does not provide any benefit to the other organ systems affected by asphyxia at birth. The aim of this review is to summarize the current knowledge of the multi-organ effects of intrapartum asphyxia, with particular reference to the findings from our laboratory using the precocial spiny mouse to model birth asphyxia. Furthermore, we reviewed the current treatments available for neonates who have undergone intrapartum asphyxia, and highlight the emergence of maternal dietary creatine supplementation as a preventative therapy, which has been shown to provide multi-organ protection from birth asphyxia-induced injury in our preclinical studies. This cheap and effective nutritional supplement may be the key to reducing birth asphyxia-induced death and disability, particularly in low-resource settings where current treatments are unavailable.

Keywords: birth asphyxia, cerebral palsy, HIE, creatine, spiny mouse, AKI, muscle

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INTRODUCTION

Each year approximately four million neonates become seriously deprived of oxygen (O_2) during birth (1). There are numerous obstetric complications that can lead to an asphyxic birth. These can be loosely defined as peripartum in nature, such as placental abruption, vasa praevia (a condition where fetal blood vessels cross the external orifice of the uterus and often rupture), or a hypoxic–ischemic event at birth (2, 3). This latter category includes uterine rupture, shoulder dystocia, cord prolapse, maternal cardiopulmonary arrest, and a difficult or prolonged delivery (4). This transient but potentially catastrophic deprivation of oxygen in the intrapartum period

is thought to be directly responsible for 691,000 deaths and 1.02 million stillbirths each year, making it the fifth most common cause of childhood deaths under 5 years (5–7). For those infants that do survive, the multi-organ damage that can ensue means the risk of developing severe life-long morbidities is high. Intrapartum asphyxia results in a burden of 42 million disability years (DALYs). To put this figure in context, this is twice the DALYs imposed by diabetes (8). Although it is a global issue, recent evaluations of the incidence of intrapartum asphyxia in high income countries, where adequate obstetric care is available during the peripartum period, have incidences ranging from 4.3 to 8.5% of term live births (9). This is in stark contrast to an incidence of around 23% in developing countries where women's health care remains under-resourced and many women delivery at home, without professional assistance (10).

The unpredictable nature of the many obstetric complications that contribute to intrapartum asphyxia, in addition to the multi-organ damage associated with intrapartum oxygen deprivation (11), presents a unique set of challenges to clinical and research professionals in their endeavor to implement effective treatments for intrapartum asphyxia. Despite the burden of intrapartum-related neonatal deaths and morbidities, research investment into intrapartum asphyxia and associated morbidities remains low, potentially due to it being a condition that is most prevalent in low resource settings. When reviewing the research investment into neonatal deaths it is clear that this is an area hampered by the "10/90 gap," meaning only 10% of research expenditure is directed toward 90% of the world's global burden of disease (12). This should be of concern to the medical community, as the Millennium Development Goal to reduce the under-five mortality by two-thirds by 2015 was not achieved (7), and neonatal death is an increasing contributor to this category of childhood survival (13).

One cannot assume there will be a dramatic shift in research investment strategies. Hence, there is a clear need to consolidate our knowledge of the overall pathophysiology of intrapartum asphyxia; evaluate our current approaches to studying intrapartum asphyxia; and develop targeted treatments, keeping in mind the limits on application of highly sophisticated medical interventions in low resource settings. In the following review, we discuss the effects of intrapartum asphyxia on the cerebral, cardiovascular, cardiorespiratory, and musculoskeletal systems, including current treatment/management strategies and their limitations. We then provide an update on the preclinical models available for research into intrapartum hypoxia and assess treatments considered in the pipeline for clinical translation.

THE MULTI-ORGAN EFFECTS OF INTRAPARTUM ASPHYXIA

Characterization of brain injury following intrapartum asphyxia has been the focus of many basic science and clinical investigations. However, in a clinical retrospective study, Hankins et al. (14) observed that for 70% of cases, low oxygen was not the direct cause of hypoxic–ischemic encephalopathy (HIE), but rather HIE was a condition that developed secondary to renal, hepatic, and cardiac dysfunction following birth asphyxia (14). While the brain is the obvious target of interventions to allay progressive damage arising from hypoxia, oxidative stress, and inflammation at birth, the need to protect other vital organs such as the heart, kidneys, lungs, and diaphragm has received much less attention. This is made pertinent by the fact that hypothermia has not been shown to offer protection to the many other organ systems affected by birth asphyxia (15, 16), and also from the plausible possibility that HIE arises *secondarily* to poor cardiorespiratory function in the minutes and hours after an asphyxic birth. These types of studies highlight the true nature of the global oxygen deprivation associated with birth asphyxia and the need to investigate all consequential injury.

Brain

The main clinical outcome observed in severely asphyxiated neonates is brain damage known as HIE. This varies in severity and can be categorized into one of three stages using the Sarnat method, which uses observations of the infant's neuromuscular control, autonomic function, level of consciousness, the presence of seizures, and electroencephalographic recordings (15, 17). For infants surviving birth asphyxia and HIE in the neonatal period, the incidence of long-term poor neurological outcomes, including mental and physical disability, seizures, and cerebral palsy (CP) is high (9).

At a cellular level, there are two phases or waves of brain injury following intrapartum asphyxia, as outlined in **Figure 1** (18–23). The initial phase occurs during and immediately after the insult and is associated with global hypoxia. Delivery and resuscitation of the neonate then leads to apparent stabilization during the first few hours of life. However, there is a second wave of injury, which occurs from around 6 h after birth, and is associated with post-hypoxic or post-ischemic hyperemia. This induces biochemical cascades such as synaptic excitotoxicity, oxidative stress, inflammation, and cytotoxicity (18–20, 22).

Currently, the only effective treatment to reduce the adverse neurological outcomes following birth asphyxia is selective head or whole-body cooling initiated within 6 h of delivery (15). This is aimed at reducing or preventing the second wave

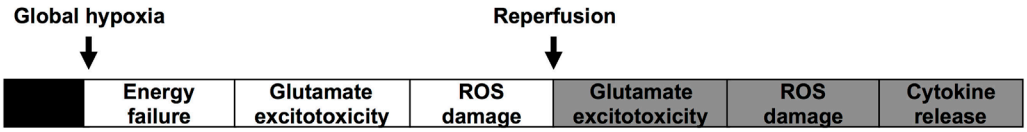

FIGURE 1 | Illustrates the commonly accepted hypothesis for the two waves of energy failure and injury in the brain after asphyxia at birth.

of injury to the brain and is thought to do so by reducing metabolic rate and ameliorating the oxidative stress that ensues (15). However, the need to stabilize the infant during the first few hours of life often delays the initiation of hypothermia, which significantly reduces the effectiveness of this treatment strategy. Even without these necessary clinical delays, therapeutic hypothermia is not a wholly effective treatment. It has been reported that as many as 10 infants need to be treated to prevent one death or major disability (15, 24). Hypothermia has also been reported to have unwanted side effects such as sclerema neonatorum, hypovolemia, glucose instability, pulmonary hypertension, and multisystem organ damage if applied to unaffected neonates (16, 24, 25). Another major limitation of hypothermia as a treatment is that it is only properly deployable in tertiary health centers (8, 15, 26). However, simpler variants such as cold "hot" water bottles have been trialed in a resource-poor hospital in Uganda and shown to be a feasible approach (27). Efficacy of this treatment, however, is yet to be reported.

Cardiac Structure and Function

It is well accepted that the physiological response to hypoxia involves the redistribution of cardiac output to maintain perfusion of vital organs, including the brain, adrenal glands, and the heart (28). However, despite the fact that blood supply to the heart is prioritized during a hypoxic event, both preclinical and clinical studies have reported deficits in cardiac function after birth asphyxia (11, 29, 30). With regard to the heart, newborns who survive intrapartum asphyxia fall into two broad categories: those who are severely ill, require urgent treatment and frequently die of heart failure during the immediate neonatal period; and those who do not have heart related complications and do not require cardiac support (14, 31). One study reported that of 46 cases of severe intrapartum asphyxia that resulted in the neonate developing HIE, 78% exhibited cardiac injury, diagnosed by elevated circulating cardiac enzymes and/or the requirement of volume support for longer than 2 h after birth (14, 15, 17). Various other clinical pathologies have also been reported, including enlargement of the heart (18–23, 32), electrocardiogram abnormalities, signs of myocardial ischemia (18–20, 22, 29, 33), arrhythmias, dysfunction of the atrioventricular valves, and sustained sinus bradycardia, as well as decreased ventricular contractility (11, 15, 29, 30). Hypotension is also a common problem encountered by neonatologists (15, 30, 34–36), often requiring treatment by volume expansion or inotropic drugs (15, 24, 25).

Despite the observation of these functional issues, the immediate and long-term structural consequences of a hypoxic birth for the heart are not well understood, with only minimal histological data reported so far. One study reported abnormalities including evidence of necrosis and phagocytosis, as well as the presence of contraction band necrosis [aggregated clumps of disorganized actin–myosin filaments (16, 24, 25, 37)] in the hearts of asphyxiated near-term lambs (8, 15, 26, 35). Human studies on non-surviving asphyxiated newborns have also reported the appearance of cardiac abnormalities (27, 32, 38), including right ventricular dilation, ventricular hypertrophy, persistent atrial shunting, and papillary muscle necrosis (39, 40). Understanding how to provide this support is hampered by a distinct lack of experimental data on the structural and functional effects of intrapartum asphyxia on the heart. Although there have been numerous studies documenting the long-term neurological outcomes for children who suffered asphyxia of varying severity during birth (11, 29, 30, 41–44), information regarding the cardiac outcomes for children with HIE and CP are not often reported. Furthermore, there appear to be no studies investigating the cardiovascular outcomes for those who suffered a mild to moderate hypoxic event at birth but who have no or little neurological disability. Consequently, there is a clear need for preclinical work using appropriate animal models that will enable these important issues to be investigated.

Renal Structure and Function

Acute kidney injury (AKI) is a syndrome characterized by a short period of loss of the kidney's excretory function, leading to a reduced capacity to filter blood, maintain blood volume, electrolyte levels, and acid–base homeostasis (45). AKI is usually caused by factors external to the kidney itself. In the neonate, these include premature birth, sepsis, congenital heart malfunction, and intrapartum birth asphyxia (46, 47).

Acute kidney injury has long been recognized as an almost inevitable consequence of intrapartum asphyxia, due to the shunting of blood away from peripheral organs to maintain cerebral, cardiac, and adrenal perfusion during the episode of hypoxia, thereby reducing oxygen supply to the kidney (48, 49). The renal parenchymal cells also have a limited capacity for anaerobic respiration and a high susceptibility to reperfusion injury (50). It is estimated that 50–72% of asphyxiated neonates with a 5 min Apgar score $\leq$6 will show signs of renal compromise (51), and studies have shown that AKI following birth asphyxia positively correlates with the risk of morbidity and mortality in asphyxiated newborns (11).

There are currently no FDA approved therapies that specifically target kidney damage after intrapartum asphyxia (52). Four, low sample number, randomized control trials have investigated the capacity for a single dose of theophylline, an adenosine receptor antagonist, in the first hour after asphyxial birth to prevent the progression of AKI (53–57). These trials were proceeded by animal studies that identified the increase in adenosine as a result of hypoxemia and renal vasoconstriction as a key contributor to the pathogenesis of AKI (58, 59). The promising results from the initial trials have led to the Kidney Disease Improving Global Outcomes (60) guidelines to suggest a single dose of theophylline to asphyxiated newborns (60); however, it is emphasized that theophylline has a narrow therapeutic window and must be well monitored as it can cause side effects, including tachycardia, hyperglycemia, vomiting, and seizures (61, 62). Experts in the field often agree that adequately powered, multicentre trials, that include assessment of long-term outcomes and theophylline as an adjunct to hypothermia are still required before the widespread adoption of this therapy (52, 57). Assessment of clinical data of babies who received hypothermia treatment alone following intrapartum asphyxia has concluded that the therapy does not reduce the rate or severity of AKI in these patients (63).

For those newborns who are accurately diagnosed with AKI, a range of management strategies can be put in place to ensure that the poorly functioning kidney does not exacerbate injury in other organs, particularly the brain (3, 47). Post-asphyxia infants presenting with oliguric AKI are at significant risk of fluid retention and hyponatremia due to decreased sodium reabsorption in the proximal tubules (64, 65). With this is mind, there is clinical recommendation to limit fluid intake in newborns with AKI; however, this is controversial as there is a fine balance between maintaining sodium retention and causing dehydration or malnutrition in these infants (3). Hyperkalemia is also of concern in newborns with AKI due to a poor capacity to produce urine and clear excess potassium from the blood. The withholding of fluids containing potassium and electrocardiographic monitoring is recommended for these babies. Imbalances in calcium and magnesium are also common complications of AKI and need to be monitored in the neonatal period (65). While these clinical guidelines can improve patient outcomes, treatment strategies focused on minimizing and repairing kidney injury are still required to combat AKI and ensure the long-term renal health of these newborns.

Furthermore, an episode of AKI in the neonatal period has also been linked to an increased risk of developing chronic kidney disease (CKD) later in life (66, 67). A recent prospective study by Mammen et al. (68) of 126 patients diagnosed with neonatal AKI aimed to assess the incidence, and risk of developing CKD in the 1–3 years after AKI. They also aimed to determine if the stage/severity of AKI at first presentation was a determinant of the development of CKD later in life. They found that 10.3% of their follow-up patients presented with CKD in the 1–3 years after AKI, as defined by the presence of albuminuria and/or decreased GFR ($\leq$60 ml/min/1.73 m^3). Severity of AKI (stage 3 AKI) was a potential predictor of CKD ($P = 0.08$). It should be noted that 24% of the patient population in this study were neonates, and these cases made up the majority of the AKI stage 3 population (median age 0.3 years). In addition to those who presented with CKD, 46.8% of follow-up patients were described as being at risk of developing CKD, based on a mildly reduced GFR, presence of hypertension and/or hypofiltration (68). The clinical recommendation arising from these studies is that, regardless of the severity of AKI, neonatal and pediatric patients should be monitored regularly for signs of long-term kidney damage and dysfunction, and not just in the period immediately after the episode of AKI. As early CKD is often silent, these studies strengthen the need to develop biomarkers of CKD following AKI (69). While treatment of neonatal AKI remains hindered by poor diagnostic techniques and the lack of a firm understanding of what molecular and structural changes occurs in the neonatal kidney following an asphyxic insult, a focus on prevention of injury rather than recovery may thus be a beneficial approach to develop treatments for neonatal AKI.

Diaphragm and the Initiation of Breathing

Term neonates take their first breaths by creating a sub-atmospheric intrathoracic pressure as high as −80 mmHg, which is essential for the clearance of lung liquid, thus facilitating lung aeration and the formation of the functional residual capacity (FRC) (70–72). However, asphyxiated neonates are often unable to produce the pressures necessary to achieve this and therefore require resuscitation and subsequent mechanical ventilation (11, 33, 71). Some work has been targeted at understanding the effect of intrapartum asphyxia, together with the effects of mechanical ventilation, on the lungs. Clinical studies have reported pathologies such as hemorrhagic pulmonary edema (73) and pulmonary hypertension (33).

However, despite the crucial role it plays in lung aeration, FRC formation and the initiation of breathing at birth, the respiratory musculature has been essentially overlooked. Some recent studies have investigated the effect of different suboptimal fetal environments on the diaphragm, concluding that intrauterine inflammation caused significant impairment of diaphragm contractility in the fetal sheep (74, 75). The same group has also reported a decrease in contractility in the fetal diaphragm after maternal steroid administration (76). As for asphyxia at birth, preterm birth usually also results in the neonate requiring ventilatory support, perhaps also a result of poor diaphragm function in this respiratory insufficiency.

The mechanical effort associated with breathing after birth is high due to the high compliance of the chest wall and the relatively low compliance of the fluid-filled lung, and it is assumed that the muscle fibers of the diaphragm must be relatively resistant to fatigue. As the fetal respiratory system prepares for the transition gas exchange, the diaphragm muscle fibers undergo important biochemical and phenotypic changes to deal with this change in workload; for many species, including humans, these significant maturational changes occur *in utero*. During this time, biochemical and histochemical changes show there is a significant fast-to-slow fiber type transition, together with substantial muscle fiber hypertrophy, which begins in the immediate neonatal period and continues postnatally (14, 31, 77, 78). This highlights the perinatal period as a time when activity plays a crucial role in the functional maturation of the diaphragm, suggesting potential vulnerability during this time should an event arise which could cause damage to the diaphragm musculature and interrupt this crucial transition. Mechanical ventilation, which is known to provoke atrophy-like changes to diaphragm muscle fibers in adults (79), is therefore a significant intervention for preterm and term neonates.

The diaphragm is highly susceptible to hypoxic injury, possibly because it has a very high-energy demand. Hypoxia has also been reported to significantly reduce the diaphragm's resistance to fatigue (14, 80–83). The mechanisms leading to this outcome are poorly understood; however, acidosis interferes with the ability of skeletal muscle to replenish ATP stores, as well as reducing the capacity of muscle fibers to utilize ATP (84). Similarly, systemic acidosis is associated with the upregulation of protein degradation pathways and result in significant structural damage and functional deficits in many different skeletal muscles (85–87). In the adult diaphragm, hypoxia reduces the ability of fibers to produce ATP using aerobic pathways, thus increasing reliance on anaerobic pathways including glycolysis and creatine phosphate degradation, a switch that has been implicated in the appearance of muscle fatigue (88–90). Hypercapnia causes structural and

functional deficits in skeletal muscle, with a study by Shiota et al. (91) reporting significant reductions in functional performance and fatigue resistance, as well as alterations in the relative proportions of the different muscle fibers present in the diaphragm, and in other skeletal muscles.

Furthermore, as mentioned previously, the immense increase in ROS and RNS (reactive oxygen and nitrogen species, respectively) that follow hypoxic events results in significant oxidative stress at a cellular level. This is particularly deleterious for the diaphragm, which generates high levels of oxidants due to the continuous contractile activity of this highly oxidative muscle (88, 89, 92). Oxidative stress has been reported to increase protein degradation in skeletal muscle (93, 94), and therefore this could have significant negative effects for the newborn diaphragm as it undergoes the essential structural and biochemical changes associated with parturition and the onset of gaseous ventilation.

EFFECT OF PERINATAL HYPOXIA ON SKELETAL MUSCLE AND ITS IMPLICATIONS FOR CP

The body is composed of almost 40% skeletal muscle, and this tissue is not only essential for locomotion, but also plays an important role in the metabolism of proteins and amino acids for various organ systems (93). Hypoxia in adult skeletal muscle increases production of ROS, which increases the degradation of myofibrillar structural proteins (93). Exposure to hypobaric hypoxia in adults reduces maximal force production and muscle endurance as assessed by static handgrip contractions (95). Acute hypoxia increases oxidative stress and reduces mitochondrial function in mouse skeletal muscle (96), and structurally, hypoxia causes severe muscle atrophy (97). Hypobaric hypoxia results in a significant reduction in muscle mass and muscle fiber cross-sectional area (CSA) (97).

Given the obvious susceptibility of the skeletal muscle to hypoxic damage, the possibility that deficits in skeletal muscle function could be contributing to the functional motor deficits observed in survivors of intrapartum asphyxia with CP should not be overlooked. As discussed previously, CP is the most common deleterious morbidity associated with birth asphyxia. It is a condition characterized by hypotonia in the neonate (98), and children with CP often suffer from a range of neuromuscular disabilities including deficits in motor coordination, gait abnormalities and, in severe cases, upper and lower limb spasticity (99–101), and reductions of muscle endurance and peak power of the arms and legs, even in children with mild CP (102). A small study reported significant reductions in lower limb mass in children with CP (103); however, investigations into the structural changes in these muscles are lacking.

A large body of work has been dedicated to the development of treatments for the muscular symptoms of CP; for example, the use of botulinum toxin A injection to treat limb muscle spasticity, which has been shown to improve movement for children with lower limb spasticity (104–106). While the body of opinion would be that most of the muscle disability arises secondarily from damage to central pathways governing motor activity, the direct effects of mild to moderate intrapartum asphyxia on the axial muscles obviously require further consideration.

PRECLINICAL MODELS OF BIRTH ASPHYXIA

A major issue faced by researchers and clinicians focusing their efforts on understanding the effects of birth asphyxia is the availability of an appropriate research model. Conventional altricial laboratory rodents such as mice and rats are commonly used to study the biochemical and pathological changes within the gray and white matter regions of the brain following intrapartum asphyxia. However, use of these species poses significant limitations due to the immaturity of their offspring at the time of birth. Therefore, any findings regarding tissue damage or alterations in normal organ development following a hypoxic episode at birth must be interpreted with caution. These would not be considered as appropriate models to study damage to peripheral organs such as the kidney after intrapartum asphyxia.

Large precocial models are much more useful in this regard as their advanced stage of development at the time of birth closely mimics the human physiological response to intrapartum asphyxia [see review in Ref. (107)]. Indeed, understanding perinatal brain injury following a hypoxic–ischemic insult was highly advanced by classic studies by Meyer et al. in the non-human primate in the 1970s (108). There is a particular ethical dilemma in the use of non-human primates, and the cost of experimentation in these species means the study of all neurological disorders in non-human primates is not always appropriate; however, they continue to be used of gain insight into the neurological outcomes of intrapartum asphyxia (109). There has also been extensive work conducted investigating the effect of birth asphyxia on the brain using both sheep and pigs. In sheep, we and others have developed and characterized a clinically relevant model of HIE in the near-term lamb (110–112), and Miller and colleagues use this model to investigate potential rescue therapies using melatonin and stem cells (113–116). Another group has used the newborn piglet to investigate the neurological effects of intrapartum asphyxia (117, 118), the effects of cooling (119) and to explore potential early biomarkers of neuronal injury (120). However, these animals are expensive, difficult to house and long-term studies, looking at the life course effect of HIE require many years.

The need for an appropriate small animal model to investigate the systemic effects of an asphyxial birth and the testing of potential interventions is met to some extent by using the spiny mouse (*Acomys cahirinis*). This is a precocial rodent native to the deserts of Africa and Middle East, where after a relatively long gestation (39 days) the neonate has completed organogenesis of major organ systems (121–124), and are fully furred, mobile and have open eyes.

Unlike other rodents, the brain of the spiny mouse is relatively well myelinated at birth (125), and the brain growth spurt in this species occurs in the days just prior to birth; this is later in gestation than the guinea pig, monkey, and sheep, but earlier than the rat and rabbit, and prior to birth as in the human.

In addition, this species has a hormone profile similar to the human, with the adrenal gland producing cortisol as its major circulating glucocorticoid instead of corticosterone as seen in most rodents. The fetal spiny mouse adrenal gland is also able to synthesis the steroid dehydroepiandrosterone, making the spiny mouse perhaps one of few rodents to have a fetal-placental unit where the fetal adrenal–hepatic–placental axis plays an important role in fetal brain development during gestation, as it does in higher primates, including humans (124, 126). Finally, one of the unique intrauterine developmental aspects of the spiny mouse is the completion of nephrogenesis (the formation of the filtering units in the kidney) before birth in this species (121). This makes the study of renal hemodynamics in the early neonatal period, and the study of insults on the kidney at birth in the spiny mouse particularly relevant to the human situation.

A model of near-term intrapartum asphyxia has been produced in the spiny mouse and is characterized by global acidemia, hypoxemia, and increased plasma lactate (127). In this model, it was noted that animals that did not survive the insult (~40%) exhibited abnormal gasping behavior and were unable to establish breathing. It was therefore proposed that the respiratory muscles may be involved in this failure, and the status of the diaphragm was assessed (127). This study revealed significant structural and functional deficits in the diaphragm 24 h after birth (127). This was characterized by muscle fiber atrophy, with a 20% decrease in CSA of all three major muscle fiber types and a 27% reduction in calcium (Ca^{2+})-activated force (127) as assessed in skinned single muscle fibers. There was an increase in the expression of two pro-atrophic genes—Atrogin-1 and MuRF-1. It is therefore reasonable to assume that these deficits may be contributing to respiratory failure in these animals and thus the high mortality rate observed in this model. Since those initial studies, the spiny mouse model of intrapartum asphyxia has been used to describe molecular, structural, and functional alternations in the neonatal brain and diaphragm, kidney, gonads, and skeletal musculature, and assess the therapeutic potential of the antioxidant melatonin and intracellular energy buffer creatine (127–135).

These preclinical studies have contributed significantly to our knowledge of the longer-term impact of intrapartum asphyxia. Some of the key findings to date include neurological injury being associated with mitochondrial derangement in the cortical subplate, thalamus, and piriform cortex (133) and significant behavioral deficits in tests that assess movement and motor coordination (132). Furthermore, when the same animals were placed in an open field on postnatal day 1, and their movement was recorded, asphyxia pups traveled less distance, spent more time immobile, and made significantly fewer jumps (132). These observations suggested that these animals may have significant deficits in neuro-motor activity.

These observations were further characterized with studies aimed at directly investigating the potential effects of intrapartum asphyxia on the skeletal muscle. At 24 h of age, as was observed in the diaphragm, all three muscle fiber types showed significantly reduced size. This deficit persisted until at least 1 month of age in males, along with a significant reduction in the proportion of type I fibers and a corresponding increase in type IIb/d fibers (135). Additionally, the neonatal gastrocnemius muscle was functionally assessed *ex vivo* and, akin to the diaphragm, exhibited reduced fatigue resistance in male offspring (128, 135). It is apparent that the skeletal muscle is indeed significantly affected in the immediate neonatal period following asphyxia at birth, and these deficits are persisting into at least early adulthood in our model. Therefore, it is not unreasonable to assume that the same may be the case for human infants who survive birth asphyxia.

Finally, the first rodent model of neonatal AKI secondary to intrapartum asphyxia has been developed in the spiny mouse. Neonatal AKI was confirmed by a twofold increase in mRNA expression of *Ngal*, an early marker of kidney injury, and plasma and urinary electrolyte imbalances 24 h after insult (128). Assessment of kidney structure following intrapartum asphyxia also showed significant levels of damage and immaturity, across the renal cortex, medulla, and renal papillae. At 1 month of age, male intrapartum asphyxia offspring had a permanent loss of nephrons. Compensatory hypertrophy of remaining nephrons was apparent in this cohort, but despite this, at 3 months of age (young adult), GFR in male asphyxia offspring was significantly lower than controls (136). It is of interest that cardiac structure and function in spiny mouse neonates was unaltered by intrapartum asphyxia. Clinically, while cardiovascular dysfunction is observed in some survivors of intrapartum asphyxia, the effects on the heart are heterogenous. Therefore, the absence of an effect in surviving spiny mouse pups after asphyxia is perhaps not surprising.

CURRENT TREATMENT STRATEGIES FOR INTRAPARTUM ASPHYXIA

When it comes to managing the risk of a hypoxic event at birth, the main issue faced by clinicians is the unpredictable nature of intrapartum asphyxia. Most often, it is not until the woman is in labor that obstetricians become fully aware that the fetus is at risk, and by this stage there is little they can do other than to deliver the baby as quickly as possible. Furthermore, apart from hypothermia, which as previously discussed has limited success, there are no other effective treatments for preventing the two waves of energy failure that ensues following an asphyxic birth.

A number of antenatally applied treatments that aim to prevent intrapartum hypoxic *brain* damage have been proposed and include the use of ascorbic acid, tetrahydrobiopterin, phenobarbital, *N*-acetylcysteine (NAC), xenon, and argon. However, these have either provided disappointing results (ascorbic acid and xenon), require specialized ventilatory equipment (xenon and argon), revealed unfavorable safety profiles (NAC), or, while showing promise (e.g., allopurinol, melatonin, and argon), currently lack full clinical evaluation, including their capacity to target hypoxic injury in organs other than the brain. Pharmacokinetically, all of these agents have a short duration of action and cannot be expected to provide a benefit lasting through birth into neonatal life unless their administration continues throughout the entire ante-, intra-, and postpartum periods.

The gold standard would be a safe treatment that could be administered maternally before birth to provide protection in the

event of a hypoxic episode during labor. Such a treatment should be cheap and easily administered so that it could be made available in the areas where the incidence of birth asphyxia is highest. It must also have the capacity to minimize the initial energy failure that occurs at the time of the insult, as well as having potent antioxidant capabilities to reduce the oxidative stress that ensues in the period immediately after birth. This would reduce or prevent the second wave of energy failure and oxidative stress and prevent the multi-organ injury that results. It will also need to be benign should intrapartum hypoxia not arise.

Elsewhere, we have proposed that antenatally administered creatine can provide the fetus and neonate with an additional pool of anaerobic energy during severe hypoxia, and it is a treatment that will provide protection not only to the brain but also to the other major organs that often damaged by "oxygen starvation" at birth (137). Creatine, as phosphocreatine, provides a phosphate group for the anaerobic regeneration of ATP from ADP (138). This system is crucial in maintaining intracellular energy homeostasis, serving as both a spatial and temporal energy buffer in cells with high and fluctuating energy demands such as striated muscle and neurons of the central nervous system (139). In addition to this role, it is also known to have other important properties. The conversion of creatine to phosphocreatine utilizes a proton, reducing intracellular acidity and thus maintaining acid–base balance (140). It has also been reported to have antioxidant properties in studies investigating the effect of hypoxia on the skeletal muscle (140, 141) and brain (133). These studies hypothesized that increasing total intracellular creatine before birth (creatine + phosphocreatine) would protect the fetus from the damaging effects of birth asphyxia by providing an additional, anaerobic source of ATP when oxidative phosphorylation fails due to the hypoxic insult. The antioxidant properties of creatine could also act to reduce the oxidative stress associated with the global hypoxia–ischemia that ensues. Using our spiny mouse model of birth asphyxia, we have shown that supplementing the maternal diet with 5% creatine monohydrate for a period of 19 days before delivery, caused significant creatine loading in the fetal brain, heart, kidney, liver, and diaphragm muscle (127, 131). These studies also reported a significant reduction in neonatal mortality rate after birth asphyxia (127, 131) and was protective for the brain (133), diaphragm (127), kidney (128, 136), and axial skeletal muscles (134, 135).

Despite these interesting and promising results, to date there have been no clinical studies investigating the potential for creatine to prevent birth asphyxia-induced injury. However, this was the subject of a recent review in which the limited amount of data available was highlighted (142). A full Cochrane has also been published (142); however, due to the lack of data for human pregnancy, this brought to light the need for clinical translation of this potentially life-saving treatment. If antenatally administered creatine proves to be effective and safe, it would be a cheap and readily available prophylactic treatment that could be recommended to all pregnant woman as a safeguard in the event of intrapartum hypoxia and neonatal asphyxia, thus reducing the high mortality, morbidity, and financial burden associated with this common and devastating event, in much the same way that folate supplementation has prevented neural tube defects. In the 1960s, Smithells and Hibbard discovered that women who gave birth to children with serious birth defects, notably neural tube defects, had evidence of impaired folate status. Some 30 years later, randomized controlled trials showed that they were right, and folate supplementation was effective at protecting against neural tube defects (143). In addition to our extensive evidence from animal studies that support a benefit for the fetus of increasing tissue creatine content above normal levels, we have recently shown that women who deliver small babies have lower urine creatine concentrations (144), suggesting that inadequate creatine availability may impact fetal growth. We are currently testing this hypothesis in a large prospective cohort of low risk pregnant women.

SUMMARY

Reducing the under-five mortality rate by two-thirds by 2015 was a Millennium Development Goal that unfortunately was not achieved (7). While advancements in obstetric monitoring and therapies such as hypothermia have helped reduce the rate of intrapartum-related brain damage and death significantly in the last decade, more needs to be done to address problems associated with the more extensive (multi-organ) compromises that may affect these infants. This has significant economical and emotional burdens that have not been adequately addressed and is of particular relevance for developing countries where medical resources may be limited. Severe hypoxia at birth is essentially a cardiorespiratory problem, and while brain damage has received the most attention, the global nature of the hypoxic–ischemic insult and myriad of biochemical disruptions that follow cause significant injury to many organ systems, as outlined in this review. Year 2016 marks the beginning of new global Sustainable Development Goals, with the aim to have the "Under-5" mortality rate below 25 per 1,000 live births by 2030 (145). As we embark on this new period it is important that we engage in preclinical and clinical studies designed to directly address the multi-faceted outcomes of intrapartum asphyxia. Careful consideration to appropriate animal models is required to ensure that the limited resources invested in this research provide the maximum, and most relevant, outcomes that further our understanding of injury to all the major organ systems in the neonates. The development of adjuncts to hypothermia and new therapies should be carefully considered for their applicability in the developing world if we are to truly combat the global burden of intrapartum asphyxia. Furthermore, experimentally, we are duty-bound to provide evidence for the effectiveness of new therapies beyond the neonatal period, i.e., into infancy, childhood, and the adult stages of life.

AUTHOR CONTRIBUTIONS

All authors contributed to writing and drafting this review.

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REVIEW
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Providing a Placental Transfusion in Newborns Who Need Resuscitation

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Over the past decade, there have been several studies and reviews on the importance of providing a placental transfusion to the newborn. Allowing a placental transfusion to occur by delaying the clamping of the umbilical cord is an extremely effective method of enhancing arterial oxygen content, increasing cardiac output, and improving oxygen delivery. However, premature and term newborns who require resuscitation have impaired transitional hemodynamics and may warrant different methods to actively provide a placental transfusion while still allowing for resuscitation. In this review, we will provide evidence for providing a placental transfusion in these circumstances and methods for implementation. Several factors including cord clamping time, uterine contractions, umbilical blood flow, respirations, and gravity play an important role in determining placental transfusion volumes. Finally, while many practitioners agree that a placental transfusion is beneficial, it is not always straightforward to implement and can be performed using different methods, making this basic procedure important to discuss. We will review three placental transfusion techniques: delayed cord clamping, intact umbilical cord milking, and cut-umbilical cord milking. We will also review resuscitation with an intact cord and the evidence in term and preterm newborns supporting this practice. We will discuss perceived risks versus benefits of these procedures. Finally, we will provide key straightforward concepts and implementation strategies to ensure that placental-to-newborn transfusion can become routine practice at any institution.

Keywords: placental transfusion, delayed cord clamping, cord milking, hypovolemia, perfusion, resuscitation, blood volume, neonatal transition

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INTRODUCTION

The transition to extrauterine life is characterized by changes in circulation and initiation of ventilation and oxygenation via the lungs. Much of the focus surrounding neonatal resuscitation has historically been on the ventilation and oxygenation of the transitioning infant, including methods of providing ventilator support and determining how much oxygen is appropriate. Placental transfusion has only recently been recognized as an important factor in this fetal/neonatal transition. Allowing a natural transition by not clamping the cord until it has stopped pulsing was the norm for centuries until the 1950s when concern over maternal anesthesia crossing the placenta to the infant caused Virginia Apgar to suggest immediate clamping of the umbilical cord. In 1962, a few years after this recommendation, data were available showing that clamping of the cord immediately after birth yielded a marked bradycardia in term infants, but practice did not change (1).

PHYSIOLOGY OF PLACENTAL TRANSFUSION

The goal of placental transfusion is to facilitate the transfer of blood volume from the placenta to the newborn. Owing to the relatively large size of the placenta compared with the fetus at mid-term, blood is equally distributed between the fetus and placenta. By term gestation, about one-third of the blood flows through the placenta and two-thirds flows through the fetus at any point in time (1). It follows that immediate cord clamping (ICC) results in one-third of total blood volume remaining in the placenta. Delaying clamping of the cord (DCC) for 60 s decreases the residual placental blood to 20% and by 3–5 min the residual placental volume is approximately 13% (2). When the umbilical cord is clamped, the low-resistance vascular bed of the placenta is disconnected, leading to an immediate increase in the newborn's systemic vascular resistance. In a study on anesthetized fetal lambs, Bhatt et al. demonstrated a 50% drop in pulmonary blood flow and an abrupt 40% drop in heart rate (due to cessation of umbilical venous flow from the placenta) in anesthetized fetal lambs receiving ICC (3).

Positioning of Infant

Yao and Lind found that gravity affects the amount of placental transfusion. Holding the neonate high above the placenta (head 40–60 cm above) decreases placental transfusion similar to ICC (4). A recent study found no difference in infant weights after DCC for 2 min with infants placed on the maternal abdomen versus at the introitus (5). However, total weight gain was half of what was previously found (6, 7), indicating that 2 min may not be enough time for a full placental transfusion for the term infant. Mercer and Erickson-Owens found that term infants placed on the maternal abdomen immediately after birth who were assigned to DCC for 5 min received a significantly larger placental transfusion than those with a 2-min delay (8), and more recently found that term infants placed skin to skin had significantly less residual placental blood volume than infants with immediate clamping (9).

METHODS OF PROVIDING A PLACENTAL TRANSFUSION

Delayed Cord Clamping in Preterm Infants

International Liaison Committee on Resuscitation (ILCOR) and other organizations recommend a 30- to 60-s delay in cord clamping during preterm birth (10, 11). Several randomized controlled trials and meta-analyses have been published on DCC in premature newborns (12–27). Although DCC decreases the *overall* incidence of intraventricular hemorrhage (IVH), enthusiasm for DCC is tempered by the lack of benefit for severe IVH and/or death in addition to the small numbers of newborns included in these trials and concerns about reporting bias (28). Recently, the largest DCC trial ($n = 208$) did not show any difference in severe IVH (9). The lack of benefit could reflect the inadequate placental transfusion during DCC for newborns delivered by cesarean section (C/S). Three trials of DCC versus ICC stratified by mode of delivery found no difference in hematocrit levels or tagged red blood cells in newborns delivered by C/S (29–31). ACOG acknowledges that there are limited data indicating whether DCC performed during C/S can improve placental transfusion (32). Various trials have had significant protocol violations, with 14–22% of newborns randomized to DCC actually receiving ICC (9, 29). It has been suggested that high pulmonary arterial pressure may be protective against fluctuating cerebral blood flow by reducing ductal shunt in extremely preterm infants (33). We speculate that improved cerebral blood flow, oxygen carrying capacity, increased pulmonary arterial pressure, and reduced ductal shunt following placental transfusion may contribute to reduced IVH observed in preterm infants following DCC (28).

Delayed Cord Clamping in Preterm Infants Who Require Resuscitation

It has been suggested that cord clamping should not occur until the newborn is breathing (3, 34), as this may result in an inadequate transfusion in depressed infants who are not breathing during the delay (35). Nevill and Meyer compared non-breathing with breathing newborns who received DCC and found that non-breathing infants had a lower 1-min Apgar score, were more likely to be intubated, and develop chronic lung disease or severe IVH (35). In a related animal study, Polglase et al. (36) demonstrated improved cerebral and systemic oxygenation in preterm lambs if ventilation was provided before cord clamping.

However, it is unclear in preterm newborns whether a few gasping breaths or positive pressure ventilation is required. In our feasibility trial in which infants were randomized to receive ventilation during DCC or DCC alone showed no difference between provision of early positive pressure (by CPAP/positive pressure ventilation) or gentle tactile stimulation with bulb suctioning for 60 s during DCC. In videotaped deliveries, the incidence of infants who failed to respond to stimulation and remained apneic during DCC in the control arm and intervention arm was 5 versus 3%, respectively ($p = 0.67$). The time until the first breath in the control and intervention arm were 23 ± 19 and 23 ± 20 s in each arm, respectively ($p = 0.93$).

Delayed Cord Clamping in Term Infants

International Liaison Committee on Resuscitation and other organizations recommend DCC for longer than 30 s in term infants (11, 13, 32). There is great variation in the timing of "late" cord clamping ranging from 30 s to 5 min to when the cord stops pulsating. There does not appear to be evidence that delay cord clamping in term newborns has a significant effect on neonatal death or morbidity outcomes such as admission to the neonatal intensive care unit or Apgar score less than 7 at 5 min (7, 11). Historically, studies have been limited to subjects who did not require resuscitation due to the perceived complexity of providing supportive interventions with the umbilical cord intact. In a comprehensive review of term infants receiving DCC (7), in 12 of the trials evaluated including 3,139 infants, mean birth weight was significantly higher in late clamping as opposed to early clamping. In 884 infants evaluated for hemoglobin (Hgb) concentrations, DCC babies had higher Hgb at 24–48 h of age. Four trials that evaluated term infants at 3–6 months of age who received DCC found a mean increase in serum ferritin with late

clamping (37–40). There was no increased risk of polycythemia [hematocrit (Hct) >65%] in three trials that reported on the risk with DCC (37, 41, 42), although Ceriani Cernadas did find that the 3-min delay group had a significantly higher prevalence (14.1%) compared to immediate clamping, which was not found with the 1 min delay group (5.9%).

Delayed Cord Clamping in Term Newborns Who Require Resuscitation

Approximately 10–15% of the babies born each year will need some sort of resuscitation at birth to successfully transition to extrauterine life. Positive pressure ventilation will be utilized in approximately 3–7% of newborns with 2% of infants requiring intubation and 0.1% needing chest compressions and/or epinephrine. In 85% of babies born at term gestation, spontaneous respirations will occur within 10–30 s of birth (10, 34, 43). Many have suggested that clamping the umbilical cord should be delayed in all births because of the associated benefits of increased blood volume, reduced need for blood transfusion, and iron deficiency (13, 15, 28, 38, 44–46). The American Academy of Pediatrics and the ILCOR do not yet recommend cord clamping for newborns who require resuscitation at birth due to limited evidence of benefit in this population (10, 47).

Neonates who are depressed at birth and require some resuscitation are the most likely to benefit from continued placental gas exchange and a placental transfusion with DCC. Beneficial cardiovascular changes can occur during DCC as pulmonary blood flow is established as a replacement for preload to the left heart before removing the placenta from the circulation. Maintaining venous return and cardiac output by avoiding ICC may help avoid adding a hypovolemic ischemic insult to an already asphyxiated infant (48). In a study of 20 healthy term newborns with 5 min of DCC, an improvement in stroke volume and cardiac output was demonstrated over the first 5 min of life. The mean time to cord pulsation cessation was 199 ± 76 s but cardiovascular benefits extended beyond the time of cessation (49). The term infant with shoulder dystocia whose umbilical cord is constricted as the neonate is squeezed in the birth canal is likely to have a portion of his blood shunted to the placenta (50, 51). The distressed newborn with a tight nuchal cord that is cut before birth may have up to 60 ml of their blood volume to remain in the placenta. Both scenarios may lead the infant to experience hypovolemia at birth (52). Hypovolemia at birth contributes to a poor transition and immediately clamping the umbilical cord can add additional cardiovascular complications with severe hypovolemia shock leading to asystole, an inflammatory cascade, hypoxic ischemic encephalopathy, seizures, and death (51, 53). The establishment of ventilation before clamping of the umbilical cord facilitates the cardiovascular changes of transition from fetal circulation and facilitates gas exchange in the lung, which is critical for adequate oxygenation of the newborn (48).

Umbilical Cord Milking (UCM)

For the purposes of this review, we will delineate UCM as intact cord milking as compared to a second less studies method of cutting the umbilical cord and milking it one to three times. Currently, neither form of cord milking is recommended by ILCOR. ILCOR states, "In light of the limited information regarding the safety of rapid changes in blood volume for extremely preterm infants, we suggest against the routine use of cord milking for infants born at less than 29 weeks of gestation outside of a research setting. In making this recommendation, we place a higher value on the unknown safety profile and less value on the simplicity/economy of this intervention." We will review the current evidence on cord milking in term and preterm infants.

Cut-Umbilical Cord Milking (C-UCM)

Cut-umbilical cord milking is another technique, whereas the cord is immediately cut approximately 25 cm from the umbilicus and the baby is passed to the pediatric team and placed on the radiant warmer. The umbilical cord is raised and milked from the cut end emptying all of the contents into the baby. Upadhyay et al. studied 200 infants >35 weeks, half received C-UCM and half received early cord clamping (within 30 s) (54). The mean Hgb and Hct of the C-UCM group was significantly higher ($p = 0.0001$) at 12 h of age. The mean blood pressure was significantly higher at 30 min, 12 h, and 48 h after birth although within normal limits. Mean Hgb and mean serum ferritin were significantly higher in the C-UCM group at 6 weeks of age. There was no significant difference in polycythemia, serum bilirubin, and need of phototherapy between groups. Jaiswal et al. compared C-UCM to DCC of 60–90 s (100 in each group) in babies born >36 weeks gestational age (55). Mean serum ferritin at 6 weeks of age in the C-UCM group (134.0 ± 89.8 ng/ml) was comparable to DCC (142.7 ± 87.1 ng/ml). Mean Hgb at 6 weeks of age was also comparable 11.0 ± 2.4 g/dl in the C-UCM group and 11.3 ± 2.6 in the DCC group. There is the potential for C-UCM to affect the cerebral flow dynamics. In a substudy, which is the first to look at cerebral flow dynamics in term infants, Jaiswal et al. measured resistive index, pulsatility index, and cerebral blood flow velocities of middle cerebral artery at one point between 24 and 48 h of life by cranial ultrasound. The cerebral blood velocities and cranial Doppler indices were similar in C-UCM and DCC. The limitations of this study are a lack of sequential measurements and the anterior cerebral artery was not evaluated.

Cord Milking in Term Infants

The mechanism in UCM is different from the passive transfusion that occurs at slow rate with DCC and which usually relies on the contraction of the uterus. UCM can be done rapidly and does not depend on uterine contraction and may be desirable in the situation of a depressed infant who requires resuscitation. In 1954, Colozzi studied 100 term infants who had their umbilical cord milked five times as compared to ICC and found improved Hgb and Hct levels and no adverse effects (56). Erickson-Owens et al. studied 24 term infants born by C/S and found improved Hgb and Hct levels at 36–48 h compared to ICC (57). In the ICC group, five infants had a capillary Hct level <47% suggestive of anemia. There was no report of symptomatic polycythemia, hyperbilirubinemia requiring hospitalization, or readmission for phototherapy.

UCM and Resuscitation

Cord milking may offer an advantage over DCC in newborns who are deemed too unstable to wait for 30–60 s required for DCC. UCM can be performed in any low-resource setting and provides adequate placental transfusion without delay. Milking can be done in 15–20 s, equivalent to the time it takes for ICC (58). Critics of UCM cite that cord milking may occur before the establishment of respirations and pulmonary blood flow (48). In fact, UCM improves onset of respirations and pulmonary blood flow immediately at birth. This has been shown with recordings of electrocardiographic changes; newborns who had cord milking had a longer P wave, PR, and QTC interval when compared with those who had early clamping of the cord (59). Jaykka demonstrated that alveolar patency occurs in response to the filling of the surrounding capillaries, which may accelerate onset of respiration (60). This could explain why UCM may enhance earlier onset of breathing compared to DCC. In a study comparing DCC to UCM, more infants were breathing by the time the cord was clamped with UCM compared to a 45-s DCC (74 versus 53%) (29). This study provided evidence that UCM may be superior, and a larger multicenter trial is being planned. Our prior work showed that UCM increased heart rate and oxygen saturation within the first 5 min of birth, suggesting optimal transition compared to ICC. We also found that UCM decreased the number of days on oxygen therapy and reduced chronic lung disease.

UCM in Preterm Infants

Umbilical cord milking has also been shown to have a positive impact on heart rate and other physiologic and hemodynamic measures when compared to ICC in preterm infants (61). Katheria et al. conducted a randomized controlled trial of 60 infants less than 32 weeks gestation randomized to UCM (20 cm stripped three times) or ICC to determine if there were differences in early physiology. They found that in the first 10 min of life, infants receiving UCM had higher heart rates, higher oxygen saturation, and were given less supplemental oxygen (all $p < 0.05$) when compared to infants receiving ICC (58). In a trial of 154 preterm infants, Katheria et al. found that UCM was more effective than DCC in preterm infants delivered by C/S as evidenced in improved blood flow (measured by echocardiography), blood pressure, renal perfusion (measured by urine output), and initial body temperature (29). Prior work has demonstrated that UCM increased heart rate and oxygen saturation within the first 5 min of birth suggesting optimal transition compared to ICC (62). UCM decreases the number of days on oxygen therapy and reduced chronic lung disease, which may be related to enhanced pulmonary blood flow at birth.

HOW TO IMPLEMENT RESUSCITATION DURING DELAYED CORD CLAMPING

In the hospital setting providing for resuscitation at the mother's bedside with the umbilical cord intact creates some challenges that require careful planning, cooperation, and communication between the mother's and the neonate's health care teams. Specialized portable equipment designed to provide all the necessary tools for a safe and effective resuscitation must be available and the users must be familiar and proficient with its function (63). The labor and delivery suites and the operating theater have unique environmental considerations, space limitations, and requirements for sterility. Performing the resuscitation of a critically ill neonate so close to the patient's mother can create stress on the medical personnel and family alike.

Planning and Cooperation

Limited space and competing interests in the care of the mother and child dictate that a careful plan must be made in advance with the obstetrician (OB), mother's nurse, and the neonatal team. The neonatal team's close proximity to the mother while caring for the infant can interfere with the ability of the mother's nurse and the OB to have access to care for the mother in the way they are accustomed. A plan must be devised ahead of the birth for stationing of equipment and personnel to avoid safety hazards and interference with the normal work flow. There should be the pre-assignment of roles in the care and the timing of interventions. The Apgar timer can be used to keep track of the time elapsed since birth, and the team should monitor and clearly announce the time every 15 s to facilitate the clamping of the cord at the desired interval. In the labor and delivery suites where more family and staff are present, one team member should be assigned to crowd control to oversee and assure an appropriate space is made for the family and critical staff. Simple tools that may usually be available during resuscitation such as the Apgar timer or newborn oxygen saturation goals must still be accessible and within view in the new arrangement.

Specialized Equipment

Careful preparation is required to assure that equipment that might be needed to perform a successful neonatal resuscitation with an intact umbilical cord is available and is functional. The Lifestart™ bed (Inditherm Medical, Rotherham, UK) has been used by ourselves and others and is designed to provide a safe, adjustable, platform for the infant with space provided for the mounting of equipment (64, 65). We outfitted our Lifestart™ beds with a T-piece resuscitator, an air–oxygen blender, an oxygen flowmeter, and 50 psi air and oxygen hoses to connect to gas supply in any environment (**Figure 1**). Air and oxygen tanks can also be utilized, but have the disadvantage of being heavy, require checking for adequate contents and need replacement, and they can also be inadvertently left on creating a situation of inadequate gas supply. In addition, we mounted a pulse oximeter and a bag to hold disposable supplies such as a water proof cover for the stand, a ventilation circuit, resuscitation mask, oximeter probe, bulb suction, and enough extension tubing to connect to the wall suction if needed. The two gas supply hoses and the electrical cord for the Lifestart™ bed were lashed together to form one to improve the safety and maneuverability of the trolley.

Considerations for Cesarean and Vaginal Deliveries

Mode of delivery may have a significant effect on placental transfusion. It has been speculated that perhaps more blood remains

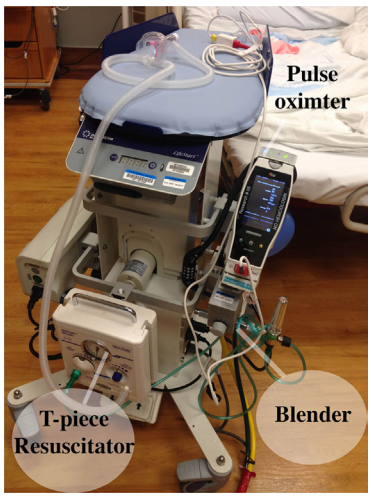

FIGURE 1 | Lifestart™ bed equipped with resuscitation equipment.

in the placenta when a neonate is delivered by C/S because the anesthetic and surgical interventions interfere with the active contraction of the uterine muscles to expel the placenta. Rabe et al. randomly assigned 58 neonates born at <33 weeks' gestation to UCM (four times) or to a 30-s delay in cord clamping. Although they did not find any differences in outcomes or Hgb levels, the infants treated with DCC had a *lower C/S* rate (58 versus 78%) (13). In 46 preterm infants 24–32 weeks GA randomized to DCC or ICC, Aladangady et al. reported lower circulating red cell volume with DCC in neonates born by C/S compared with vaginal delivery (15). Because a greater number of infants undergoing DCC were delivered by vaginal delivery, the lower proportion of C/S in this group may have reduced the difference seen between the two approaches.

Neonatal resuscitation staff must be aware of all of the procedures in their operating rooms that are utilized to assure the maintenance of the sterile environment when working close to the surgical field. These can include proper scrubbing, gowning, and gloving, as well as the equipment and surfaces that are sterile. Training should be provided by the operating room staff to assure there is confidence that the neonatal team is competent and that they will follow all of the established procedures. Sterile ventilation masks and circuits are not yet available commercially but some vendors are willing to provide sterile equipment for clinical trials at this time. The Lifestart™ bed is lowered to at least the level of the uterine incision and the neonatal provider in sterile attire will provide support as needed (64) (**Figure 2A**). An additional resuscitation team member should be in the operating room to provide assistance as needed. Thermo-conservation is especially challenging in the operating room, as the temperature tends to be cooler than in other environments. For infants <28 weeks gestation, we used a combination of a chemical mattress on the surface of the Lifestart™ bed, a Mayo stand cover for a sterile water proof barrier, warm sterile towels, and then a sterile polyethylene wrap to cover the infant. When the infant's umbilical cord was too short to reach the surface of the bed these items were placed directly on the mother. For a vaginal delivery, the Lifestart™ bed is set up and staged near the foot of the bed opposite the OB and brought forward at the level of the mother's introitus at time of delivery (**Figure 2B**). This allows the OB to simply set the infant right on the surface of the bed immediately after birth. The Lifestart™ bed is not suitable for transport of the neonate after resuscitation.

Resuscitation Team Concerns

Usually a baby who requires resuscitation will have the umbilical cord immediately cut and the infant will be removed to a remote location to a radiant warmer. This arrangement provides some advantages to the neonatal team. All of their equipment is readily available in a familiar setup. They should have adequate lighting and a secure, warm, flat platform for the child. They often have some physical separation from the family, which allows them to focus on the neonate. Clinicians also have satisfactory access to the baby as well as an adequate space for the team to work. In a survey of caregivers utilizing the Lifestart™ bed for 78 infants, 24–41 weeks gestational age during DCC, about 12% felt the new arrangement was worse, 61% the same, and 25% better or much better for the clinician (65). The ease of access to the baby and the resuscitation equipment were the primary concerns while using the Lifestart™ bed. In 30% of the deliveries, the length of the umbilical cord was too short to allow the baby to reach the trolley platform. However, the authors' felt that this number decreased as their skill increased with maneuvering the Lifestart™ bed into position. Interventions successfully provided on the Lifestart™ bed included mask ventilation, endotracheal intubation, surfactant administration, cardiopulmonary resuscitation, and umbilical venous catheterization with intravenous drug administration. The authors concluded that the Lifestart™ bed could be safely and effectively used for resuscitation at both vaginal and C/S births. No adverse events were reported as a result of utilizing the trolley. In a feasibility trial by Yoxall et al. to evaluate whether the Lifestart™ bed could be utilized for a future delayed cord clamping trial, 20 clinicians were interviewed to determine their views on providing resuscitation at birth beside the mother (66). An insufficient cord length to place the baby on the trolley was mentioned by seven clinicians. The majority (10) stated they had no preference between the Lifestart™ bed and the standard equipment, while 5 preferred the standard equipment and 3 preferred to use the trolley. The primary disadvantage of the trolley was felt to be a smaller surface, inadequate space to lie out equipment and concern about the safety of the trolley for the child. Some clinicians may have reservations about the potential to be uncomfortable performing procedures in such close proximity to the family. Of the 16 clinicians who commented on this topic in the study by Yoxall et al., most did not report being uncomfortable themselves but 5 felt that inexperienced clinical staff may be more likely to feel uneasiness.

Parental Benefits

Parents prefer delayed cord clamping, which has received a lot of media attention and is discussed widely on social media (10). Very little is known about parents' feelings about witnessing the

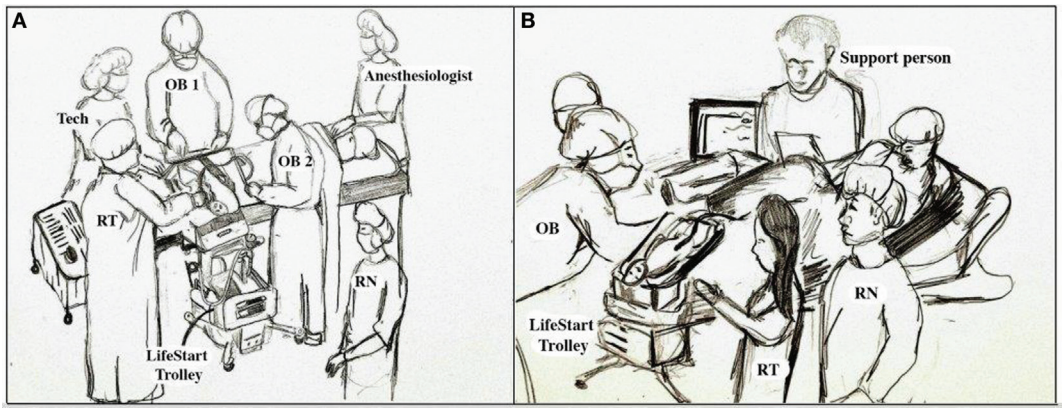

FIGURE 2 | **Personnel and equipment arrangement for neonatal resuscitation with an intact umbilical cord**. **(A)** Operating room and **(B)** labor and delivery suite.

resuscitation of their newborn during delayed cord clamping. Traditionally, infants who require resuscitation are removed to a remote location away from the mother's bedside. Often the caregiver's backs are blocking any view of the child and the clinicians are communicating with each other and no one is communicating with the family. This can create a lot of anxiety for the father who may be worried for both the mother and the child, does not know what is happening, and feels they are not allowed to be with their child (67). Father's reported feeling stressed, worried, and scared during resuscitation in traditional arrangements. European resuscitation guidelines encourage communication with parents before, during, and after the event as well encouraging parents to touch or hold the baby as soon as possible (68). Resuscitation with an intact cord brings the baby and neonatal care team close to the mother and increases the opportunity for interaction between the baby, the family, and the resuscitation team. Yoxall et al. reported that during cesarean section parents were not able to see due to the screen and where the Lifestart™ bed is stationed (66). Parental interaction may be more pronounced for vaginally delivered infants. Thomas et al. reported that during resuscitation with the Lifestart™ bed the ease of communication and the overall experience for the family was rated as better or much better by two-thirds of clinicians. Some mothers were able to touch their babies and many appreciated being able to see their babies during airway management including endotracheal intubation (65). In the Yoxall et al. feasibility study of using the Lifestart™ bed, 18 clinicians mentioned that parents were able to see and touch their baby during bedside resuscitation and were aware of what was happening with their child (66).

RISKS

Delaying clamping of the cord in preterm infants is well tolerated, and the majority will establish respirations within at least 30 s (35, 64). It appears that for non-breathing infants, a delay in cord clamping may have adverse outcomes of CLD or severe IVH but not death; however, larger trials are needed to confirm this. Two points to consider are, UCM may be a more efficient and time-sensitive technique than a 60-s delay (29), and providing tactile stimulation may be as good as providing PPV in initiating respirations in the newborn (64).

CONCLUSION

A placental transfusion with DCC or UCM is an important element in providing a smooth transition for the newborn to extrauterine life. DCC and UCM can enhance arterial oxygen content, hemodynamic stability, and be easily provided in a low-resource setting. Factors including cord clamping time, uterine contractions, umbilical blood flow, respirations, and gravity play an important role in determining placental transfusion volumes. Premature and term newborns who require resuscitation may be the most in need of the benefits of a placental transfusion. While it is possible to provide resuscitation during delayed cord clamping, there are a number of logisitical challenges particularly in the sterile operative field and in premature infants. UCM has not been recommended by any governing body, but may be the most efficient methods to provide a placental transfusion in infants who require resuscitation. Further studies will be required before this practice can come standard of care.

AUTHOR CONTRIBUTIONS

AK contributed to the drafting, revision, and final approval of the manuscript. MB contributed to the drafting, revision, and final approval of the manuscript. WR contributed to the drafting, revision, and final approval of the manuscript. KA contributed to the drafting, revision, and final approval of the manuscript.

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REVIEW
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Optimal Chest Compression Rate and Compression to Ventilation Ratio in Delivery Room Resuscitation: Evidence from Newborn Piglets and Neonatal Manikins

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Cardiopulmonary resuscitation (CPR) duration until return of spontaneous circulation (ROSC) influences survival and neurologic outcomes after delivery room (DR) CPR. High quality chest compressions (CC) improve cerebral and myocardial perfusion. Improved myocardial perfusion increases the likelihood of a faster ROSC. Thus, optimizing CC quality may improve outcomes both by preserving cerebral blood flow during CPR and by reducing the recovery time. CC quality is determined by rate, CC to ventilation (C:V) ratio, and applied force, which are influenced by the CC provider. Thus, provider performance should be taken into account. Neonatal resuscitation guidelines recommend a 3:1 C:V ratio. CCs should be delivered at a rate of 90/min synchronized with ventilations at a rate of 30/min to achieve a total of 120 events/min. Despite a lack of scientific evidence supporting this, the investigation of alternative CC interventions in human neonates is ethically challenging. Also, the infrequent occurrence of extensive CPR measures in the DR make randomized controlled trials difficult to perform. Thus, many biomechanical aspects of CC have been investigated in animal and manikin models. Despite mathematical and physiological rationales that higher rates and uninterrupted CC improve CPR hemodynamics, studies indicate that provider fatigue is more pronounced when CC are performed continuously compared to when a pause is inserted after every third CC as currently recommended. A higher rate (e.g., 120/min) is also more fatiguing, which affects CC quality. In post-transitional piglets with asphyxia-induced cardiac arrest, there was no benefit of performing continuous CC at a rate of 90/min. Not only rate but duty cycle, i.e., the duration of CC/total cycle time, is a known determinant of CC effectiveness. However, duty cycle cannot be controlled with manual CC. Mechanical/automated CC in neonatal CPR has not been explored, and feedback systems are under-investigated in this population. Evidence indicates that providers perform CC at rates both higher and

Abbreviations: CPR, cardiopulmonary resuscitation; DR, delivery room; CC, chest compressions; ROSC, return of spontaneous circulation; C:V ratio, chest compression to ventilation ratio; VF, ventricular fibrillation; CPP, coronary perfusion pressure; CSF, cerebrospinal fluid; CCaV, continuous CC with asynchronous ventilation; DBP, diastolic blood pressure; MAP, mean arterial blood pressure.

lower than recommended. Video recording of DR CRP has been increasingly applied and observational studies of what is actually done in relation to outcomes could be useful. Different CC rates and ratios should also be investigated under controlled experimental conditions in animals during perinatal transition.

Keywords: newborn, cardiopulmonary resuscitation, chest compression, manikins, piglet

INTRODUCTION

Observational data indicate that prolonged cardiopulmonary resuscitation (CPR) in the delivery room (DR) is associated with poor survival and neurologic outcomes (1). High quality chest compressions (CC) improve cerebral and myocardial perfusion. Improved cerebral perfusion ensures brain cell survival during CPR, whereas enhanced myocardial perfusion increases the likelihood of a fast return of spontaneous circulation (ROSC). Thus, optimizing CC quality may improve outcomes both by preserving cerebral blood flow during cardiac arrest and by reducing recovery time. The effectiveness of CC is influenced by (i) CC rate, (ii) CC to ventilation (C:V) ratio, and (iii) applied force, which are all influenced by the CC provider (**Figure 1**). Thus, besides CPR mechanics and mathematical modeling, educational, emotional, and physical aspects of provider performance need to be considered when addressing the optimal CC algorithm. Ultimately, the physiological effects in the infant determine the most optimal CC intervention.

In animals with ventricular fibrillation (VF) cardiac arrest, adequately oxygenated blood can be circulated with CC for up to 4–6 min even without assisted ventilation (2). In addition, pediatric and adult animal data demonstrate better coronary perfusion pressures (CPP) with less CC interruption (3–6). Thus, more uninterrupted CC in a series is generally regarded to be beneficial. However, because cardiovascular collapse in the DR is almost invariably due to hypoxia, neonatal resuscitation guidelines recommend a 3:1 C:V ratio (7). CCs should be delivered at a rate of 90/min synchronized with ventilations at a rate of 30/min to achieve a total of 120 events/min (7). There is a lack of scientific evidence to support this standard of care in neonatal CPR, and the unique physiology of perinatal transition as well as cerebral and cardiovascular immaturity call for special considerations in DR CPR. However, investigations of alternative CC interventions in the critically ill human neonate are ethically challenging. Also, the infrequent occurrence of extensive CPR in the DR makes randomized controlled trials difficult to perform. Thus, many biomechanical aspects of CC have been studied in animal and manikin models. In such models, operator performance can also be assessed in a systematic fashion. Because of physical similarities between piglets and human infants including broader chest compared to other non-primate species, and similar chest size and stiffness (8), the porcine model of neonatal CPR has been extensively studied. The aim of this review is to provide an overview about the current knowledge of optimal CC rate and C:V ratio during neonatal CPR.

A summary of studies investigating different CC rates and C:V ratios in neonatal CPR is presented in **Table 1**.

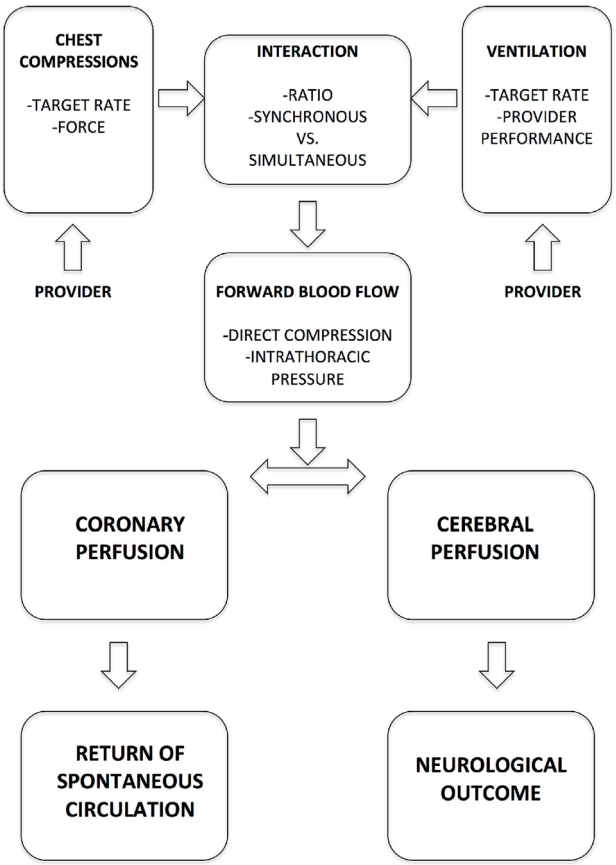

FIGURE 1 | Key determinants of chest compression effectiveness in delivery room cardiopulmonary resuscitation.

Piglets

Hemodynamic Effects of CC

Biomarkers of Cerebral Perfusion

As an indirect measure of cerebral "well-being" during CPR, Dannevig et al. (9) measured inflammation markers [interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and S100] in cerebrospinal fluid (CSF), and gene expression of matrix metalloproteinases (MMPs), intercellular adhesion molecule-1 (ICAM-1), caspase 3, IL-6, and TNF-α in hippocampus and frontal cortex tissue. They found that the CSF cytokine concentrations and tissue quantitative real-time PCR in the three C:V ratio groups 3:1, 9:3, and 15:2 were not different (9). This might indicate that in asphyxia, higher C:V ratios do not improve cerebral perfusion in asphyxiated infants and contrasts to the improved neurological outcomes when CC are not being interrupted in VF cardiac arrest (10).

TABLE 1 | Summary of studies exploring different CC rates and C:V ratios in neonatal resuscitation.

Reference	Design	Subjects	Interventions	Outcomes	Conclusion
Solevåg et al. (13)	Randomized controlled animal trial	Piglets 1–3 days of age weight 1.7–2.4 kg ($n = 32$)	Asphyxiated piglets were randomized to 3:1 C:V CPR or CCaV CPR (CC rate 90/min)	Time to ROSC was similar for 3:1 C:V CPR and CCaV CPR; $p = 0.84$ Post mortem analysis of left ventricle lactate was increased in the CCaV group	Overall recovery may be similar, but CCaV might impair myocardial perfusion compared to 3:1 C:V CPR
Solevåg et al. (11)	Randomized controlled animal trial	Piglets 12–36 h old ($n = 32$)	Asphyxiated piglets were randomized to receive a C:V ratio of 3:1 or 9:3	Time to ROSC (median and interquartile range) was 150 (115–180) s vs. 148 (116–195) s for 3:1 and 9:3, respectively ($p = 0.74$). There were no differences in diastolic blood pressure (DBP) during compression cycles or in markers of hypoxia and inflammation	The C:V ratio 9:3 was not better than 3:1
Solevåg et al. (12)	Randomized controlled animal trial	Piglets 12–36 h old ($n = 22$)	Asphyxiated piglets were randomized to receive a C:V ratio 3:1 or 15:2	Mean (SD) increase in DBP (mmHg) during compression cycles was significantly higher with 15:2 than 3:1 C:V [7.1 (2.8) vs. 4.8 (2.6)]. Median (interquartile range) time to ROSC for the 3:1 group was 150 (140–180) s, and 195 (145–358) s for the 15:2 group	The C:V ratio 15:2 is not better than 3:1 in neonatal resuscitation
Dannevig et al. (9)	Randomized controlled animal trial	Piglets 12–36 h old ($n = 94$)	Asphyxiated piglets were resuscitated with a C:V ratio of 3:1, 9:3, or 15:2	Interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and S100 in CSF, and gene expression of matrix metalloproteinases (MMPs), intercellular adhesion molecule-1 (ICAM-1), caspase 3, IL-6 and TNF-α in hippocampus and frontal cortex tissue were similar across C:V groups	Higher C:V ratios did not change the brain inflammatory response compared with the 3:1 C:V ratio
Dannevig et al. (17)	Randomized controlled animal trial	Piglets 12–36 h old ($n = 72$)	Asphyxiated piglets were resuscitated with a C:V ratio of 3:1, 9:3, or 15:2	IL-8 and TNF-α in BAL fluid and MMP2, MMP9, ICAM-1, and TNFα in lung tissue were similar across C:V groups	Higher C:V ratios did not change the lung inflammatory response compared with the 3:1 C:V ratio
Boldingh et al. (30)	Randomized crossover manikin trial	Doctors, nurses, and midwifes ($n = 34$)	5 min CPR, with either a 3:1 C:V ratio or CCaV (CC rate 120/min). All participants performed all interventions in a randomized order	The CC proportion with adequate depth was 90.5% for the 3:1 C:V ratio and 60.1% in CCaV CCaV resulted in a greater increase in rescuer heart rate and mean arterial blood pressure, and perceived fatigue, compared to 3:1 C:V CPR	CCaV is more exhausting than a 3:1 C:V ratio
Li et al. (28)	Randomized crossover manikin trial	Neonatologists, neonatal-perinatal fellows, neonatal nurse practitioners, and registered nurses ($n = 30$)	10 min CPR with a 3:1 C:V ratio, CCaV-90 (CCaV at a 90/min rate), and CC at a rate of 120/min (CCaV-120) (CCaV at a 120/min rate). All participants performed all interventions in a randomized order	Peak CC pressure decreased significantly after 156, 96, and 72 s in the 3:1, CCaV-90, and CCaV-120 groups, respectively	3:1 C:V CPR was the least fatiguing and the most preferred method
Boldingh et al. (29)	Randomized crossover manikin trial	Doctors, nurses, midwives, and last-year medical students ($n = 84$)	2 min of CPR with C:V ratios 3:1, 9:3, or 15:2—and CCaV (CC rate 120/min). All participants performed all interventions in a randomized order	3:1 C:V and 9:3 C:V were comparable in terms of CC and ventilation dynamics The 15:2 C:V ratio resulted in less ventilation vs. the 3:1 C:V ratio The mean CC depth with CCaV vs. the 3:1 method was 32.7 vs. 34.6 mm ($p < 0.001$) There was a significant decrease in CC depth from baseline after 60 s ($p = 0.025$) with CCaV The two-person CRP coordination was rated easiest with the 3:1 C:V ratio	The results of the study support the currently recommended 3:1 C:V ratio
Solevåg et al. (31)	Randomized crossover manikin trial	Two medical students	Ten times 2 min 3:1 C:V CPR, 9:3 C:V, and 15:2 C:V—and CCaV (CC rate 120/min) were performed in a randomized order	Minute ventilation in mL/kg was significantly lower at the C:V ratios 9:3 [140 (134–144)] and 15:2 [77 (74–83)] vs. 3:1 [191 (183–199)]	Higher C:V ratios than 3:1 compromised ventilation

CC, chest compression; CPR, cardiopulmonary resuscitation; CCaV, continuous chest compression and asynchronous ventilation; ROSC, return of spontaneous circulation; CSF, cerebrospinal fluid; BAL, bronchoalveolar lavage.

Myocardial Perfusion

Diastolic blood pressure (DBP) is a proxy for myocardial perfusion during CPR. Solevåg et al. reported similar DBP between 3:1 and 9:3 C:V ratio CPR in a piglet model of asphyxia-induced cardiac arrest (11). Interestingly, using a 15:2 C:V ratio resulted in a higher mean (SD) DBP of 7.1 (2.8) vs. 4.8 (2.6) mmHg during standard 3:1 C:V CPR ($p = 0.004$) (12). Unfortunately, time to ROSC was similar between 15:2 and 3:1 C:V CPR. In a similar

study (13), CCaV had similar DBP compared to 3:1 C:V CPR. Post mortem analysis of left ventricle lactate was increased in the CCaV group, which might indicate either anaerobic metabolism or physical trauma, or a combination of both (13).

Physical Trauma/Inflammation

There is a lack of knowledge about lung injury resulting from neonatal CPR. Clinical studies reported an increase in inflammatory markers in blood early after thoracic trauma (14–16). Dannevig et al. (17) analyzed IL-8 and TNF-α in bronchoalveolar lavage (BAL) fluid and MMP2, MMP9, ICAM-1, and TNFα in lung tissue of asphyxiated piglets after CPR. They observed no differences in IL-8 or gene expression in lung tissue between piglets resuscitated with a C:V ratio of 3:1 or 9:3. However, median (IQR) TNF-α was 1.26 (0.92–1.55) pg/ml in the 9:3 group vs. 0.88 (0.67–1.28) pg/ml in the 3:1 group ($p = 0.047$). Furthermore, inflammatory markers in BAL and lung tissue were increased in piglets where CC were initiated after a 30-s ventilation period compared to 60 and 90 s suggesting that a higher total number of CC during CPR might negatively influence outcome through inflammatory pathways (17).

Epinephrine

Through its α-adrenergic effects, epinephrine mediates peripheral vasoconstriction while forward flow is generated with CC (18), thus elevating the aortic pressure and CPP in pigs (19). Epinephrine has been thought to be essential for ROSC in severe perinatal compromise (20). However, recent experimental data in lambs (21) and piglets (11, 12, 22, 23) are conflicting. Pytte et al. (24) speculated that the hemodynamic effects of epinephrine depend on CC quality, which might explain the conflicting results in different animal models. In asphyxiated piglets, Linner et al. (23) and McNamara (25) found that ROSC could be achieved with CC alone without epinephrine, whereas Solevåg et al. (11, 12) reported that piglets almost invariably required epinephrine for ROSC. Similar findings were made in lambs by Sobotka et al. (21). One important difference between the study protocols was that Linner et al. (23) targeted CC to a mean arterial blood pressure (MAP) of 35–40 mmHg, whereas Solevåg et al. (11, 12) targeted the CC to a MAP of 20 mmHg. McNamara (25) did not specify a pressure target but aimed to compress the chest by one-third of the anteroposterior diameter. Lambs have different chest geometry than piglets, and the two models are not easily comparable in terms of CC quality (26).

Manikins

CC Rate

Neonatal CPR guidelines recommend 120 events/min, which comprise 90 CC and 30 inflations (7). CC duty cycle is the CC duration divided by total cycle time. Increasing the CC rate increases the effective duty cycle by decreasing the total cycle time provided that the CC duration remains constant (8). In fact, mathematical models suggest that the optimal CC rate in newborn infants should exceed 120/min (27). Manikin studies have investigated the feasibility of performing neonatal CC at different rates. Li et al. (28) showed that even though it was possible for neonatal staff to perform continuous CC at rates of 90 and 120/min, a significant decay in CC pressure occurred after 96 and 72 s, respectively. In contrast, when performing standard 3:1 C:V CPR, significant decay occurred only after 156 s. This means that good quality CC might be maintained for more than twice as long with 3:1 C:V CPR compared with uninterrupted CC at a rate of 120/min (CCaV-120). In addition, the 3-min CC depth decline was 50% if CC was performed at a rate of 120/min vs. 30% at a rate of 90/min (28). Similarly, Boldingh et al. (29) found that the CC depth was lower in CCaV-120 compared with the 3:1 C:V ratio method, with a significant decline in CC depth from baseline after 60 s in CCaV-120 vs. no significant decline after 120 s in 3:1 C:V CPR. Boldingh et al. (29) did not investigate continuous CC at a rate of 90/min, but quite unanimously, studies indicate that rescuer fatigue is more pronounced when CC are performed continuously compared to when a pause is inserted after every third CC as currently recommended (28, 29). This is further supported by the preference of resuscitators of the 3:1 C:V ratio over CCaV (28–30), and the two-person coordination is easier with the 3:1 C:V ratio (29). On the other hand, CCaV has been shown to improve minute ventilation during manikin CPR (29, 31).

Educational, Emotional, and Physical Aspects of Operator Performance

Educational

The International Liaison Committee on Resuscitation stated, in their 2015 treatment recommendations (7), that despite very low quality evidence in favor of the 3:1 C:V ratio, they chose to retain the recommendation for educational reasons, as the value of consistency of the algorithm was thought to be significant. There is a lack of data demonstrating educational advantages of alternative C:V ratios.

Emotional

Rescuers' perceptions of self-efficacy may influence skills acquisition and retention. "Perceived control," determined by knowledge, competencies, skills, ability, and experience, is a determinant of behavior (32). Education about CC dynamics and physiology, as well as practical CC training can therefore both through knowledge and skills acquisition, and also through enhanced perceived control, positively influence CC performance. Perceived control in the DR may also alleviate the stress experienced during CPR. Some investigators have tried to incorporate the element of stress in simulated CC scenarios (29), but practicing CC in an artificial simulated environment can never replicate the stress of real-life CPR.

Physical

Boldingh et al. (30) assessed heart rate (HR), MAP, and respiratory rate of rescuers as measures of physical fatigue during CPR with either 3:1 C:V CPR or CCaV-120. In addition, they investigated whether body mass index (BMI) and weekly physical activity influenced CC performance. CCaV-120 resulted in a greater increase in rescuer HR and MAP compared to a 3:1 C:V ratio. In agreement with this, continuous CC were perceived as being more fatiguing. Weekly physical activity and BMI did not seem to influence CC performance.

DISCUSSION

In asphyxiated newborn piglets, harm caused by the trauma of CC may counterbalance the beneficial effects of more CC on hemodynamics seen in pediatric and adult animals. The reasons for this are at least twofold: (1) Dean et al. (33) speculated that "standard" CPR is already quite effective in animals with small and compliant chests. Thus, increasing CC rates may not have additive effects in infant CPR, (2) as the cause of profound bradycardia or cardiac arrest in the DR is almost invariably asphyxia, the inflammatory cascade is already highly activated at the time CPR with CC is commenced. The additional trauma of performing CC may add to the injury of vital organs and result in a poor outcome.

The asphyxial etiology of arrest in the DR is of course complicating the picture in a multitude of other ways. Piglet studies suggest that in severe asphyxia, the systemic vascular resistance (SVR) initially increases and then decreases (34). Almost concurrently with the drop in SVR, the MAP declines (34). Aaltonen et al. (34) speculated that this drop in MAP could not be explained by a reduced left ventricular output. This is supported by results from Li et al. (35) that cardiac output in asphyxiated newborn piglets after CPR was not different from control piglets. Thus, a more likely reason for hypotension in the asphyxic neonate is the profound acidosis and lack of substrate (ATP). ATP is required for maintaining vascular tone, and sustained asphyxia will eventually result in maximal vasodilation (36). Thus, blood flow generated with CC preferentially goes through a dilated aorta and into the peripheral circulation rather than into the smaller, higher-resistance coronary arteries (36). This is a plausible explanation for why attempts at increasing coronary perfusion by increasing the C:V ratio or even CC rate has not been successful in models of perinatal asphyxia. CCaV has not proven to be of benefit in asphyxiated piglets, unless they are combined with a sustained inflation (35, 37). Manikin studies support that continuous CC and asynchronous standard positive pressure ventilation might not provide benefit. In fact, this method may result in suboptimal CC quality (28, 29). Rescuers typically prefer standard 3:1 C:V CPR (28, 29).

Knowledge Gaps

Effects of CC in the Absence of a Functioning Cerebral Autoregulation

As cerebral oxygen delivery depends on cerebral blood flow and arterial oxygen content, cerebral oxygen delivery is maintained during hypoxia by an increase in cerebral blood flow (38). However, even brief hypoxia (20 min) results in impairment of cerebral blood flow autoregulation, especially during hypotension episodes in animal models (39, 40). Rosenberg (41) demonstrated in newborn lambs that after asphyxia, the lambs exhibited a markedly impaired vasodilation in response to hypoxia, and no cerebral vasodilation with systemic hypotension (41), quite different from adult models where cerebral autoregulation is intact after asphyxia (42). These differences between newborns and adults could be the result of maturation and should be taken into account when attempts are made to establish the best CC strategy in asphyxiated infants. Since asphyxia causes an impairment of cerebral autoregulation in the newborn infant, the risk of brain damage resulting from fluctuations in blood pressure caused by CC and inotropes should not outweigh the benefits of improved coronary and systemic perfusion. The focus of CC research has been on systemic and coronary hemodynamics with the primary endpoint often being ROSC. Even though neurological adverse effects of epinephrine in preterm infants have been described (43, 44), less attention has been given to the effects of CC alone on cerebral circulation in asphyxiated term infants.

Preterm Infants

Preterm infants requiring CPR with CC have a high mortality and many of the infants that survive develop neurodevelopmental impairment (45). A fragile germinal matrix and poor cerebral autoregulation in preterm infants predispose for intraventricular hemorrhage and may be among the reasons why preterm infants potentially need different CPR strategies compared to term or near-term infants.

Oxygen Fractions

One of the proposed mechanisms behind the impaired cerebral autoregulation after asphyxia is vascular endothelial injury secondary to oxygen-free radical production during reperfusion (46). Hyperoxia during CPR in perinatal asphyxia is detrimental in a multitude of other ways. This has been extensively studied in animals and humans needing positive pressure ventilation. Far less is known about the balance between damage caused by hypoxia and hyperoxia when CC are needed (47).

Duty Cycle and Automated CC

Duty cycle, i.e., the duration of CC/total cycle time, is a known determinant of CC effectiveness in pediatric and adult models. In animals, the optimal CC rate and duty cycle differ between pediatric and adult models. This may also be the case in human children and adults and should thus be studied further. However, duty cycle cannot be controlled with manual CC. Mechanic CC in neonatal CPR has not been thoroughly explored.

CC Depth and Force

Most studies of CC efficacy in neonatal CPR have used CC depth as measure of CC quality. However, the CC depth that optimizes cerebral and myocardial perfusion remains unknown. Even though some studies have assessed leaning during CC administration, little attention has been given to over-compression of the chest, i.e., the slogan from adult CPR "push hard and fast" (48) has not been properly challenged in neonatal CPR. The depth of CC can be translated into compressive force, which is related to intrathoracic pressure (49). Feedback systems for both depth and force during neonatal CPR are insufficiently explored and deserve attention (50).

Future Research Objectives

In real-life resuscitation, it is not uncommon that CC and assisted ventilations are being performed in a more or less asynchronous fashion. Evidence indicates that compliance with the algorithm is poor (51–53). Video recording of DR CRP has been increasingly applied and observational studies of what

is actually done in relation to outcomes could potentially be useful.

The extensively used manikin models cannot replicate the complex mechanisms of antegrade blood flow during CPR. Manikins are one-dimensional with respect to the fact that blood flow during CC is a product of direct compression forces and the complex changes in intrathoracic pressure that occur. To reliably determine the effects of different CC interventions on regional and systemic hemodynamics, the use of transitioning animal models that more accurately replicate the newborn circulation with patent fetal shunts is required.

In conclusion, the very unique physiology of perinatal transition and asphyxia make DR resuscitation different from resuscitation at any time later in life. Most of what we know about CC dynamics from pediatric and adult basic and clinical research has to be challenged in appropriate neonatal models. Thus far, no CC study has been performed in a transitioning animal model, and is urgently needed.

AUTHOR CONTRIBUTIONS

AS and GS: substantial contributions to all of the following: (1) the conception and design of the manuscript, (2) drafting the manuscript or revising it critically for important intellectual content, and (3) final approval of the version to be submitted.

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A Novel Prototype Neonatal Resuscitator That Controls Tidal Volume and Ventilation Rate: A Comparative Study of Mask Ventilation in a Newborn Manikin

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The objective of this randomized controlled manikin trial was to examine tidal volume (V_T) delivery and ventilation rate during mask positive pressure ventilation (PPV) with five different devices, including a volume-controlled prototype Next Step™ device for neonatal resuscitation. We hypothesized that V_T and rate would be closest to target with the Next Step™. Twenty-five Neonatal Resuscitation Program providers provided mask PPV to a newborn manikin (simulated weight 1 kg) in a randomized order with a self-inflating bag (SIB), a disposable T-piece, a non-disposable T-piece, a stand-alone resuscitation system T-piece, and the Next Step™. All T-pieces used a peak inflation pressure of 20 cmH_2O and a positive end-expiratory pressure of 5 cmH_2O. The participants were instructed to deliver a 5 mL/kg V_T (rate 40–60/min) for 1 min with each device and each of three test lungs with increasing compliance of 0.5, 1.0, and 2.0 mL/cmH_2O. V_T and ventilation rate were compared between devices and compliance levels (linear mixed model). All devices, except the Next Step™ delivered a too high V_T, up to sixfold the target at the 2.0-mL/cmH_2O compliance. The Next Step™ V_T was 26% lower than the target in the low compliance. The ventilation rate was within target with the Next Step™ and SIB, and slightly lower with the T-pieces. In conclusion, routinely used newborn resuscitators over delivered V_T, whereas the Next Step™ under delivered in the low compliant test lung. The SIB had higher V_T and rate than the T-pieces. More research is needed on volume-controlled delivery room ventilation.

Keywords: newborn, critical care, ventilation, bronchopulmonary dysplasia, tidal volume, resuscitation

INTRODUCTION

Inappropriate tidal volume (V_T) delivery during positive pressure ventilation (PPV) has been associated with an increased risk of both brain and lung injury in preterm infants (1, 2). Thus, modern mechanical ventilators use flow sensors to deliver volume-targeted ventilation. Perinatal transition involves rapidly changing lung mechanics (3), and despite the increasing focus on volume-targeted

ventilation, commonly used neonatal resuscitation devices (4, 5) [e.g., self-inflating bags (SIBs) or T-piece devices] are pressure limited. If PPV is required, the inflation pressure and inflation time should be adjusted to deliver an adequate V_T as the lungs are gradually aerating and clearing lung liquid (6–8). However, complicating the task of providing PPV in the delivery room (DR) is the fact that the "appropriate" V_T varies in the first minutes after birth (9, 10). We have previously demonstrated that T-piece and SIB V_T were above the target in an intubated model with high airway compliance when a set peak inflation pressure (PIP) was used during PPV (11). However, mask ventilation differs from ventilation using an endotracheal tube (ETT) in many aspects. Distension of the facemask and upper airways during PPV might contribute to a difference in V_T needed to achieve adequate lung inflation during mask PPV compared to ETT ventilation (12). Mask leak and airway obstruction are other significant complicating factors during mask PPV (13, 14).

Thus, the primary aim of this study was to compare the same commonly used neonatal resuscitators that we used in our previous ETT study (11), to assess V_T delivery and ventilation rate during mask PPV with changing airway compliance in a newborn manikin. Also, similar to our previous study, we added a prototype ventilation device designed to deliver a predetermined V_T and ventilation rate irrespective of airway compliance (Next Step™, KM Medical, Auckland, New Zealand) for comparison. We hypothesized that the Next Step™ V_T delivery and ventilation rate would be most consistent compared to all other devices.

MATERIALS AND METHODS

Environment and Subjects

The study was carried out in July 2015 at The Royal Alexandra Hospital, Edmonton, a tertiary perinatal center with an annual delivery rate of >7,000, and admitting approximately 1,500 infants to the Neonatal Intensive Care Unit (NICU) each year. The Northern Alberta Neonatal Program Research Committee and Health Ethics Research Board, University of Alberta approved the study. Registered Neonatal Resuscitation Program (NRP) healthcare professionals including neonatologists, neonatal fellows, neonatal nurse practitioners, respiratory therapists, and neonatal nurses were included after written informed consent. The most commonly used neonatal resuscitator used by the participants was either T-piece device tested in the present study. The SIB was infrequently used.

Randomization

This was a randomized, prospective, experimental study. All participants performed PPV with five ventilation devices in a randomized order. The primary investigator (Anne Lee Solevåg) conducted the randomization using an online tool[1] and a code list. As this was a manikin study, the trial was not registered in the clinical trials database.[2]

[1] http://www.randomizer.org.
[2] http://clinicaltrials.gov.

Sample Size Estimation

Our primary outcome was V_T delivery. A sample size of 25 NRP providers would be sufficient to detect a 40% more accurate V_T delivery with the Next Step™ device compared to a pressure-limited device, which we considered clinically important with 80% power and a two-tailed alpha error of 0.05.

Manikin

We used a NeoNatalie manikin (Laerdal Medical, Stavanger, Norway) modified with rubber tubing connecting the manikin's pharynx with test lungs with three different compliance levels (**Figure 1**). The manikin did not exhibit chest rise, and its exterior resembled a term infant.

Test Lungs and Integrated Flow Sensor

Details about the three aluminum cylinder test lungs with integrated flow sensor are presented in Ref. (11). In agreement with clinical data (15), the test lungs had compliances of (i) 0.5 mL/cmH_2O, (ii) 1.0 mL/cmH_2O, and (iii) 2.0 mL/cmH_2O, respectively. The test lungs were kept in a case and connected to the upper airways of the manikin by rubber tubing (**Figure 1**). The test lung settings were masked to participants during the study. Prior to each study day, the test lungs were checked for accuracy using a 10-mL glass syringe.

Ventilation Devices and Mask

Prior to the experiments, the participants had time to familiarize themselves with each ventilation device. (1) A SIB with a 35-cmH_2O pop-off valve (Laerdal Medical, Stavanger, Norway), no PEEP valve, or manometer attached; (2) Neo-Tee disposable T-piece (Mercury Medical, Clearwater, FL, USA) with PIP 20 cmH_2O and PEEP 5 cmH_2O; (3) Neopuff™ Infant T-piece (Fisher & Paykel, Auckland, New Zealand) with PIP 20 cmH_2O and PEEP 5 cmH_2O; (4) Giraffe Stand-alone Infant Resuscitation System T-piece (GE Healthcare, Buckinghamshire, UK) with PIP 20 cmH_2O and PEEP 5 cmH_2O; and (5) The Next Step™ (KM Medical, Auckland, New Zealand) with a 5-cmH_2O PEEP valve. The Next Step™ neonatal resuscitator (**Figure 2**) controls V_T and ventilation rate and monitors airway pressure. The 800g prototype is operated *via* a tablet displaying PIP, PEEP, and V_T in real time. According to the manufacturer, the device delivers V_T with an accuracy of 0.1–0.3 mL and has an internal battery with a life of ≥4 h in the standard configuration. For all devices, a Neonatal Clear Anatomical Face Mask (Mercury Medical) was used.

Experimental Protocol

Each participant used all five ventilation devices in a randomized order, delivering PPV with each device for 3 × 1 min (1 min for each compliance level) targeting a rate of 40–60/min. The Next Step™ ventilation rate was set at 50/min. The 1-min ventilation sessions were separated by a minute during which compliance and/or ventilation device was changed and the participants were allowed to recover. The compliance levels were used in a predetermined order (0.5, 1.0, and 2.0 mL/cmH_2O) for each device to simulate the changing airway compliance after birth (15, 16). Although participants knew that the compliance would change after each minute of PPV, they were unaware of the starting

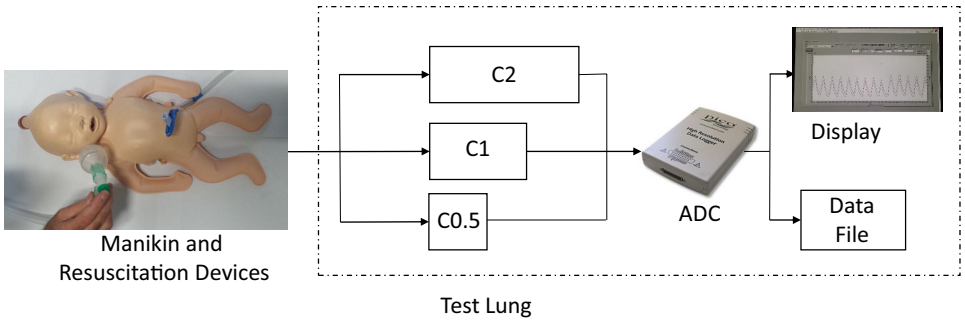

FIGURE 1 | Test lung components. The upper airway of the manikin was connected *via* rubber tubing to three external test lungs. The cylinder test lungs were designed to exhibit a compliance of 0.5 mL/cmH_2O (C0.5), 1.0 mL/cmH_2O (C1), and 2.0 mL/cmH_2O (C2), respectively. ADC, analog-to-digital converter.

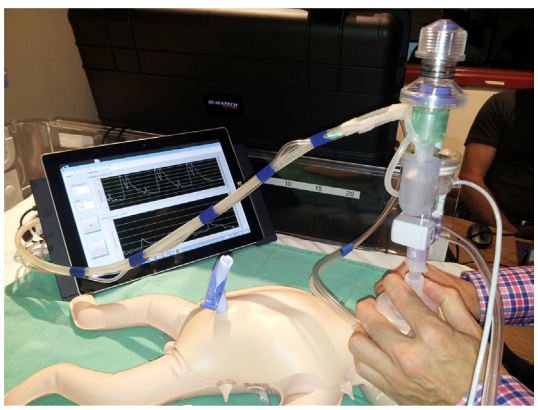

FIGURE 2 | Current prototype of the KM Medical Next Step™.

compliance level. Since small preterm infants are most prone to ventilation-induced lung injury (17), the experimental setup was that of a 1-kg infant and a target V_T of 5 mL/kg (18). During the experiments, participants were reminded to provide a targeted V_T of 5 mL/kg, but were blinded to respiratory data recordings, except when using the Next Step™, which has a screen displaying airway pressures and V_T in real time. After completion of all experiments, each participant was asked to complete a brief questionnaire. Questions included (i) "difficulty of providing PPV with each device"; (ii) "comfort with each device to provide PPV"; and (iii) preferred ventilation device; as well as profession, years of experience, and gender. Questions (i) and (ii) were rated using a Likert scale [1 (very difficult/uncomfortable) to 5 (very easy/comfortable)].

Data Processing and Statistical Analyses

Demographical data and device preferences are presented as numbers and percentages or median with range or interquartile range (IQR). The primary outcome parameters of the study (V_T and ventilation rate with each device and compliance level) were tested for normality and presented as mean with 95% confidence interval. The outcome parameters were nested within participants, and a cluster effect was likely to be present in the data. As observations within the same participant tended to be correlated, differences between ventilation devices were estimated using a linear mixed model treating device and compliance as fixed effects and participants as random effects. Adjustments were made for multiple comparisons. Categorical data were compared between devices with the Pearson's Chi-squared test.

Statistical analyses were performed in IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY, USA). A p-value <0.05 was considered significant.

RESULTS

Twenty-five NRP providers were recruited for the study [neonatologists ($n = 4$), neonatal fellows ($n = 5$), neonatal nurse practitioners ($n = 4$), respiratory therapists ($n = 8$), and neonatal nurses ($n = 4$)]. Nineteen (76%) of the participants were female. Participants had a median (range) of 6 (1–26) years of neonatal experience, and 10 (0–22) months had passed since their last NRP update.

Tidal Volume Delivery

The Next Step™ delivered the most consistent V_T at all compliance levels, but the V_T was 26% lower than the target at the lowest compliance level (0.5 mL/cmH_2O). The SIB delivered a higher V_T than all other devices at all compliance levels. V_T delivery was similar between T-piece devices in all three compliance levels. In summary, all ventilation devices except the Next Step™ delivered V_T, which was twofold to sixfold higher than our target V_T with increasing compliance levels (**Table 1**).

Ventilation Rate

Insignificant variation in the Next Step™ ventilation rate was observed (**Table 2**). By the design of the study, the ventilation rate with the Next Step™ was significantly different from that of the other devices i.e., set at 50 inflations/min, whereas the rate for the other devices was operator dependent. For the other devices, the ventilation rate was within 40–60/min at all compliance levels only with the SIB. The T-piece ventilation rates were slightly below the target at all compliance levels.

Questionnaire results are presented in **Table 2**. The Next Step™ was rated the easiest and the SIB the most difficult device to use.

TABLE 1 | Tidal volumes during 1 min of positive pressure ventilation with different ventilation devices and compliance levels.

	V_T (mL)			Rate (per minute)		
Compliance	**0.5 mL/cmH_2O (*n* = 25)**	**1.0 mL/cmH_2O (*n* = 25)**	**2.0 mL/cmH_2O (*n* = 25)**	**0.5 mL/cmH_2O (*n* = 25)**	**1.0 mL/cmH_2O (*n* = 25)**	**2.0 mL/cmH_2O (*n* = 25)**
SIB	11.4 (8.9–13.9)**	17.6 (13.2–22.0)**	23.5 (17.9–29.0)**	43 (38–49)**	42 (37–48)**	44 (38–50)**
Neo-Tee	5.6 (4.4–6.7)*	11.2 (9.0–13.3)*	19.3 (15.4–23.1)*	39 (32–46)**	38 (29–47)**	39 (32–46)**
Neopuff	6.1 (5.2–7.0)**	10.0 (7.4–12.5)**	21.3 (18.5–24.0)**	32 (26–38)**	40 (34–45)**	37 (32–42)**
Giraffe	5.7 (4.5–6.9)**	10.9 (8.5–13.3)**	19.8 (16.3–23.3)**	39 (35–43)**	39 (33–45)**	39 (33–44)**
Next Step™	3.7 (3.2–4.2)	4.9 (4.5–5.3)	4.5 (3.8–5.1)	48 (47–49)	49 (49–50)	50 (49–50)

Values are presented as mean with 95% confidence interval.
V_T, tidal volume; SIB, self-inflating bag.
**p-Value = 0.018 vs. the Next Step™.*
***p-Value ≤0.001 vs. the Next Step™.*

TABLE 2 | Health-care professionals' Likert scale rating of how difficult and comfortable [1 (very difficult/uncomfortable) to 5 (very easy/comfortable)] it was to use the different ventilation devices.

	How difficult was ventilation with the device? (*n* = 25)	**How comfortable was the use of the ventilation device? (*n* = 25)**
Self-inflating bag	3 (2–4)*	3 (2–4)*
Neo-Tee disposable T-piece	4 (3–4)	4 (3–4)
Neopuff infant T-piece	4 (4–5)	4 (4–5)
Giraffe stand-alone T-piece	4 (4–5)	4 (4–5)
Next step	5 (4–5)†	4 (3–5)

Values are presented as median with interquartile range (IQR).
**p < 0.05 vs. all the other devices.*
†p < 0.05 vs. all the other devices.

There was a significant difference in the number of participants preferring each device: 10 (40%) participants preferred the Next Step™, 9 (36%) preferred the Neopuff T-piece, 4 (16%) preferred the Giraffe T-piece, 1 (4%) preferred the Neo-Tee, and 1 (4%) answered "any T-piece device" ($p < 0.001$). The main difference was between the Neo-Tee and the Next Step™ ($p = 0.002$), and the SIB and the Next Step™ ($p < 0.001$).

DISCUSSION

In this randomized, controlled study comparing V_T delivery during mask ventilation at different compliance levels, we found that V_T delivery with widely used neonatal resuscitators was twofold to sixfold higher than our targeted V_T at high airway compliance, whereas volume delivery was lower than targeted with a prototype volume-controlled resuscitator at the lowest compliance.

During mask ventilation, the proportion of the V_T that enters the gas exchanging regions of the lungs may be affected by some of the volume being retained in the oropharynx and upper trachea (12). van Vonderen et al. (12) found that equivalent inflation pressures (25 cmH_2O) resulted in significantly higher V_{Ti} (11.1 vs. 5.8 mL/kg) and V_{Te} (8.3 vs. 4.9 mL/kg) during mask ventilation in 10 preterm infants compared to ETT ventilation in the same infants after intubation. We have previously studied ETT ventilation in our manikin model (11), and when we compare the ETT results with mask data from the present study, we also find higher V_T delivery at the low and high compliance setting using a facemask compared to ETT. However, with a compliance of 1 mL/cmH_2O, there is no difference in V_T delivery using a facemask or ETT with either device in our model.

T-Piece Resuscitators

The participants in the current study were not allowed to adjust the PIP on the T-piece devices, which potentially could have yielded even higher V_T than measured. On the other hand, a decrease in PIP with increasing compliance might have resulted in lower V_T delivery. Although compliance changes during lung aeration at birth might be detected during PPV using a flow-inflating bag (19), it remains challenging using either a SIB or T-piece device (20–22). In fact, our results support this claim as we observed increasing V_T with increasing compliance levels (**Table 1**), despite the fact that the T-pieces are the devices most extensively used by the study participants. This is further supported by Huynh et al. (23), who reported that participants are unable to assess effectiveness of V_T delivery during compliance changes.

T-piece resuscitators have several advantages compared to a SIB, including more consistent V_T delivery (24, 25) and airway pressure (5, 10, 26–28), which was also observed in the current study and our previous ETT study (11).

Self-Inflating Bag

The fact that SIBs are readily available in our NICU but rarely used might partly explain the fact that the participants found the SIB relatively difficult and uncomfortable to use during mask PPV (**Table 2**). A T-piece requires a gas source resulting in pressurizing the facemask, which could cause higher mask leak and lower V_T compared to the SIB. We did not measure mask leak, but this might have contributed to the higher V_T delivery with the SIB. However, the general lack of experience with the SIB might also have introduced a bias toward a greater deviation from target V_T with this device in our participants.

The Next Step™

The prototype volume-controlled resuscitator used in this experiment utilizes room air and does not require a pressurized gas source. It can deliver supplementary oxygen if connected to a gas tank or oxygen outlet. Similar to our findings in an intubated manikin (11), the Next Step™ provided the most consistent V_T

of all devices in the current study using a facemask (**Table 1**). Participants mentioned that the mask hold with the Next Step™ was unfamiliar, which might have resulted in a higher mask leak and V_T below target in the low compliance setting, especially since the low compliance was the first compliance tested. This suggests that health-care personnel should be familiar with the ventilation device they commonly use. However, despite this, the Next Step™ was ranked number one for preferred device as well as easiest to be used (**Table 2**). These are very important attributes, as the DR is often a stressful environment, where decisions are made quickly and resuscitators need to have good mask ventilation skills. In addition, the Next Step™ provides visual feedback by displaying delivered airway pressures and V_T during PPV. Although respiratory function monitoring is routinely used in the NICU (29), it is not commonly used in the DR during resuscitation (28, 30). Compared to a respiratory function monitor, the Next Step™ is expected to be cheaper. Also, being smaller and portable, the Next Step™ offers an advantage in units without a designated resuscitation area, i.e., where resuscitation is performed in the delivery suite. With these features, the Next Step™ device is a promising new device for neonatal resuscitation.

Ventilation Rate

Even though the ventilation rate was close to the 40–60/min target with the SIB and T-piece devices, the 95% confidence intervals indicate a variable rate during manual PPV. Preterm infants may have impaired cerebral autoregulation (31), and changes in minute ventilation caused by inconsistent ventilation rate may result in blood CO_2 fluctuations, which again have a theoretical potential for causing damage to the immature brain (32). Achieving more consistent ventilation rates in the DR offers a potential for improved outcomes.

Limitations

Using a manikin to simulate DR resuscitation has its limitations, as it does not resemble real-life resuscitation. However, new ventilation devices have to undergo extensive bench-top testing prior to introduction into the DR. During real-life resuscitation, clinicians can use clinical cues (e.g., changes in heart rate) to adjust their ventilation efforts (33), which manikins do not have. Furthermore, the manikin resembled a term infant rather than a 1-kg preterm infant and chest rise was not visible as the manikin was connected to the external test lungs, which might have caused higher V_T delivery. We tried to reduce this bias by continuously reminding the participants that they should aim for a 5-mL V_T/kg.

In conclusion, the Next Step™, a volume-controlled device, had the most consistent V_T delivery and ventilation rate compared to all other devices, and the SIB over delivered to the greatest extent. Participants were unable to recognize compliance changes. The Next Step™, a volume-targeted neonatal resuscitation device has the potential to provide a lung-protective strategy from birth both using a facemask and ETT, but requires further investigation.

AUTHOR CONTRIBUTIONS

AS conceptualized and designed the study; performed the data collection, data analysis, and data interpretation; and wrote the manuscript. EH, P-YC, and GS conceptualized and designed the study, was involved in the data analysis and data interpretation, critically reviewed the manuscript, and approved the final manuscript as submitted. SO and KB conceptualized and designed the study, was involved in the data interpretation, critically reviewed the manuscript, and approved the final manuscript as submitted.

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