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Chapter

A Porcine Model of Neonatal Hypoxia-Asphyxia to Study Resuscitation Techniques in Newborn Infants

Megan O'Reilly, Po-Yin Cheung, Tze-Fun Lee and Georg M. Schmölzer

Abstract

Two to three million newborn infants worldwide need extensive cardiopulmonary resuscitation (CPR), and approximately one million of these infants die annually worldwide. Therefore, resuscitation techniques require further refinement to provide better outcomes. To investigate the effectiveness of various interventions and to understand the pathophysiology and pharmacology of neonatal CPR, it is important to have animal models that reliably reproduce features observed in neonates who require resuscitation. Herein, we describe an experimental animal model in newborn piglets that simulates neonatal asphyxia and enables us to examine resuscitation interventions, reoxygenation, and recovery processes. The newborn piglet has several advantages including similar development to a human fetus at 36–38 week's gestation, and comparable body systems and body size, allowing for surgical instrumentation, monitoring, and collection of biological samples. Furthermore, using this model of neonatal asphyxia, we are also able to describe an increasingly important clinical situation in the laboratory setting—pulseless electrical activity (PEA). Since the integration of electrocardiogram into the neonatal resuscitation guidelines, there has been an increased awareness of PEA in newborn infants. The animal model we describe can therefore serve as a valuable tool to bridge the knowledge gap and improve the outcome of asphyxiated newborns in the delivery room.

Keywords: infants, newborn, neonatal resuscitation, asphyxia, heart rate, electrocardiography, auscultation

1. Introduction

Most newborn infants successfully transition from fetal to neonatal life without any help [1]. However, approximately 10–20% of newborns (13–26 million worldwide) need some degree of respiratory support at birth [2–4], which remains the most critical step of neonatal resuscitation. Furthermore, an estimated 0.1% of term infants and up to 15% of preterm infants (2–3 million worldwide) requires extensive cardiopulmonary resuscitation (CPR) at birth,

which entails chest compressions (CC) and 100% oxygen with or without administration of epinephrine [5–9]. Despite receiving CPR, approximately 1 million newborns die annually worldwide. Even with successful resuscitation, infants receiving extensive CPR in the delivery room have a high incidence of mortality (40–80%) and neurologic morbidity (e.g. 57% hypoxic–ischemic encephalopathy and seizures) [5, 6, 9]. Therefore, resuscitation techniques require further refinement to provide better outcomes. The guidelines for neonatal resuscitation recommended by the American Academy of Pediatrics/American Heart Association Neonatal Resuscitation Program [2–4] are based, in part, on the recognition that the cause of cardiovascular collapse in most newborns is asphyxia. However, in many cases the guidelines rely on data from studies in the adult population and extrapolate it to the neonatal population. Such data may not be entirely applicable to the neonatal population, because the most common cause of cardiovascular collapse in the adult population is primary cardiac compromise/ventricular fibrillation, not asphyxia. Therefore it is imperative that pre-clinical studies with appropriate animal models are carried out to determine the optimal resuscitation techniques before they are translated into the delivery room for newborn infants.

2. Asphyxia at birth

Asphyxia at birth, also known as perinatal asphyxia, is the most common reason that newborn infants fail to make a successful transition to ex-utero life [10]. Asphyxia may occur from several perinatal events, such as failure of placental gas exchange prior to delivery (e.g. placental abruption, uterine rupture, umbilical cord prolapse, chorioamnionitis), or deficient pulmonary gas exchange immediately after birth (e.g. apnea, airway obstruction, respiratory distress syndrome) [10]. Asphyxia is a condition of impaired gas exchange with simultaneous hypoxia and hypercapnia, leading to a mixed metabolic and respiratory acidosis [10]; it depresses myocardial function leading to cardiogenic shock, pulmonary hypertension, mesenteric reperfusion, acute renal failure, and ultimately cardiac arrest. The cascade of hypoxic–ischemic insults results in dysfunction of one or more organ systems in over 80% of asphyxiated newborn infants [11], leading to significant mortality and long-term morbidity. Newborns affected by perinatal asphyxia often present with an inadequate heart rate that does not respond to positive pressure ventilation (PPV). This is due to depressed myocardial function, vasodilation, and very low diastolic blood pressures through which the heart is unable to efficiently contract. Ineffective pumping of enough blood to the lungs inhibits the exchange and consumption of oxygen that is being delivered via PPV [10]. This inevitably leads to the need for CC to mechanically pump the blood through the heart until the myocardium is adequately oxygenated to resume spontaneous contraction and blood circulation [10].

3. Current neonatal resuscitation guidelines

Heart rate (HR) is the most important clinical indicator to evaluate the status of compromised newborns and to guide resuscitation efforts in the delivery room [3]. An increase in the newborn's HR remains the most reliable indicator of adequate ventilation [3]. Until recently, HR assessment in the newborn was achieved via (i) palpation of the umbilical cord, (ii) auscultation of the precordium, and/or

(iii) pulse oximetry [12]. In 2015, the neonatal resuscitation guidelines were updated to integrate the use of electrocardiography (ECG) as a tool for HR assessment immediately after birth [2–4]. This recommendation was based on observational data and small randomized controlled trials showing that ECG displays reliable HR faster than pulse oximetry [2–4]. However, the use of ECG does not replace the need for pulse oximetry, but rather compliment it.

The current neonatal resuscitation guidelines recommend initiation of PPV if the HR is below 100 beats per minute (bpm). If HR does not increase in response to PPV, several ventilation corrective steps are recommended: (i) check the seal of the face mask, (ii) reposition the neonate's head in "sniffing" position, (iii) suction obstructing secretions, (iv) open the mouth to decrease resistance to gas flow, (v) increase the peak inflating pressure, and (vi) establish an advanced airway (intubate or use a laryngeal mask device). If the above ventilation corrective steps fail to improve HR and it decreases to below 60 bpm, CC and 100% oxygen are recommended. If HR persists below 60 bpm despite CC and 100% oxygen, administration of intravenous epinephrine is recommended at a dose of 0.01–0.03 mg/kg. If epinephrine administration is required prior to the establishment of intravenous access, it can be administered endotracheally at a higher dose of 0.05–0.1 mg/kg. The currently recommended technique of delivering CC to a neonate is using a coordinated 3:1 compression-to-ventilation ratio (3:1 C:V). This approach is comprised of 90 CC and 30 ventilation inflations per minute, with a pause after every third CC to deliver one effective ventilation. This technique achieves approximately 120 events per minute. The CC are delivered on the lower third of the sternum and to a depth of approximately one-third of the anterior–posterior chest diameter, and the 2-thumb-encircling hands technique is the preferred method. However the chest compression ratio recommendation is based more on expert opinion and consensus rather than strong scientific evidence, since there is currently very-low-quality evidence to suggest otherwise, according to the guidelines [4].

4. Pulseless electrical activity

Pulseless electrical activity (PEA) is a form of cardiac arrest characterized by cardiac electrical activity, detected by ECG, but with the absence of a detectable pulse [13]. Although PEA is a commonly seen cardiac rhythm in adult and pediatric resuscitations (referred to as a "nonshockable rhythm"), occurring in approximately 32 and 24% of cardiac arrests, respectively [14], its occurrence in neonatal resuscitation is unusual and not widely recognized. In response to the inclusion of ECG in the 2015 neonatal resuscitation guidelines, there has been a rise in awareness of PEA in neonatal resuscitation. ECG displaying PEA could falsely mislead health care providers into overestimating the HR and delay necessary resuscitation techniques. It is possible that PEA may be common in asphyxiated newborns but has been undetected in the clinical setting prior to the recent use of ECG in the delivery room. Recent case reports have raised concerns over the reliability of ECG use during neonatal resuscitation, and the detection of PEA has been cited as a potential limitation of ECG use to guide delivery room resuscitation [15, 16]. Data from studies in the pediatric population indicate decreased survival following resuscitation with PEA events [17, 18], however this is inconsistent throughout the literature. Recent case studies in newborn infants presenting with cardiac arrest with PEA rhythm, as indicated on ECG [15, 16], suggest dire outcomes. Further studies (animal and prospective clinical) are needed to determine the cause and actual incidence of PEA in order to improve the survival of newborns experiencing PEA in the delivery room.

5. Porcine model of hypoxia-asphyxia

Herein we describe an experimental animal model from our research laboratory in newborn piglets that simulates neonatal hypoxia-asphyxia. Using this animal model, we are able to examine the systemic and regional hemodynamic changes during hypoxia-asphyxia, resuscitation interventions, reoxygenation, and the recovery process. The described experimental animal model is a non-survival acute procedure in neonatal pigs, aged between 1 and 3 days old and weighing approximately 1.5–2 kg. The approximate duration of the procedure is between six to eight hours and can be divided into the following sections: (i) anesthesia and surgical instrumentation, (ii) monitoring and stabilization, (iii) hypoxia and asphyxia, (iv) resuscitation intervention, and (v) reoxygenation and recovery.

5.1 Anesthesia and surgical instrumentation

Surgical procedures enable the establishment of mechanical ventilation, arterial and central venous access, and placement of catheters and flow probes for continuously monitoring intravascular pressures and blood flow across the common carotid artery, respectively. Anesthesia is induced using 5% inhaled isoflurane in 100% oxygen (delivered via a nose cone), and is then maintained at 2–3% with fine adjustment by 0.5% as appropriate, depending on the condition of the piglet.

Following induction of anesthesia, an incision is made in the right groin and the right femoral artery and vein are exposed. An area of approximately 1 cm is dissected around each of the vessels, which are then isolated by threading two lengths of suture ties under each vessel. The vessel is ligated distally using a suture tie, a small cut is made in the vessel wall, and then an Argyle catheter (3.5 or 5 French, Covidien, Mansfield, MA) is inserted into the vessel. A double-lumen catheter is used for the femoral vein and is inserted to 15 cm so it is placed close to the right atrium. The venous catheter can be used for medication and maintenance fluid infusions as well as continuous central venous pressure measurement. A single-lumen catheter is used for the femoral artery and is inserted to 5 cm so it is placed at the infra-renal aorta. The single-lumen arterial catheter can be used for continuous mean arterial pressure measurement and blood sampling. The groin incision is then sutured closed. Once vascular access has been established, the inhaled anesthesia can be switched to intravenous anesthesia using morphine and propofol infusions via the venous catheter. This is done after the piglet has been connected to the ventilator machine (see below).

The piglet is then intubated via tracheostomy. A horizontal incision is made at the neck, the trachea is dissected and exposed, and two lengths of suture ties are threaded around the trachea. An endotracheal tube (3.0 or 3.5) is inserted, connected to a ventilator and pressure-controlled ventilation (Acutronic Fabian HFO; Hirzel, Switzerland) is commenced at a respiratory rate of 16–20 breaths/min and pressures of 20/5 cm H_2O. Oxygen saturation is kept within 90–100% by adjusting the fraction of inspired oxygen between 21 and 30%.

The right common carotid artery is dissected and exposed, and one length of suture tie is threaded around to isolate the artery. A real-time ultrasonic flow probe (2 mm; Transonic Systems, Ithaca, New York, USA) is placed around the artery and secured, and ultrasonic gel is placed between the flow probe and artery to allow for optimal signal transduction. The flow probe provides continuous carotid blood flow (CBF) measurement. The neck incision is sutured closed. **Figure 1** shows the surgical instrumentation of the piglet.

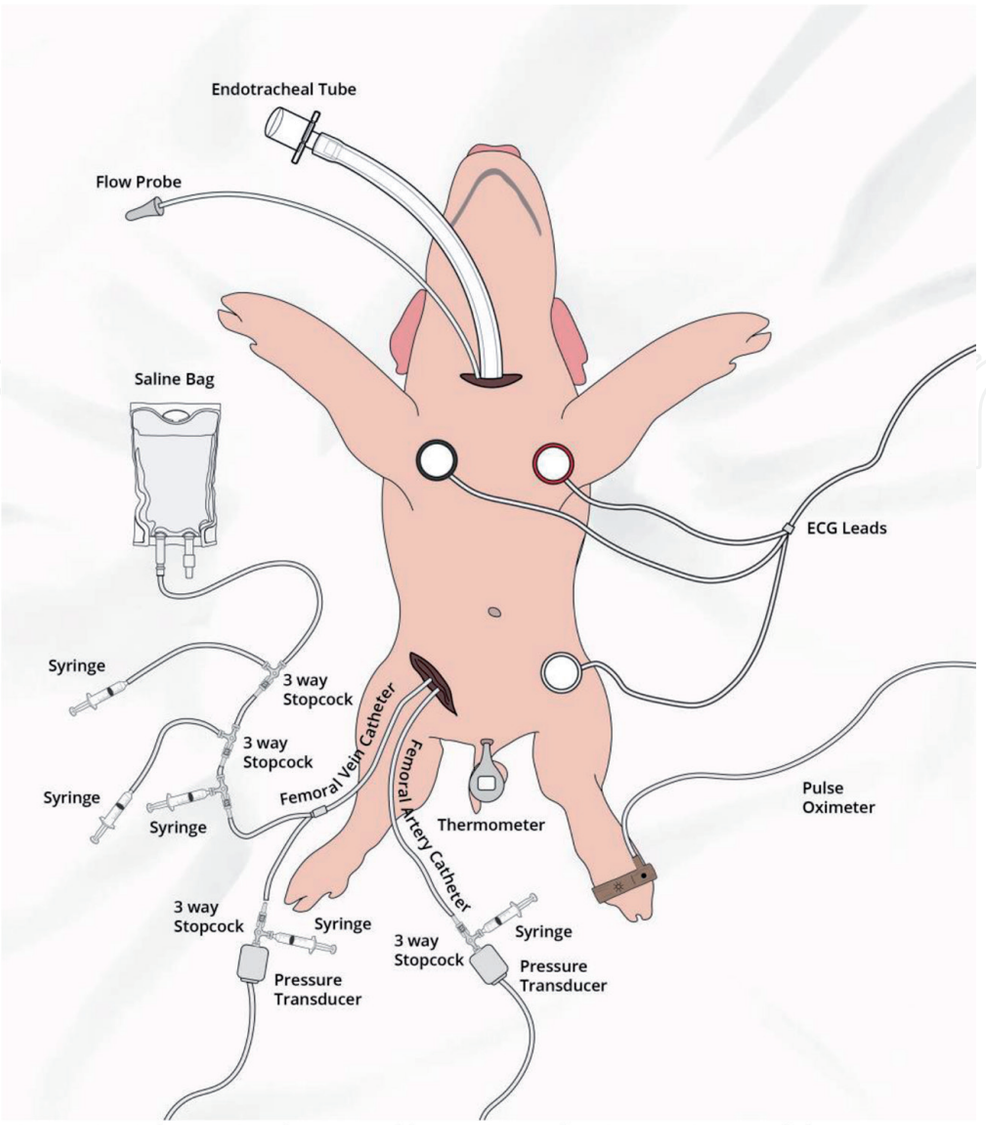

Figure 1.
Schematic of neonatal hypoxia-asphyxia porcine model (copyright https://www.playretain.com).

5.2 Monitoring and stabilization

A pulse oximeter is placed on the piglet's left hind limb for measuring percutaneous oxygen saturation. Continuous monitoring of the HR is achieved by attaching a 3-lead ECG to the piglet's skin (continuously measured and recorded with Hewlett Packard 78833B monitor, Hewlett Packard, Palo Alto, California, USA). Generally, baseline HR is between 150 and 200 bpm. Glucose level and hydration is maintained with an intravenous infusion of 5% dextrose at 10 mL/kg/hour. The piglet's body temperature is maintained at 38–40°C using an overhead warmer and a heating pad. During the experiment, anesthesia is maintained with intravenous propofol (5-10 mg/kg/hour) and morphine (0.1 mg/kg/hour). Additional doses of propofol (1–2 mg/kg) and morphine (0.05–0.1 mg/kg) are given as needed. The anesthetic state of the piglet is regularly monitored throughout the entire experiment using various criteria: neurological (body movements), behavioral (agitation), cardiovascular (tachycardia and hypertension), and respiratory (tachypnoea). The piglet is allowed to stabilize for 1 hour post surgery before the hypoxia-asphyxia protocol is commenced. **Figure 1** shows the placement of the monitoring devices on the piglet's body.

5.3 Hypoxia and asphyxia

The piglet is exposed to severe hypoxemia, which is induced via 30–60 min of normocapnic alveolar hypoxia. The piglet is ventilated with low inspired oxygen concentration delivered by increasing the inhaled concentration of nitrogen gas to induce hypoxemia. The inspired oxygen concentration is adjusted between 10 and 15% to obtain arterial oxygen saturations (SaO_2) of 30–40% and partial pressure of oxygen (PaO_2) of 20–40 mmHg. Arterial blood sampling is conducted to assess the partial pressure of carbon dioxide ($PaCO_2$) and the ventilator rate is then adjusted accordingly.

Hypoxia is followed by asphyxia, which is achieved by disconnecting the ventilator and clamping the endotracheal tube. Asphyxia can be conducted until either bradycardia, asystole or PEA (cardiac arrest). In this experimental animal model, bradycardia is defined as 25% of baseline heart rate, and asystole or PEA is defined as zero CBF and confirmed by auscultation of no HR. Following hypoxia-asphyxia, the resuscitation intervention protocol is commenced.

5.4 Resuscitation intervention

The primary goal of this experimental animal model is to provide a platform to investigate various resuscitation interventions in a pre-clinical scenario. Although the exact details of resuscitation interventions vary, they are predominantly comprised of the following elements: PPV (performed with a Neopuff T-Piece, Fisher and Paykel, Auckland, New Zealand), CC, ventilations, oxygen, and epinephrine administration. The ultimate outcome of the resuscitation intervention is to achieve return of spontaneous circulation (ROSC) in a timely manner, defined as an unassisted HR ≥100 bpm for at least 15 s. Section 8 summarizes the various resuscitation interventions published from our research group using this experimental animal model.

5.5 Reoxygenation and recovery

Following the resuscitation intervention and ROSC, the piglet is then reconnected to the ventilator with 100% oxygen briefly, and weaned down to 21% oxygen for the 4-hour post-resuscitation recovery period. At the end of the recovery period, the piglet is euthanized with an intravenous overdose of sodium pentobarbital (120 mg/kg). Tissue samples are collected as required.

6. Pulseless electrical activity in the porcine model of neonatal hypoxia-asphyxia

Using our porcine model of neonatal hypoxia-asphyxia, we are able to describe an increasingly important clinical situation in the laboratory setting. Recent studies from our group have identified the presence of PEA rhythms in nearly half of neonatal pigs that were subjected to hypoxia-asphyxia in animal models of neonatal resuscitation [19–21]. In the study by Patel et al., 43% of piglets (23/54) had no CBF or HR on auscultation but had a HR of 15–80 bpm displayed on ECG, indicating PEA rhythm [20]. Luong et al. reported that 49% of piglets (22/45) presented with PEA rhythms, as indicated by no CBF or HR on auscultation but a HR of 17–75 bpm was displayed on ECG [19]. Solevag et al. also reported that 43% of piglets (9/21) presented with PEA rhythm on ECG, as confirmed by zero CBF and no audible HR/pulse; however, only 56% of piglets with PEA rhythms achieved ROSC compared to 100% of piglets with non-PEA rhythms ($p = 0.02$) [21]. Furthermore, survival

to 4-hours post-ROSC occurred in only 33% of PEA piglets versus 58% of non-PEA piglets [21]. These studies indicate that cardiac arrest in the presence of a non-perfusing cardiac rhythm is common in asphyxiated neonatal piglets. Furthermore, this animal data is in agreeance with clinical observations of reduced CPR success in the presence of PEA in the delivery room in newborn infants [15, 16].

Studies from other research groups have also reported on the presence of PEA rhythms in their porcine model [22, 23]. It is important to note, however, that these studies were conducted in older piglets (2-month old "infant/pediatric" pigs) and were subjected to asphyxial cardiac arrest without the preceding hypoxia period. In the study by Lopez-Herce et al., 62% of piglets (44/71) had a PEA rhythm at the time of cardiac arrest [23]. However, there was no significant difference in the rate of ROSC between piglets with PEA rhythm (43%; 19/44) and piglets with non-PEA rhythm (30%; 7/23). Another study by the same research group, Gonzalez et al., also reported the presence of PEA rhythm at the time of cardiac arrest: 45% of piglets (22/49) [22]. Interestingly, the rate of ROSC was greater in piglets with PEA rhythm (45%; 10/22) versus non-PEA rhythm piglets (20%; 4/20) ($p = 0.037$).

The apparent discordance in the rate of ROSC post-PEA event between neonatal piglets [21] and pediatric piglets [22, 23] highlights the need for strong scientific evidence obtained from appropriate neonatal models to further our knowledge of delivery room resuscitation, rather than extrapolating data gained from the pediatric or adult populations. The percentages of PEA in our above-described neonatal model indicate relative consistency and can therefore be generalizable as a methodology. In this neonatal animal model, PEA is confirmed by electrical activity recorded on ECG in combination with no HR/pulse detected by auscultation and pulse oximetry and zero CBF. This animal model is beneficial for research directed at the management of PEA in newborns. Due to the increased awareness of PEA events in newborn infants, it is necessary to further investigate specifically tailored resuscitation techniques or changes in the resuscitation guideline algorithms to improve their survival. This translational model will therefore serve as a valuable tool to bridge the knowledge gap and improve the outcome of newborns that experience PEA in the delivery room.

7. Advantages and limitations of the porcine model of neonatal hypoxia-asphyxia

Owing to its many advantages, the clinically relevant porcine model of neonatal hypoxia-asphyxia has provided a platform to extensively investigate neonatal resuscitation. The newborn piglet is equivalent to a human infant at 36–38 weeks of gestational age, and has a comparable size and weight (1.5–2 kg body weight). This allows for relatively easy instrumentation to invasively monitor hemodynamic and physiological measurements, such as blood pressure and blood gases, as well as the ability to monitor the degree of hypoxia-asphyxia and reoxygenation in the recovery phase. The large size of this animal model (compared to smaller rodent models) allows the repeated collection of biological samples (plasma, whole blood) during the experimental period for biochemical assays. The piglet's cerebral metabolic data and many of the body systems, including cerebrovascular and cardiovascular systems, are also comparable to the human counterparts. This allows for better interpretation of the findings and makes it an exceptional animal model to study resuscitation interventions. The porcine model of neonatal hypoxia-asphyxia closely simulates delivery room events, with the gradual onset of severe hypoxia-asphyxia leading to cardiac arrest. Bradycardia or asystole (cardiac arrest) in newborn infants is usually caused by hypoxia/asphyxia, rather than

primary cardiac compromise/ventricular fibrillation observed in adult patients. Furthermore, using our newborn piglet model, we are able to describe an increasingly important clinical situation in the laboratory setting – PEA, which is not well described in newborns in the delivery room. However, the asphyxia model uses piglets that have already undergone the transition from fetal to neonatal circulation and have cleared their lung fluid, which may present as a limitation. Furthermore, our model requires piglets to be intubated with a tightly sealed endotracheal tube to prevent any endotracheal tube leak. This may not occur in the delivery room where infants are either intubated (larynx bypassed, leak present) or receive respiratory support via a facemask, resulting in the possibility of airway obstruction or mask leaks. Nevertheless, many of its advantages make up for the few limitations of the model.

8. Contribution of the porcine model of neonatal hypoxia-asphyxia to current knowledge

The porcine model of neonatal hypoxia-asphyxia has proven to be an invaluable tool through which new resuscitation techniques can be studied pre-clinically. It has also proven to be a crucial element in increasing our understanding of physiological and pharmacological changes surrounding neonatal resuscitation. Below is a summary of studies that have utilized the model to gain further knowledge in various aspects of neonatal resuscitation. Knowledge gained from the below described studies are key in shaping the future neonatal resuscitation guidelines [24, 25].

8.1 Sustained inflations

The current neonatal resuscitation guidelines and the previous guidelines in 2010 [2–4, 26] recommend using a 3:1 C:V ratio when CC are needed, however these recommendations are not based on strong scientific evidence and the most effective C:V ratio in newborns remains controversial. Using our porcine model, Schmölzer et al. investigated an alternative approach to providing ventilation during CPR in the means of sustained inflations (SI) [27]. Rather than the standard coordinated 3:1 C:V technique, Schmölzer et al. proposed that SI during CC would passively deliver an adequate tidal volume into the lungs and improve survival. SI was delivered with a peak inflating pressure of 30 cmH2O for duration of 30 s. During the SI, CC was delivered at a rate of 120/min; SI was interrupted after 30 s for 1 s before a further 30 s of SI was provided [27]. The results showed that piglets resuscitated with SI during CC not only achieved ROSC faster than piglets resuscitated with the standard 3:1 C:V technique, but also had improved hemodynamic recovery and survival [27]. Following that study, Li et al. investigated the optimal rate of CC during SI by comparing CC rates of 90/min and 120/min [28]. Both groups had a similar time to ROSC, survival rates, and hemodynamic and respiratory parameters during CPR, and the hemodynamic recovery in the subsequent 4-hours was also similar in both groups. This leads the authors to suggest that resuscitation with a CC rate of 120/min during SI did not show a significant advantage compared to 90/min and higher CC rates are not necessarily an advantage [28]. To assure this suggestion, another study by Li et al. compared SI with CC at a rate of 90/min to the standard 3:1 C:V technique [29]. Piglets resuscitated with SI during CC at 90/min had significantly improved time to ROSC and also a reduced requirement for 100% oxygen and improved respiratory parameters compared to piglets resuscitated with 3:1 C:V [29]. Mustofa et al. investigated the optimal length of SI during CC by comparing

resuscitation with SI duration of either 20 s or 60 s [30]. Using SI duration of 60 s resulted in a similar time to ROSC as SI duration of 20 s, as well as similar survival rate and hemodynamic recovery [30]. Furthermore, Mustofa et al. showed no significant differences in lung and brain pro-inflammatory cytokine concentrations between the SI groups and the 3:1 C:V group, suggesting that the SI technique does not promote more acute brain and lung injuries that the currently practiced technique of 3:1 C:V [30].

8.2 Asynchronous ventilation

Using the porcine model of neonatal hypoxia-asphyxia, Schmölzer et al. investigated a different approach to neonatal resuscitation with asynchronous ventilation during continuous CC; the rationale being that giving continuous CC without pausing for ventilation (as with 3:1 C:V) may avoid interruption in coronary perfusion and may improve minute ventilation during CPR [31]. Piglets were resuscitated with either the standard 3:1 C:V technique or the asynchronous ventilation technique, which delivered continuous CC at a rate of 90/min with asynchronous ventilation at a rate of 30 inflations/min [31]. Both groups had a similar time to ROSC, survival rates, epinephrine and oxygen administration, and hemodynamic and respiratory parameters during CPR; systemic and regional hemodynamic recovery in the subsequent 4-hour recovery period was also similar. This suggests that asynchronous ventilation during continuous CC is not more beneficial to the standard 3:1 C:V technique. In a following study, Patel et al. examined whether the outcome will improve by using different CC rates with asynchronous ventilation, namely 90/min, 100/min, and 120/min [32]. Even though rate and time to ROSC were similar between groups, increasing the CC rate to 120/min with asynchronous ventilation significantly improved hemodynamic recovery, as indicated by CBF, and cerebral and renal perfusion [32].

8.3 Oxygen

Current neonatal resuscitation guidelines recommend the use of 100% oxygen when CC are needed, however this is based on minimal evidence and 100% oxygen is also associated with increased oxidative stress [2–4, 33], and increased morbidity and mortality [34, 35]. Solevåg et al. examined the effect of using 21% oxygen (air) or 100% oxygen during resuscitation using either the 3:1 C:V technique or continuous CC with asynchronous ventilation (rate of 90/min) [36]. Time to achieve ROSC was similar between groups, however resuscitation with air was associated with a higher left ventricular stroke volume after ROSC and less myocardial oxidative stress compared to resuscitation with 100% oxygen [36]. This suggests that air during CC may reduce myocardial oxidative stress and improve cardiac function compared to 100% oxygen. However, the use of continuous CC with asynchronous ventilation in this study was less effective than the standard 3:1 C:V technique [36].

8.4 Chest compressions

Pasquin et al. used the porcine model of neonatal hypoxia-asphyxia to examine different ratios of CC to ventilations; the standard 3:1 C:V technique was compared to a C:V ratio of 2:1 and 4:1 [37]. Time to ROSC, mortality, oxygen requirements, epinephrine administration, and hemodynamic recovery were similar between all groups, indicating no difference in the efficacy of various C:V ratios in asphyxial-induced cardiac arrest of neonatal piglets.

8.5 Respiratory parameters

The purpose of inflations during CC is to deliver an adequate tidal volume to facilitate gas exchange [38], however limited information exists regarding tidal volume delivery during CC. Therefore, Li et al. examined the changes in tidal volume during CC and their effect on lung aeration in the porcine model of hypoxia-asphyxia [39]. Li et al. shows that when resuscitating using the SI with CC technique, passive lung ventilation/aeration can be achieved. In contrast, although use of the 3:1 C:V technique delivered tidal volume, it also resulted in a relative loss of tidal volume per 3:1 C:V cycle of up to 4.5 mL/kg [39]. This suggests that tidal volume delivery is greater when using SI with CC to resuscitate compared to the standard 3:1 C:V technique; this may lead to better alveolar oxygen delivery and lung aeration [39].

Using an objective method to evaluate recovery or predict the outcome of resuscitation may help decision-making during resuscitation. Therefore, Li et al. examined the temporal changes in end-tidal CO_2 ($ETCO_2$), volume of expired CO_2 (VCO_2), and the partial pressure of exhaled CO_2 ($PECO_2$) and their relationship with survivability and hemodynamic changes during CPR in the neonatal porcine model [40]. Li et al. reported that surviving piglets had significantly higher values of $ETCO_2$, VCO_2, and $PECO_2$ during CPR compared to non-surviving piglets, suggesting that continuously monitoring $ETCO_2$, VCO_2, and $PECO_2$ during CC has the potential to be a non-invasive method to indicate ROSC [40]. To further investigate if other parameters could be used as early outcome predictors after CPR, Solevåg et al. examined if cerebral and renal tissue oxygen saturation was different between surviving piglets and non-surviving piglets that were resuscitated after asphyxia-induced cardiac arrest [41]. The relationship of the tissue oxygen saturations with cardiac output, blood pressure, and biochemical variables was also examined [41]. No correlation between cardiac output or blood pressure and cerebral or renal tissue oxygen saturation was observed.

8.6 Hemodynamics

Espinoza et al. examined the changes in HR during adequate PPV following severe bradycardia in the porcine model of hypoxia-asphyxia [42]. The Neonatal Resuscitation Program (NRP) states that if adequate PPV is given for low HR, then the infant's HR should increase within the first 15 s of PPV. However in contrast to the NRP, Espinoza et al. showed that adequate PPV does not increase HR within 15 s of ventilation in piglets with asphyxia-induced bradycardia; after 30 s of PPV only half of piglets had an increase in HR. This study challenges the current NRP statement and suggests that clinicians should not expect an increase in HR after 15 s of PPV if there is severe bradycardia [42].

8.7 Epinephrine

Current neonatal resuscitation guidelines recommend the administration of intravenous epinephrine during if HR persists below 60 bpm despite CC and 100% oxygen [2–4]. However there is currently a lack of data evaluating the hemodynamic effects of epinephrine during neonatal resuscitation. Wagner et al. utilized the porcine model of hypoxia-asphyxia to examine hemodynamic changes after epinephrine administration during resuscitation and compare surviving and non-surviving piglets; epinephrine was administered at a dose of 0.01 mg/kg [43]. Epinephrine had no effect on either HR or cardiac output in survivors versus non-survivors during resuscitation; it did not increase survival rates or ROSC [43].

The abovementioned studies highlight the practicality of this neonatal animal model not only in driving progress in our understanding of neonatal resuscitation, but also in paving the way for new techniques into the delivery room.

9. Conclusions

Animal models that reliably reproduce the events surrounding neonatal resuscitation in the delivery room are imperative to improve the outcome of newborn infants requiring CPR and may also lead to benefits for the pediatric population. Due to its many advantages, the porcine model of neonatal hypoxia-asphyxia is one of the most commonly used large animal models for neonatal resuscitation studies. Not only has this model provided a further understanding of the effects of various resuscitation interventions, but it has also enabled the study of an increasingly important clinical situation in the laboratory setting – pulseless electrical activity. Using this animal model will further accelerate knowledge on neonatal resuscitation that will ultimately benefit patients.

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