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Title: Neonatal Resuscitation with Continuous Chest Compressions and High Frequency Percussive Ventilation in Preterm Lambs

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Category of Study: Basic Science

Impact Statement:

- Ventilation is the most important intervention in newborn resuscitation.
- Currently recommended 3:1 compression-to-ventilation ratio is associated with hypercarbia and poor oxygen delivery to the brain.

- Providing uninterrupted continuous chest compressions during high frequency percussive ventilation is feasible in a lamb model of perinatal cardiac arrest, and demonstrates improved gas exchange and oxygen delivery to the brain.
- This is the first study in premature lambs evaluating high frequency percussive ventilation with asynchronous chest compressions and lays the groundwork for future clinical studies to optimize gas exchange and hemodynamics during chest compressions in newborns.

ABSTRACT

Background: Cerebral oxygen delivery (cDO_2) is low during chest compressions (CC). We hypothesized that gas exchange and cDO_2 are better with continuous CC with high frequency percussive ventilation (CCC+HFPV) compared to conventional 3:1 compressions-to-ventilation (C:V) resuscitation during neonatal resuscitation in preterm lambs with cardiac-arrest induced by umbilical cord compression.

Methods: Fourteen lambs in cardiac arrest were randomized to 3:1 C:V resuscitation (90CC+30 breaths/min) per the Neonatal Resuscitation Program guidelines or CCC+HFPV (120CC+HFPV continuously). Intravenous epinephrine was given every three minutes until return of spontaneous circulation (ROSC).

Results: There was no difference in the incidence and time to ROSC between both groups. Median (IQR) $PaCO_2$ was significantly lower with CCC+HFPV during CC, at ROSC and 15 min post-ROSC-[104 (99-112), 83 (77-99), and 43 (40-64)], respectively compared to 3:1 C:V-[149 (139-167), 153 (143-168), and 153 (138-178) mmHg. PaO_2 and cDO_2 were higher with CCC+HFPV during CC and at ROSC. PaO_2 was similar 15 min post-ROSC with a lower FiO_2 in the CCC+HFPV group 0.4 (0.4-0.5) vs. 1 (0.6-1).

Conclusion: In preterm lambs with perinatal cardiac-arrest, continuous chest compressions with HFPV does not improve ROSC but enhances gas exchange and increases cerebral oxygen delivery compared to 3:1 C:V during neonatal resuscitation.

INTRODUCTION

The successful transition from fetal to extrauterine life requires optimal lung inflation, [1] a rapid increase in pulmonary blood flow, [2] and clearance of lung liquid to establish lungs as the site for gas exchange. In the severely asphyxiated neonate born with profound bradycardia or cardiac arrest, this transition may not occur optimally unless adequate ventilatory and circulatory support is provided. The underdeveloped, surfactant-deficient, and less compliant lungs of a premature infant further complicates resuscitation.

Neonates presenting with profound bradycardia or cardiac arrest have marked acidosis with high $PaCO_2$.[3] High-frequency ventilation (HFV) can quickly eliminate CO_2 and is less injurious to the fragile lungs of premature infants if appropriate lung recruitment is achieved.[4] The optimal ventilation strategy during chest compressions for neonatal bradycardia/ cardiac arrest in preterm infants is not known.[3,5] Studies in term lambs in cardiac arrest have shown that continuous chest compressions with asynchronous ventilation with a T-piece device result in higher carotid blood flow and higher cerebral oxygen delivery (cDO_2) compared to resuscitation with conventional 3:1 compression-to-ventilation (C:V) ratio.[6] Experiments in term asphyxiated and severely bradycardic piglets demonstrated that continuous chest compressions during sustained inflations resulted in quicker time to return of spontaneous circulation (ROSC) and improved minute ventilation when compared to 3:1 C:V.[7] However, sustained inflation in preterm infants was associated with increased early mortality in an international multicenter randomized controlled trial[8] and hence may not be the preferred mode of ventilation in preterm infants.

Premature and severely asphyxiated newborns lack robust cerebrovascular autoregulation,[9] placing them at increased risk of severe fluctuations in cerebral blood flow when

subjected to rapid changes in systemic blood pressure and $PaCO_2$ concentrations. High $PaCO_2$ concentrations may increase the risk of reperfusion injury to the brain. Optimizing gas exchange during neonatal resuscitation and normalizing $PaCO_2$ early may prevent rapid fluctuations in $PaCO_2$, and stabilize cerebral blood flow, which could improve neurological outcomes in surviving infants. There are no studies to date that have evaluated gas exchange in premature infants or preterm animal models during chest compressions and in the immediate period post-ROSC. In this study we aim to compare the Textbook of American Academy of Pediatrics-Neonatal Resuscitation Program (AAP-NRP) recommended 3:1 C:V resuscitation[10-12] to continuous chest compressions (CCC) and high frequency percussive ventilation (HFPV) using the portable TXP5 (Percussionaire, Sandpoint ID, - Figure 1) in a perinatal asphyxial cardiac-arrest preterm lamb model. Our primary outcome was evaluation of $PaCO_2$ during chest compressions. Our secondary outcomes were PaO_2 during chest compressions, ROSC success, and time to ROSC.

Insert Figure 1

METHODS

Animal preparation:

The protocol was approved by the Institutional Animal Care and Use Committee (IACUC, protocol #22544) at the University of California, Davis. All experiments were performed according to animal ethical guidelines, in compliance with the ARRIVE guidelines.[13] Time-dated preterm (124-126 days gestation, equivalent to a human gestation of 25-26 weeks) pregnant ewes (Dorper-cross) were procured from Van Laningham Farm, Arbuckle, CA. Following an overnight fast, the ewe was anesthetically induced using a combination of ketamine and propofol and intubated with a cuffed 9.5-mm endotracheal tube (ETT). General anesthesia was maintained by 2-5% inhaled isoflurane. After a cesarean section, the fetal lamb was partially exteriorized to expose the head and neck. The fetus was intubated with a 3.5-mm cuffed ETT and lung fluid was passively drained by gravity. The right carotid artery was catheterized for pre-ductal arterial blood sample collection. The right jugular vein was catheterized for fluid administration. A 2 or 3-mm ultrasonic flow probe (Transonic, Ithaca, NY) was placed around the left carotid artery to measure cerebral blood flow. Following fetal instrumentation, the umbilical cord was occluded to induce asphyxia until cardiac arrest with heart rate of 0 beats per min (bpm - asystole). Then the cord was clamped and cut and the lamb delivered, weighed, and placed on a radiant warmer. A pulse oximeter was placed on the right forelimb for continuous capillary oxyhemoglobin saturation (SpO_2) monitoring. The umbilical cord was transected and catheterized. A low-lying umbilical venous catheter (UVC) was placed to a depth of 4 cm for epinephrine administration and an umbilical arterial catheter was placed for continuous arterial blood pressure monitoring without any interruptions during right carotid arterial sampling.

Experimental Protocol:

Lambs were randomized into the control or intervention groups using opaque sealed envelopes. Hemodynamic parameters were continuously recorded using a computer with AcqKnowledge Acquisition & Analysis Software (BIOPAC systems, Goleta, CA). After a five-minute period of asystole, lambs were resuscitated by initiating positive pressure ventilation (PPV), using a T-piece resuscitator at 40/7 cm H_2O and an FiO_2 of 0.3 at 40 breaths per minute for 30 seconds. Pressures of 40/7 cm H_2O are required to achieve observable chest rise and achieve desired tidal volume in extremely premature lambs that have non-compliant, surfactant-deficient lungs. Pressures were adjusted based on chest rise.

Lambs were randomized into the following two groups:

Control Group (3:1 C:V resuscitation): If the heart rate remained < 60 bpm following 30 seconds of PPV, chest compressions were started, and the FiO_2 increased to 1.0. Positive pressure ventilation was continued using a T-piece resuscitator at pressures of 40/7 cm H_2O and synchronized with compressions at a C:V ratio of 3:1 (90 compressions and 30 breaths per minute). The estimated mean airway pressure (Paw) at these settings is 14-15 cm H_2O. The first dose of epinephrine (0.02 mg/kg) was administered at three minutes after onset of PPV via the UVC if the heart rate was < 60 bpm and repeated every three minutes until ROSC or until a total of four doses of epinephrine had been given. Each dose of epinephrine was followed by a 3mL normal saline flush. Arterial blood samples were collected every minute during chest compressions, at ROSC, and 1, 2, 3, 4, 5, 10, 15, 30, 45, and 60 minutes post-ROSC for blood gas analysis. Lambs that achieved ROSC were placed on intermittent mandatory ventilation via a conventional ventilator (Puritan Bennett 840, Medtronic, MN). Ventilator settings (peak

inspiratory pressure, positive end expiratory pressure, inspiratory time, rate) were adjusted and FiO_2 titrated to maintain SpO_2 between 90-95% and $PaCO_2$ between 40-60 mm Hg.

Intervention Group (CCC with HFPV): Similar to the control group, if the heart rate remained < 60 bpm following 30 seconds of PPV, chest compressions were started, and the FiO_2 increased to 1.0. Continuous asynchronous chest compressions were given at a rate of 120 compressions per minute and the lamb was placed on the TXP 5 ventilator. The frequency was set at 200 breaths per minute and amplitude at 50. This amplitude was needed to achieve adequate chest wiggle. The low frequency was chosen to reduce Paw:amplitude ratio and prevent barotrauma. At these settings, the inspiratory to expiratory ratio was 1:2. Paw was set at 15 cm H_2O to match the estimated Paw in the control group. Epinephrine administration and arterial blood gas sampling were similar to the control group. Lambs that achieve ROSC remained on the TXP for respiratory support. FiO_2 was adjusted to maintain SpO_2 between 90-95%. Amplitude, followed by frequency, were titrated to maintain $PaCO_2$ between 40-60 mm Hg.

Statistical Analysis:

Non-parametric continuous variables were analyzed for statistical significance by Mann–Whitney U test. Some of the baseline characteristics were evaluated using chi-square test or Fisher's exact test for proportions as appropriate. Hemodynamic data were acquired using BIOPAC AcqKnowledge software (Biopac Systems Inc, Goleta, CA), which has an acquisition sample rate of 2000 Hz. Data was extracted by 15 seconds increments and averaged over one minute.

Sample size: We calculated our sample size for the outcome of $PaCO_2$ at the time of ROSC. Prior data with standard 3:1 compression to ventilation approach demonstrated a $PaCO_2$ of 138±18 mmHg at ROSC. Using data from pilot studies with CCC+HFPV, we expected a difference of 30 mmHg in $PaCO_2$ compared to 3:1 approach. Seven lambs in each group had a probability (power) of 0.8 and a Type I error probability of 0.05. We did not have preliminary data to calculate sample size based on incidence of ROSC.

RESULTS

Baseline Characteristics and ROSC Success:

Characteristics of the fourteen lambs were not statistically different between the two groups (Table 1). All lambs achieved ROSC and there was no difference in time to achieve ROSC (Table 1). Thirteen of the fourteen lambs achieved ROSC after a single dose of epinephrine and one of the intervention lambs required a second dose.

Insert Table 1

Blood Gas Analysis:

$PaCO_2$ in the intervention group were significantly lower throughout resuscitation and at 15 minutes post-ROSC compared to the control group (Figure 2). PaO_2 in the intervention group were significantly higher during resuscitation and at ROSC (Figure 2). There was no difference in PaO_2 15 minutes post-ROSC between groups. However, there was a significantly lower FiO_2 need in the intervention group compared to the control group at 15 min after ROSC (Figure 3).

Insert Figures 2 and 3

Carotid Blood Flow, Oxygen Delivery to the Brain and Hemodynamics:

Carotid blood flow as well as systolic, diastolic, and mean arterial blood pressures were similar at baseline and throughout the study in both groups (Table 2). The intrinsic heart rate at baseline and post-ROSC were similar (Table 2). As per study design, the chest compression rates differed between the groups. The measured chest compression rate in the control group was 90 (83-98) beats per minute and the measured chest compression rate in the intervention group was 113 (113-120), which was slightly below the intended target of 120/min (Table 2). Content of

arterial oxygen (CaO_2) was higher in the intervention group during chest compressions and at time of ROSC, but similar at all other time points (Table 2). Median cerebral oxygen delivery (cDO_2) during chest compressions and at time of ROSC was significantly higher in the intervention group (Figure 4).

Insert Table 2 and Figure 4

DISCUSSION:

Following cardiac arrest, optimizing oxygen delivery to the brain and avoiding hypocapnia and hypercapnia may potentially improve neurological outcomes among survivors.[14] Cerebral hypoxia occurs during chest compressions followed by reperfusion injury following ROSC due to hypercapnic cerebral vasodilation.[15,16] In the current study, using a lamb model of perinatal arrest, we demonstrate improving brain oxygen delivery and normalizing $PaCO_2$ concentrations using a portable high-frequency ventilator during resuscitation. To our knowledge, this is the first study using high-frequency percussive ventilation for neonatal resuscitation in a lamb model of perinatal arrest and supports a recent case report of oscillatory ventilation during neonatal resuscitation.[17]

Advanced resuscitation requiring chest compressions and medications is associated with an increased risk of mortality and impaired neurodevelopment among survivors.[18,19] The unique physiology of the preterm newborn following birth, with fluid-filled immature lungs, increased pulmonary vascular resistance, and a patent ductus arteriosus can make resuscitative efforts more difficult. Optimal oxygenation[20] and avoiding fluctuations in carbon dioxide concentrations are important to minimize brain injury in preterm infants.[21]

The current NRP guidelines recommend chest compressions be coordinated with ventilation in a 3:1 ratio with approximately 90 compressions and 30 ventilations per minute for severe bradycardia (HR< 60bpm) or asystole.[10-12] Preclinical studies have shown that this method of resuscitation results in ROSC but is not very effective in facilitating gas exchange in the presence of cardiac arrest.[6,9,22,23] Studies in term animal models (lambs and piglets) of higher chest compression rates have shown improved ventilation and oxygenation[6,7] and we cannot ascertain how much of an effect the chest compression rate vs. high-frequency ventilation had on

our data. However, preliminary data from our lab in preterm lambs using continuous chest compressions at 120/min with asynchronous ventilation via positive pressure ventilation using a T-piece resuscitator showed no difference in gas exchange, carotid flow, and cerebral oxygen delivery throughout resuscitation when compared to 3:1 C:V.[24]

High-frequency ventilation (HFV) has been shown to effectively recruit lung volume in premature infants and improve ventilation. Recent data indicate no hemodynamic instability on HFV if Paw is optimized.[25] In a retrospective study of 100 premature infants who were transitioned from conventional mechanical ventilation to HFV, there was no deterioration in hemodynamics assessed by echocardiography and no increased risk of intraventricular hemorrhage.[25] A recent case report demonstrated feasibility of using HFV in the resuscitation of a premature infant in the delivery room.[17] In the current study, lambs randomized to HFPV achieved a physiological $PaCO_2$ by 15 minutes post-ROSC and required significantly lower FiO_2 to maintain normoxia.

The two most common types of HFV, high frequency jet ventilators and high frequency oscillatory ventilators (HFOV), are bulky and resource intensive to use, adding an additional barrier to implementing their use in the delivery room. The TXP, a HFPV ventilator, is smaller, lighter, and not electrically driven, making it an ideal candidate for use in resource limited environments and in delivery rooms with space restrictions (Figure 1). HFPV has a device called a Phasitron. The Phasitron is a pneumatically driven combined inhalation and exhalation valve that acts as a flow interrupter via a sliding venturi mechanism. When powered by high gas pressure, the Phasitron delivers high frequency, sub-tidal, pressure-limited, time-cycled breaths. These sub-tidal volumes enable gas exchange within the bronchioles while maintaining an expiratory pressure for peripheral lung recruitment. The TXP ventilator is the simplest of the

HFPV devices providing monophasic distending pressure with passive exhalation. The TXP has only three controllable parameters: Paw, amplitude, and frequency. Mean airway pressure is used to improve lung expansion and oxygenation, while frequency and amplitude are used to alter ventilation. Frequent monitoring is needed to avoid hypocapnia as end-tidal CO_2 measurements are not feasible during HFPV. The TXP plays a pivotal and high successful role in interfacility neonatal transport. Not only is often used to enable the safe movement of critically ill neonates via air and ground to tertiary and quaternary facilities, it has been demonstrated to reduce FiO_2 requirement and normalize pH during the transport process[26] without an increase in complication rate (air leak or tube dislodgement).[27]

There are several limitations to this study. The 100% ROSC success rate in the control group precludes the ability to evaluate for a higher ROSC success rate in the intervention group. While preliminary data from our lab demonstrating that providing a higher chest compression rate in preterm lambs had a negligible improvement in gas exchange, carotid flow, or cerebral oxygen delivery, these results cannot uncouple the applied intervention of HFPV atop a higher chest compression rate.[24] As such, it cannot be concluded the higher chest compression in some way contributed to observed results of this study. The PaO2 and PaCO2 at time of ROSC differed between the groups which impacts the comparison at 15-minutes ROSC. The study was conducted in a controlled setting by personnel with clinical experience using TXP. Results obtained by inexperienced resuscitators or without access to frequent blood gas monitoring may potentially be different. While all versions of the TXP are pneumatically powered, our study utilized the TXP-5 that requires A/C power to operate the alarm and manometer. A similar version on the market called the TXP-2D utilizes a simple disposable battery to operate the manometer, allowing for its application in resource limited environments. The TXP-2D weighs

a mere 0.89 kilograms and is only 16 x 11 x 10 cm in dimensions, making it a viable option for implementation in the delivery room.

CONCLUSIONS:

In a preterm asphyxial cardiac-arrest lamb model, continuous chest compressions with asynchronous ventilation provided by a portable high frequency percussive ventilator resulted in improved gas exchange and oxygen delivery to the brain. Incidence and time to ROSC were comparable to the current NRP recommended 3:1 C:V resuscitation. Further animal studies and clinical trials evaluating high frequency ventilators during advanced neonatal resuscitation in the delivery room are warranted.

Data Availability: The datasets generated during and analyzed from the current study are available from the corresponding author on request.

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Other Statements

Author Contributions:

Contributed to study design, study conduction, and data analysis: E.G, D.S., A.L., H.J., M.H., V.H., L.Z., S.L., P.V.

Drafted and provided critique of manuscript: E.G., D.S., A.L., S.L., P.V.

Final approval: E.G., D.S., S.L., P.V.

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Informed Consent Statement: Not required.

Figure legends:

Figure 1: Picture of the TXP-5 ventilator and Phasitron next to a ruler in inches for comparison. The TXP-5 is a compact, pneumatically powered, high frequency percussive ventilator. Using its unique circuit, called the Phasitron, this ventilator generates a constant distending pressure intertwined with high frequency, sub-tidal, pressure-limited, and time-cycled breaths. The three knobs rotate to control the only three parameters: amplitude, frequency, and mean airway pressure.

Figure 2: Changes in preductal $PaCO_2$ in CCC + HFPV group and 3:1 C:V group at baseline, after asphyxia, during chest compressions, at time of ROSC, and 15 minutes post-ROSC. CCC on HFPV: continuous chest compressions on high frequency percussive ventilation. ROSC: return of spontaneous circulation. * $p < 0.01$ (Mann-Whitney U test).

Figure 3: Changes in preductal PaO_2 and FiO_2 in CCC + HFPV group and 3:1 C:V group at baseline, after asphyxia, during chest compressions, at time of ROSC, and 15 minutes post-ROSC. CCC on HFPV: continuous chest compressions on high frequency percussive ventilation. ROSC: return of spontaneous circulation. * $p < 0.01$ (Mann-Whitney U test).

Figure 4: Changes in Cerebral Oxygen Delivery in CCC + HFPV group and 3:1 C:V group at baseline, after asphyxia, during chest compressions, at time of ROSC, and 15 minutes post-ROSC. CCC on HFPV: continuous chest compressions on high frequency percussive ventilation. ROSC: return of spontaneous circulation. * $p < 0.05$ (Mann-Whitney U test).

Note: $^{a}n = 5$ and $^{b}n = 6$ for CCC on HFPV owing to probe malfunction.