Cardiopulmonary Resuscitation with Chest Compressions during Sustained Inflations: A New Technique of Neonatal Resuscitation that Improves Recovery and Survival in a Neonatal Porcine Model

Running title: Schmölzer et al.; Compressions and sustained inflations in newborns

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Abstract

Background—Guidelines on neonatal resuscitation recommend 90 chest compressions (CC) and 30 manual inflations (3:1) per minute in newborns. The study aimed to determine if CCs during sustained inflations (SI) improves recovery of asphyxiated newborn piglets compared to coordinated 3:1 resuscitation.

Methods and Results—Term newborn piglets (n=8/group) were anesthetized, intubated, instrumented and exposed to 45-minute normocapnic hypoxia followed by asphyxia. Piglets were randomized to receive either 3:1 resuscitation (3:1-group), or CCs during SIs (SI-group) when heart rate decreased to 25% of baseline. Piglets randomized to SI-group received SIs with a pressure of 30 cmH2O for 30 sec. During the SI, CCs at a rate of 120/min were provided. SI was interrupted after 30 sec for one second before a further 30 sec SI was provided. CCs were continued throughout SIs. CC and SI were continued until return of spontaneous circulation (ROSC). Continuous respiratory parameters, cardiac output, mean systemic and pulmonary artery pressures, and regional blood flows were measured. Mean (SD) time for ROSC was significantly reduced in SI-group vs. 3:1-group [32(11) sec vs. 205(113) sec, respectively]. In the SI-group, administration of oxygen and epinephrine was significantly lower, whilst minute ventilation and exhaled CO2 were significantly increased. The SI-group had significantly higher mean systemic and pulmonary arterial pressures during resuscitation compared to the 3:1-group [51(10) vs. 31(5) mmHg; 41(7) vs. 31(7) mmHg, respectively; all p<0.05], with improved cardiac output and carotid blood flow.

Conclusions—Combining CCs and SIs significantly improved ROSC with better hemodynamic recovery in asphyxiated newborn piglets when compared to standard coordinated 3:1 resuscitation.

Key words: neonatal ischemia, cardiopulmonary resuscitation, chest compression resuscitation, Sustained Inflation
Introduction

Although chest compressions (CC) are an infrequent event in newly born infants (~0.08% for near-term and term deliveries)\(^1,2\), outcome studies of delivery room resuscitations have reported high rates of mortality and neurodevelopmental impairment in those infants receiving CC or epinephrine\(^1,2\). The poor prognosis associated with receiving cardiac compressions alone or with medications in the delivery room raises questions as to whether improved cardiopulmonary resuscitation (CPR) methods specifically tailored to the newborn could improve outcomes\(^3\).

Current resuscitation guidelines recommend 3:1 Compression:Ventilation (C:V) ratio, however the most effective C:V ratio in newborns remains controversial\(^4\).

Antegrade blood flow during CPR can be achieved by either direct cardiac compression between the sternum and vertebral column or increased intrathoracic pressure produced by CC alone\(^5\). Animal studies and human randomized trials have demonstrated that continuous CC without rescue breaths increase return of spontaneous circulation (ROSC) and survival after sudden cardiac collapse\(^6,7\). However, in newborns when cardiac arrest is due to asphyxia the combination of ventilation and CC is necessary to achieve ROSC\(^6,8\).

Furthermore, maneuvers that raise the intrathoracic pressure can dramatically increase carotid blood flow during CPR further augmenting antegrade blood flow\(^9,10\). Chandra et al. combined ventilation at high airway pressure while simultaneously performing CC in an animal model and demonstrated increased carotid flow, without compromising oxygenation\(^9\). Further, animal studies have demonstrated that a sustained inflation (SI) also increase intrathoracic pressure without impeding blood flow\(^11\). However, no study has been carried out to examine whether combined simultaneous CC and SI will increase intrathoracic pressure to improve blood flow, resulting in increased ROSC and survival. We hypothesized that the use of SI during CPR
would reduce the time needed to achieve ROSC. In addition, we also compared to the hemodynamic recovery and survival between SI and CC and 3:1 CPR.

**Methods**

Twenty newborn mixed breed piglets (1-4 days of age, weighing 1.6-2.1 kg) were obtained on the day of experimentation from the University Swine Research Technology Centre. All experiments were conducted in accordance with the guidelines and approval of the Animal Care and Use Committee (Health Sciences), University of Alberta. A graphical display of the protocol is presented in Figure 1.

**Randomization**

Piglets were randomly allocated to sham-operated, 3:1 or SI groups. Allocation was block randomized with variable sized blocks (2 to 4) using a computer-generated randomization program (http://www.randomizer.org). A sequentially numbered, sealed, opaque envelope containing the allocation was opened before the start of the experimental protocol.

**Animal preparation**

Piglets were instrumented as previously described with some modifications[12,13]. Briefly, following the induction of anesthesia, piglets were intubated via a tracheostomy and pressure-controlled ventilation (Sechrist infant ventilator, model IV-100; Sechrist Industries, Anaheim, CA) was commenced at a respiratory rate of 16-20 breaths/min and pressure of 19/4 cmH2O. Oxygen saturation was kept within 90-100%, glucose level and hydration was maintained with an intravenous infusion of 5% dextrose at 10 mL/kg/h and a 0.9% NaCl at 2 mL/kg/h, respectively. During the experiment anesthesia was maintained with intravenous propofol 10 mg/kg/h and pancuronium 0.05-0.1 mg/kg/h. Additional doses of propofol (0.5-1 mg/kg) and
acepromazine (0.25 mg/kg) were also given as needed. The piglet’s body temperature was maintained at 38.5-39.5°C using an overhead warmer and a heating pad. A double-lumen catheter was inserted into the right atrium via the femoral vein for administration of fluids and medications and central venous pressure (CVP) measurements. A single-lumen catheter was inserted into the distal aorta via the femoral artery for continuous arterial blood pressure monitoring. After intubation, the left common carotid artery was exposed and encircled with a real-time ultrasonic flow probe (2mm; Transonic Systems Inc., Ithica, NY) to measure blood flow. A left flank incision was used to open the retroperitoneum to measure superior mesenteric (SMA) and left renal arterial blood flow with Transonic® flow probes (3mm and 2mm, retrospectively). A left anterior thoracotomy was then performed to place a 6-mm Transonic® flow probe around the main pulmonary artery (PA) to measure blood flow, which served as the surrogate of cardiac output. In addition, a 20G Arrow® angiocatheter (Arrow International, Reading, PA) was inserted to continuously measure mean pulmonary artery pressure (PAP). The ductus arteriosus was ligated and the thoracotomy was closed in two layers. Mean systemic arterial pressure (MAP), heart rate, percutaneous oxygen saturation, PAP, CVP were measured with a Hewlett Packard 78833B monitor (Hewlett Packard Co., Palo Alto, CA). Piglets were put to supine position and allowed to recover from surgical instrumentation until baseline hemodynamic measures were stable. Ventilator rate was adjusted to keep the partial arterial CO2 between 35-50 mmHg as determined by periodic arterial blood gas analysis. Heart rate, oxygen saturation, MAP, PAP, CVP, and the blood flow at PA, left common carotid, SMA and left renal arteries were continuously monitored and recorded throughout the experiment12.

Respiratory parameters

A respiratory function monitor (Respironics, Philips, Andover, MA) was used to continuously
measure tidal volume ($V_T$), airway pressures, gas flow, and exhaled CO$_2$ (ECO$_2$). The combined
gas flow and ECO$_2$ sensor was placed between the endotracheal tube and the ventilation device.
$V_T$ was calculated by integrating the flow signal. ECO$_2$ was measured using non-dispersive
infrared absorption technique. According to the manufacturer the accuracy for the gas flow is
±0.125 L/min and for ECO$_2$ ±2 mmHg. Respiratory function data were only recorded in 12
asphyxiated piglets (six in each group) due to a malfunction of the respiratory function monitor.

**Experimental protocol**

Piglets were randomized to receive either coordinated CPR with 3:1 ratio or CC during
continuous SI (Figure 1). All piglets were exposed to 45-minute normocapnic hypoxia. Hypoxia
was followed by an asphyxia period until heart rate decreased to 25% of baseline, which was
achieved by disconnecting the ventilator and clamping the endotracheal tube. 15 seconds after
heart rate reached 25% of baseline positive pressure ventilation was commenced for 30 seconds
with a Neopuff T-Piece (Fisher & Paykel, Auckland, New Zealand). The default settings were a
peak inflating pressure of 30 cmH$_2$O, a positive end expiratory pressure of 5 cmH$_2$O, and a gas
flow of 8 L/min. CCs were performed using the two-thumb encircling technique by a single
operator (GMS) in all piglets. Piglets were positioned supine during CC. A Metronome was used
to achieve the targeted CC rate. After 30 seconds of CC, 100% oxygen was commenced.
Epinephrine was administered if no increase in heart rate or ROSC was observed despite
adequate ventilation and CC. At 1 minute after CC were commenced, epinephrine (0.01 mg/kg
per dose) was given intravenously and then every minute as needed to a maximum of 4 doses.
ROSC was defined as an increase in heart rate >150/min for 15 seconds. After ROSC piglets
were allowed to recovery for four hours before the piglets were euthanized with an intravenous
overdose of phenobarbital (100 mg/kg). The sham-operated group was randomized to the same
surgical protocol, stabilization and equivalent experimental periods with no hypoxia, asphyxia nor resuscitation.

CPR in the 3:1 group was performed according to the current resuscitation guidelines with 90 CC per minute and 30 inflations (Figure 2A)\(^1\). Piglets randomized to the SI group received a SI with a peak inflating pressure of 30 cm H\(_2\)O for the duration of 30 sec. During the SI, chest compressions with a rate of 120 per minute were provided (Figure 2B). SI was interrupted after 30 sec for one second before a further 30 sec SI was provided. Chest compressions were delivered continuously until ROSC was achieved.

**Sample size and power estimates**

Our primary outcome measure was CPR time to achieve ROSC. Previous observational data showed a mean ± standard deviation ROSC of 180±25 seconds. We hypothesized that the use of SI during CPR would reduce time to achieve ROSC. A sample size of 16 piglets (8 per group) was sufficient to detect a clinically important (33%) reduction in time to achieve ROSC (i.e. 180 sec vs. 120 sec), with 80% power and a 2-tailed alpha error of 0.05.

**Data collection and analysis**

Demographics of study piglets were recorded. Transonic flow probes, heart rate and pressure transducer outputs were digitized and recorded with custom Asyst programming software (Data Translation, Ontario, Canada). Peak inflating pressure, positive end expiratory pressure, \(V_T\), inflation time, ventilation rate, minute ventilation and ECO\(_2\) were measured and analyzed using Flow Tool Physiologic Waveform Viewer (Philips Healthcare, Wallingford, CT, USA). The data are presented as mean±standard deviation for normally distributed continuous variables and median (interquartile range - IQR) when the distribution was skewed. Kaplan-Meier survival graphs were used and proportions of surviving piglets to 4 hours after resuscitation of two
intervention groups were compared by z test. Data during the resuscitation from the intervention groups were compared using Student’s *t*-test for parametric and Mann-Whitney *U* test for nonparametric comparisons of continuous variables, and Fisher’s exact test for categorical variables. For all respiratory parameters, the median value for each piglet during CPR was calculated first and then the mean of the median calculated was compared with Student’s *t*-test. Hemodynamic parameters were compared using one-way ANOVA and two-way repeated measures ANOVA with Bonferroni post hoc analysis as appropriate. *P*-values are 2-sided and *p*<0.05 was considered statistically significant. Statistical analyses were performed with Stata (Intercooled 10, Statacorp Texas, USA).

**Results**

Twenty newborn pigs were randomized to the 3:1 group (n=8), to the SI group (n=8), and sham-operated group (n=4). There were no differences in baseline parameters between the groups (Table 1). The median (IQR) duration of asphyxia was similar within groups; 80 (72-123) seconds in the 3:1 group vs. 116 (63-127) seconds in the SI group (p=0.958). Heart rate prior to commencement of CC was also comparable between groups 53 (15-62) bpm in the 3:1 group vs. 42 (15-49) bpm in the SI group, respectively (p=0.490). Table 1 represents values of pH, pCO₂, lactate and hemoglobin at start of CPR (end of asphyxia), as well as values of pH, pCO₂, and lactate after re-establishment of ROSC.

**Resuscitation**

Time to ROSC was significantly decreased in the SI group with 38 (23-44) seconds, compared to 143 (84-303) seconds in the 3:1 group (p=0.0008). In the SI group, significantly more piglets survived to 4 hours after resuscitation compared to the 3:1 group (7/8 (87.5%) vs. 3/8 (37.5%).
respectively, p=0.038) (Figure 3).

During CPR, significantly fewer piglets in the SI group compared to the 3:1 group received 100% oxygen 3/8 vs. 8/8 (p=0.0042). In addition, no piglet in the SI group required intravenous epinephrine bolus to achieve ROSC compared to the 3:1 group (vs. 7/8, p<0.0001), which received 17 boluses in total (p=0.0026). In 3:1 group, there were 2.1±1.6 doses of epinephrine per piglet administered, with a maximum of 4 doses.

During CPR, SI group had 119 (119-121) inflations/min until ROSC was achieved compared to 30 (29-32) inflations/min in the 3:1 group (p<0.0001). In addition, numbers of CCs in the SI group were significantly increased compared to the 3:1 group 119 (119-121) vs. 90 (89-93) CC/minute (p<0.001), respectively.

Hemodynamic parameters during chest compressions

PAP and MAP were significantly higher in the SI group compared to the 3:1 group during CPR (Table 2). However, no difference in CVP or MAP/PAP ratio among groups was observed. Cardiac output as a reference for recovery was significantly increased in the SI group compared to the 3:1 group (47±27% vs. 14±23% of normoxic baseline, respectively, p<0.05). Figure 4 summarizes changes in PA and regional blood flows during the first 5 minutes after CPR was commenced. The piglets in SI group had better systemic and regional hemodynamic recovery with significantly faster recovery of both PA and common carotid blood flows in the SI group than the 3:1 group (p<0.05) (Figure 4).

Respiratory parameters during chest compressions

V_T was significantly higher in the 3:1 group vs. SI group (Table 3). However, compared to the 3:1 group, the SI group had a significant increase in minute ventilation, secondary to a two-fold increase in the number of inflations per minute (Table 3). ECO_2, peak inspiratory flow, peak
inflation pressure and positive end expiratory pressure were significantly higher in the SI group during CC (Table 3).

**Hemodynamic parameters during recovery after CPR**

In the 3:1 group, 3 piglets survived to the end of experimentation (4 hours after CPR commenced) and had lower cardiac output compared to the sham-operated piglets (Table 4). The common carotid arterial and SMA, but not renal, blood flows and MAP of both SI and 3:1 groups were lower than those of sham-operated group (Table 4). The heart rate, PAP and CVP were not different among groups (Table 4). The arterial pH and lactate level of the surviving piglets in the SI and 3:1 groups were 7.30±0.07 and 6.0±2.8 mmol/L vs. 7.25±0.17 and 5.8±3.3 mmol/L, respectively.

**Discussion**

Current resuscitation guidelines recommend 3:1 C:V ratio, however the most effective C:V ratio in newborns remains controversial4. Recent neonatal piglet cardiac arrest studies compared various C:V ratios (3:1 vs. 9:2 vs. 15:2) and did not report any difference in ROSC, mortality, oxygen delivery, hemodynamics or epinephrine administration15,16. In addition, current resuscitation guidelines recommend 120 events per minute, which compromises 90 CC and 30 inflations4. A recent mathematical study suggests that the most effective CC frequency during CPR depends upon body size and weight17. For newborn infants, CC rates >120/min may be more beneficial and improve survival17. To our knowledge, no study has examined the differences of CC during SI and compared this to the current standard of 3:1 C:V ratio. In the current study, we delivered 120 CC/min during SI, which passively delivered an adequate V_T. The results of this study can be summarized as follows: i) CC with SI significantly reduced time
to ROSC, mortality (Figure 3), epinephrine administration, and improved systemic and regional hemodynamic recovery (Table 2, Figure 4); ii) minute ventilation, and therefore alveolar oxygen delivery, was significantly increased in the SI group (Table 3); iii) CC during SI forced VT out of the chest, and the passive chest recoil allowed air to be drawn back into the lungs (Figure 2B). We speculate that i) a significant increase in MAP (and therefore possibly higher coronary artery pressure) (Table 2), ii) faster recovery of systemic and regional blood flows (Figure 4), and iii) increased minute ventilation, and therefore increased alveolar oxygen delivery (Table 3), may have contributed to the improved survival.

Mechanisms to generate systemic blood pressure and blood flow include “cardiac pump theory” and “thoracic pump theory”9,10,18-21. The “cardiac pump theory” postulates that direct cardiac compression ejects blood into the circulation22, where as the “thoracic pump theory” states that antegrade blood flow is a result of phasic increases in intrathoracic pressure5,9,23,24. In the current study, continuous CC during SI significantly improved PAP, MAP, cardiac output and regional blood flow to the brain, kidneys, and intestines. Our results are supported by other large animal studies, which have demonstrated that simultaneous CC and ventilation generates higher intrathoracic and vascular pressure, and enhances myocardial and cerebral perfusion9,10,19,20,25-27. Similar observations in regards to increased blood pressure and carotid blood flow during simultaneous CC and ventilation have been reported in a human trial10. In contrast, interrupting CC to deliver manual inflations resulted in substantial decreases in the aortic diastolic pressures and coronary perfusion pressures24. Interestingly, studies in infant piglets were unable to demonstrate an increase in intrathoracic pressure or enhanced myocardial and cerebral perfusion during uninterrupted CC21,28. However, our model differentiates substantially from Berkowitz and Hou21,28. Berkowitz and Hou delivered 60 CC/min in addition
to 60 inflations/min. Our studies used 120 CC per minute, which is twice as many as Berkowitz and Hou in their studies. The higher CC rate might have contributed to the improved blood flow. In addition, our model used peak inflation pressures of 30 cm H₂O compared to the 60 cm H₂O in Berkowitz and Hou studies²¹,²². The increased PIP might have impaired blood flow. In addition, the delivered VT in our study was around 14 mL/kg. Berkowitz and Hou used a PIP of 60 cm H₂O for their rescue breaths, which potentially delivered even higher VTs and might have caused increased lung tissue injury in the experimental group in Hou’s study²⁸. Overall, our model uses constant peak inflation pressure of 30 cm H₂O for the duration of the SI to passively ventilate the lung, in comparison to Berkowitz and Hou studies were 60 inflations/minute were delivered. The VT in our study was potentially limited to the force used to deliver CC. Current resuscitation guidelines recommend 120 events per minute, which compromise of 90 CC and 30 inflations. In the SI group, we used 120 CC/min, which may have contributed to the increased survival and improved hemodynamic parameters. In addition, animal studies have demonstrated that any maneuver which increases intrathoracic pressure can increase carotid blood flow⁹,²⁷. Chandra et al. used total airway occlusion during CC to significantly increase carotid blood flow⁹. In the current experiment we applied sustained inflations, which have been shown to increase intrathoracic pressures. In addition, animal experiments demonstrated the delivery of a SI achieves uniform lung aeration and does not adversely affect cardiac output and cerebral blood flow and stabilizes neonatal cerebral oxygen delivery¹¹,²⁹. Furthermore, a recent study in near-term asphyxiated lambs reported that a single SI of 30 seconds immediately after birth improved the speed of circulatory recovery and lung compliance²⁹. We combined continuous CC with SI to maximize the increase in intrathoracic pressure, which significantly improved minute ventilation, regional and systematic hemodynamics. Improved lung aeration results in marked
increases in pulmonary blood flow\textsuperscript{11}. An increase in oxygenated blood flow returning from the lungs restores cardiac function, resulting in increased coronary perfusion and cerebral blood flow during resuscitation\textsuperscript{11,29}. Furthermore, we did not observe any impairment of venous return or an increase in vascular shunts (Table 2).

The current resuscitation guidelines recommend a C:V ratio of 3:1, suggesting that CC are interrupted after every 3\textsuperscript{rd} CC to deliver one inflation (Figure 2A), which would result in a decrease in intrathoracic pressure\textsuperscript{5}. The purpose of inflations during CPR is to deliver an adequate V\textsubscript{T} to facilitate gas exchange. In addition, each inflation increases intrathoracic pressure which augments antegrade blood flow\textsuperscript{5}. Recent studies measuring respiratory function in the delivery room demonstrated that V\textsubscript{T} in the initial stabilization period varies considerably in newborn infants\textsuperscript{30,31}. However, no study has measured the delivered V\textsubscript{T} during neonatal CPR to understand the effect of CC on lung aeration and V\textsubscript{T} delivery. In the current study, we demonstrated that air is forced out of the chest during CC, and an adequate V\textsubscript{T} is delivered during the passive chest recoil and (Figure 2B). Figure 2B clearly demonstrated that when CCs are performed during SI air moves in and out of the chest. In this model, rescue breaths were not delayed as previously described in adults or adult models\textsuperscript{7}; instead ventilation was passively achieved during CC. This is a novel finding which has not been reported previously. The current resuscitation guidelines recommend 30 inflations per minute compared to the 120 inflations per minute employed in the current study. Our approach increases the number of inflations per minute by a fourfold, thus resulting in significantly increased in minute ventilation. In addition, ECO\textsubscript{2} was significantly increased in the SI group, indicating increased alveolar ventilation, pulmonary perfusion (right cardiac output), and CO\textsubscript{2} production due to metabolism\textsuperscript{32,33}.

Administration of 100% oxygen is recommended during CPR and can be reduced once
an adequate heart rate and oxygen saturation is achieved. However, concerns have been raised about the potential adverse effects of increased fraction of inspired oxygen within the first 6 hours of life in newborns treated with therapeutic hypothermia. In the current study, only 3/8 piglets in the SI group required 100% oxygen during CPR compared to all 8/8 piglets in the 3:1 group. This is of important clinical relevance because hyperoxia slows cerebral blood flow, and can lead to the generation of oxygen free radicals, a major cause in reperfusion injury after asphyxia.

Animal studies during asphyxia-mediated arrest have demonstrated that epinephrine increases systemic vascular resistance, coronary artery perfusion pressure, and blood flow to the myocardium. However, the optimal dose and route to administer epinephrine in newborn infants remains controversial. In the current study, no piglet in the SI group required epinephrine compared to 7/8 in the 3:1 group due to their fast ROSC. This is of considerable clinical relevance because we demonstrated that optimal ventilation is the key for successful resuscitation. It is most likely that the increase in intrathoracic pressure causing significant increased PAP, MAP, PA and regional blood flows, minute ventilation, as well as higher oxygen delivery may contributed to less epinephrine administration in the SI group. Further, Schmittinger et al. recently demonstrated histological features of stress-induced cardiotoxicity correlated with doses of epinephrine administration, thus cautioning potential adverse effects with the use of epinephrine.

Our use of a piglet asphyxia model is a considerable strength of this translational study because this model closely mimics delivery room events with a gradual onset of severe asphyxia leading to bradycardia. However, several limitations should be considered before general application of simultaneous CC and SI in future clinical neonatal resuscitation trials. The current...
model is one where the piglets have already undergone fetal to neonatal transition and piglets are sedated/anesthetized. In addition, piglets in our model were all intubated using a tightly secured endotracheal tube to prevent any endotracheal tube leak; this is different from clinical situation where mask ventilation may be frequently used. Nevertheless, our findings remain relevant despite these limitations, because the distribution of cardiac output in the fetus and post-transitional neonate during asphyxial episodes are qualitatively similar. Further, in the current study the ductus arteriosus was ligated in all piglets, which to help ensure that cardiac output could be accurate assessed by PA blood flow. This is a limitation of translation to delivery room resuscitations as this method will contribute to decrease in vascular shunting. This warrants further studies using animal models with patent ductus arteriosus. Of note, giving 100% oxygen after 30 sec of CC and the administration of epinephrine at 60 sec after CC was started and continued every minute, are not in line with the current resuscitation guidelines. This might have influenced our results, however piglets randomized to the SI group did not require a single dose of epinephrine compared to 7/8 in the 3:1 group to achieve ROSC. The current resuscitation guidelines recommend a peak inflation pressure of 20-25 cmH2O during positive pressure ventilation in the delivery room, but higher opening pressures may be needed until functional residual capacity is established. In the current study, a peak inflation pressure of 30 cmH2O resulted in large delivered tidal volumes, which has been shown to cause lung injury to the premature lung. As it is still unclear whether a SI during the transition is injurious to the lung, an examination for lung injury may have broadened the outcomes and significance of this study. In addition, future assessment should include assessment of cerebral hemodynamics and brain injury.
Conclusions

Simultaneous CC and sustained inflation during CPR in newborn piglets significantly improved ROSC and survival in a porcine model of neonatal resuscitation. This is of considerable clinical relevance because improved respiratory and hemodynamic parameters potentially minimize morbidity and mortality in newborn infants.

Acknowledgments: Author contributions: Conception and design: GMS, PYC; Collection and assembly of data: GMS, JLB, TFL, SC, SQ, MOR, DLB, PYC; Analysis and interpretation of the data: GMS, JLB, TFL, SC, SQ, MOR, DLB, PYC; Drafting of the article: GMS, JLB, TFL, SC, SQ, MOR, DLB, PYC; Critical revision of the article for important intellectual content: GMS, JLB, TFL, SC, SQ, MOR, DLB, PYC; Final approval of the article: GMS, JLB, TFL, SC, SQ, MOR, DLB, PYC.

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Conflict of Interest Disclosures: None.

References:


ML. Determinants of blood flow to vital organs during cardiopulmonary resuscitation in dogs. 

27. Luce JM, Ross BK, O'Quin RJ, Culver BH, Sivarajan M, Amory DW, Niskanen RA, Alferness CA, Kirk WL, Pierson LB, Butler J. Regional blood flow during cardiopulmonary resuscitation in dogs using simultaneous and nonsimultaneous compression and ventilation. 

28. Hou SH, Lue HC, Chu SH. Comparison of conventional and simultaneous compression-ventilation cardiopulmonary resuscitation in piglets. 

*Arch Dis Child Fetal Neonatal Ed.* 2013;98:F222-227


*Resuscitation.* 2011;82:175-179

32. Chalak LF, Barber CA, Hynan L, Garcia D, Christie L, Wyckoff MH. End-tidal CO₂ detection of an audible heart rate during neonatal cardiopulmonary resuscitation after asystole in asphyxiated piglets. 


37. Saugstad OD. Oxygen for Newborn Resuscitation: How Much Is Enough? 
*Pediatrics.* 2006;118:789-792.


**Table 1.** Characteristics of newborn piglets at baseline, at commencement of CPR and once ROSC was restored.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>3:1 group (n=8)</th>
<th>SI group (n=8)</th>
<th>Sham-operated group (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days)</td>
<td>2±1</td>
<td>2±1</td>
<td>2±1</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>1800±107</td>
<td>1800±107</td>
<td>1675±125</td>
</tr>
<tr>
<td>Male/female</td>
<td>7/1</td>
<td>6/2</td>
<td>4/0</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>237±42</td>
<td>222±29</td>
<td>214±17</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.35±0.07</td>
<td>7.37±0.06</td>
<td>7.41±0.08</td>
</tr>
<tr>
<td>Arterial pCO2 (mm Hg)</td>
<td>47±5#</td>
<td>46±4</td>
<td>38±7</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>3.9±1.2</td>
<td>4.1±0.6</td>
<td>4.5±1.5</td>
</tr>
<tr>
<td>Arterial hemoglobin (g/L)</td>
<td>83.4±11.4</td>
<td>84.6±12.4</td>
<td>77.3±23.5</td>
</tr>
</tbody>
</table>

**Characteristics at commencement of CPR**

| Arterial pH                                      | 6.92±0.12       | 6.98±0.07      | 7.37±0.08                |
| Arterial pCO2 (mm Hg)                            | 87±26           | 79±12          | 42±8                     |
| Lactate (mmol/L)                                | 12±3.4          | 11.5±2.5       | 4.3±1.6                  |
| Base Excess (mEq/L)                             | -20±4.7/        | -18.6±2        | -1.3±3.3                 |
| Arterial hemoglobin (g/L)                       | 84.7±11         | 89±16          | 79±24                    |

**Characteristics after ROSC**

| Arterial pH                                      | 7.1±0.8         | 7.09±0.67      | 7.37±0.07                |
| Arterial pCO2 (mm Hg)                            | 55±10           | 52±6           | 43±7                     |
| Lactate (mmol/L)                                | 9.9±4.4         | 10.4±2.5       | 4.3±1.9                  |
| Base Excess (mEq/L)                             | -13.5±4.6       | -14.5±2.7      | -0.9±2.8                 |

**Table 2.** Mean pulmonary, systemic arterial pressures (PAP and MAP, respectively) and central venous pressure (CVP) over the duration of chest compressions.

<table>
<thead>
<tr>
<th></th>
<th>3:1 group (n=8)</th>
<th>SI group (n=8)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAP (mm Hg)</td>
<td>31±7</td>
<td>41±7</td>
<td>0.038</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>31±5</td>
<td>51±10</td>
<td>0.001</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>23±12</td>
<td>22±10</td>
<td>NS</td>
</tr>
<tr>
<td>MAP/PAP ratio</td>
<td>0.98±0.1</td>
<td>0.82±0.2</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 3. Respiratory parameters over the duration of chest compressions

<table>
<thead>
<tr>
<th></th>
<th>3:1 group</th>
<th>SI group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=6)</td>
<td>(n=6)</td>
<td></td>
</tr>
<tr>
<td>Tidal volume (mL/kg)</td>
<td>21.1±3.5</td>
<td>14.5±2.6</td>
<td>0.0039</td>
</tr>
<tr>
<td>Minute ventilation (mL/kg/min)</td>
<td>623±116</td>
<td>936±201</td>
<td>0.0080</td>
</tr>
<tr>
<td>Exhaled CO₂ (mm Hg)</td>
<td>12±10</td>
<td>32±10</td>
<td>0.0065</td>
</tr>
<tr>
<td>Peak inspiratory flow (L/min)</td>
<td>6.7±0.8</td>
<td>8.3±0.9</td>
<td>0.0086</td>
</tr>
<tr>
<td>Peak expiratory flow (L/min)</td>
<td>-10.0±2.3</td>
<td>-11.7±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Peak inflation pressure (cm H₂O)</td>
<td>30.4±0.6</td>
<td>43.2±2.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Positive end expiratory Pressure (cm H₂O)</td>
<td>4.3±1.2</td>
<td>19.5±2.7</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 4. Hemodynamic parameters of newborn piglets at 4 hours after cardiopulmonary resuscitation.

<table>
<thead>
<tr>
<th></th>
<th>3:1 group</th>
<th>SI group</th>
<th>Sham-operated group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=3)</td>
<td>(n=7)</td>
<td>(n=4)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>241±6</td>
<td>249±32</td>
<td>218±24</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>35±11*</td>
<td>40±9*</td>
<td>45±12</td>
</tr>
<tr>
<td>Pulmonary arterial pressure (mm Hg)</td>
<td>30±5</td>
<td>35±6</td>
<td>29±3</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>5±1</td>
<td>6±2</td>
<td>6±1</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>55±17*</td>
<td>86±58</td>
<td>137±21</td>
</tr>
<tr>
<td>Common carotid arterial flow (mL/kg/min)</td>
<td>12±7*</td>
<td>13±8*</td>
<td>19±4</td>
</tr>
<tr>
<td>Superior mesenteric arterial flow (mL/kg/min)</td>
<td>22±11*</td>
<td>26±21*</td>
<td>36±14</td>
</tr>
<tr>
<td>Renal arterial flow (mL/kg/min)</td>
<td>2±2</td>
<td>7±6</td>
<td>4±3</td>
</tr>
</tbody>
</table>

Values are mean±SD, *p-values <0.05 vs. sham-operated

Figure Legends:

Figure 1. Study flow diagram.

Figure 2. Respiratory wave forms during CPR in the (A) 3:1 and (B) SI groups (Gas flow, airway pressure, ECO₂, and tidal volume).

Figure 3. Kaplan-Meier survival graph for the two intervention groups after CPR in minutes.
Figure 4. Mean (SD) Percentage changes from normoxic baseline of blood flow in A) pulmonary artery (PA), B) common carotid artery (CA), C) superior mesenteric artery (SMA), and D) renal artery (RA) in 20 second intervals during CPR in the SI group (full circles) and the 3:1 group (open circles). *p <0.05 vs. 3:1 group at specific time.
Figure 1

Animal preparation
~ 90 min

Stabilization
60 min

Normocapnic Hypoxia
45 min

Asphyxia
≤ 5 min

Ventilation
30 sec

CPR
≤ 5 min

Recovery
4 hours

Euthanasia

Induction of anesthesia
Sevoflurane 5% i.v.

Propofol & Pancuronium
Additional doses of Propofol & Aacepromazine

Surgical procedures

Nitrogen gas added during ventilation to achieve fraction of inspired oxygen levels around 0.15

Clamping of endotracheal tube until heart rate decreased to 25% of baseline

21% oxygen

CC and epinephrine
After 30 sec of CC 100% oxygen
Figure 2A
Figure 2B
Figure 3

Kaplan-Meier survival estimates

Survival time in minutes after CPR

3:1 group

SI group

p = 0.038
Cardiopulmonary Resuscitation with Chest Compressions during Sustained Inflations: A New Technique of Neonatal Resuscitation that Improves Recovery and Survival in a Neonatal Porcine Model
Georg M. Schmölzer, Megan O'Reilly, Joseph LaBossiere, Tze-Fun Lee, Shaun Cowan, Sharon Qin, David L. Bigam and Po-Yin Cheung

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