

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, MD, PhD; Megan O'Reilly, PhD; Joseph LaBossier, MD, MSc; Tze-Fun Lee, PhD; Shaun Cowan; Sharon Qin; David L. Bigam, MD, MSc; Po-Yin Cheung, MBBS, PhD

Background—Guidelines on neonatal resuscitation recommend 90 chest compressions (CCs) and 30 manual inflations (3:1) per minute in newborns. The study aimed to determine whether CCs during sustained inflations (SIs) improves the recovery of asphyxiated newborn piglets in comparison with 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 randomly assigned to receive either 3:1 resuscitation (3:1 group) or CCs during SIs (SI group) when the heart rate decreased to 25% of baseline. Piglets randomly assigned to the SI group received SIs with a pressure of 30 cm H₂O for 30 s. During the SI, CCs at a rate of 120/min were provided. SI was interrupted after 30 s for 1 s before a further 30-s SI was provided. CCs were continued throughout SIs. CCs and SI were continued until the return of spontaneous circulation. Continuous respiratory parameters, cardiac output, mean systemic and pulmonary artery pressures, and regional blood flows were measured. Mean (standard deviation) time for return of spontaneous circulation was significantly reduced in SI group versus 3:1 group (32 [11] s versus 205 [113] s, respectively). In the SI group, administration of oxygen and epinephrine was significantly lower, whereas minute ventilation and exhaled CO₂ were significantly increased. The SI group had significantly higher mean systemic and pulmonary arterial pressures during resuscitation in comparison with the 3:1 group (51 [10] versus 31 [5] mm Hg; 41 [7] versus 31 [7] mm Hg, respectively; all *P*<0.05), with improved cardiac output and carotid blood flow.

Conclusions—Combining CCs and SIs significantly improved the return of spontaneous circulation with better hemodynamic recovery in asphyxiated newborn piglets in comparison with standard coordinated 3:1 resuscitation. (*Circulation*. 2013;128:2495-2503.)

Key words: cardiopulmonary resuscitation ■ chest wall oscillation ■ infant, newborn ■ ischemia ■ resuscitation

Although chest compressions (CCs) are an infrequent event in newly born infants ($\approx 0.08\%$ 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 a 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 increases the return of spontaneous circulation (ROSC) and survival after sudden cardiac collapse.^{6,7} However, in newborns, when cardiac arrest is attributable 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 al⁹ combined ventilation at high airway pressure while simultaneously performing CC in an animal model and demonstrated increased carotid flow, without compromising oxygenation.

Editorial see p 2468
Clinical Perspective on p 2503

Received February 27, 2013; accepted August 30, 2013.

From the Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada (G.M.S., M.O., T.-F.L., P.-Y.C.); Neonatal Research Unit, Royal Alexandra Hospital, Edmonton, Alberta, Canada (G.M.S., M.O., S.C., S.Q., P.-Y.C.); Department of Pediatrics, Medical University Graz, Graz, Austria (G.M.S.); Department of Surgery, University of Alberta, Edmonton, Alberta, Canada (J.L., D.L.B., P.-Y.C.); and Faculty of Science, University of Alberta, Edmonton, Alberta, Canada (S.C.).

Correspondence to Georg M. Schmölzer, MD, PhD, Neonatal Research Unit, Royal Alexandra Hospital, 10240 Kingsway Ave NW, T5H 3V9, Edmonton, Alberta, Canada. E-mail georg.schmoelzer@me.com

© 2013 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.113.002289

Further, animal studies have demonstrated that a sustained inflation (SI) also increases intrathoracic pressure without impeding blood flow.¹¹ However, no study has been conducted 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 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 (2–4) by 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} In brief, 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 to 20 breaths/min and pressure of 19/4 cm H₂O. Oxygen saturation was kept within 90% and 100%, and glucose level and hydration were maintained with an intravenous infusion of 5% dextrose at 10 mL·kg⁻¹·h⁻¹ and a 0.9% NaCl at 2 mL·kg⁻¹·h⁻¹, respectively. During the experiment, anesthesia was maintained with intravenous propofol 10 mg·kg⁻¹·h⁻¹ and pancuronium 0.05 to 0.1 mg·kg⁻¹·h⁻¹. 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°C to 39.5°C by using an overhead warmer and a heating pad. A double-lumen catheter was inserted into the right atrium via the femoral vein for the 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

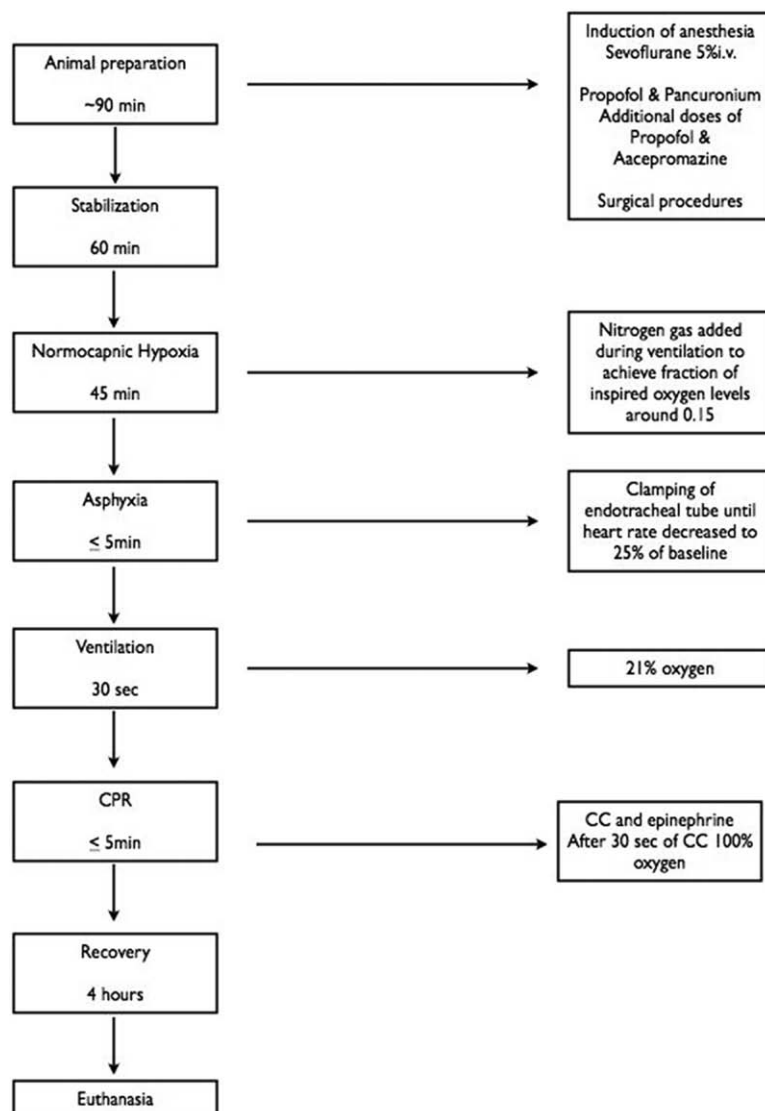


Figure 1. Study flow diagram. CC indicates chest compressions; and CPR, cardiopulmonary resuscitation.

carotid artery was exposed and encircled with a real-time ultrasonic flow probe (2 mm; Transonic Systems Inc, Ithaca, NY) to measure blood flow. A left flank incision was used to open the retroperitoneum to measure superior mesenteric and left renal arterial blood flow with Transonic flow probes (3 mm and 2 mm, respectively). 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 20 gauge 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 2 layers. Mean systemic arterial pressure (MAP), heart rate, percutaneous oxygen saturation, PAP, and CVP were measured with a Hewlett Packard 78833B monitor (Hewlett Packard Co, Palo Alto, CA). Piglets were put in a supine position and allowed to recover from surgical instrumentation until baseline hemodynamic measures were stable. The ventilator rate was adjusted to keep the partial arterial CO₂ between 35 and 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, superior mesenteric, and left renal arteries were continuously monitored and recorded throughout the experiment.¹²

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 CO₂ (ECO₂). The combined gas flow and ECO₂ sensor was placed between the endotracheal tube and the ventilation device. V_T was calculated by integrating the flow signal. ECO₂ was measured by using nondispersive infrared absorption technique. According to the manufacturer, the accuracy for the gas flow is ±0.125 L/min and for ECO₂ ±2 mmHg. Respiratory function data were only recorded in 12 asphyxiated piglets (6 in each group) because of a malfunction of the respiratory function monitor.

Experimental Protocol

Piglets were randomly assigned to receive either coordinated CPR with a 3:1 ratio or CCs 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. Fifteen seconds after the heart rate reached 25% of baseline, positive pressure ventilation was commenced for 30 s with a Neopuff T-Piece (Fisher & Paykel, Auckland, New Zealand). The default settings were a peak inflating pressure of 30 cm H₂O, a positive end expiratory pressure of 5 cm H₂O, and a gas flow of 8 L/min. CCs were performed by using the 2-thumb encircling technique by a single operator (G.M.S.) in all piglets. Piglets were positioned supine during CC. A metronome was used to achieve the targeted CC rate. After 30 s 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 CCs 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 s. After ROSC, piglets were allowed to recovery for 4 hours before the piglets were euthanized with an intravenous overdose of phenobarbital (100 mg/kg). The sham-operated group was randomly assigned to the same surgical protocol, stabilization, and equivalent experimental periods with no hypoxia, asphyxia, or resuscitation.

CPR in the 3:1 group was performed according to the current resuscitation guidelines with 90 CCs/min and 30 inflations (Figure 2A).¹⁴ Piglets randomly assigned to the SI group received a SI with a peak inflating pressure of 30 cm H₂O for the duration of 30 s. During the SI, CCs with a rate of 120/min were provided (Figure 2B). SI was interrupted after 30 s for 1 s before a further 30 s of SI was provided. CCs 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 s. We hypothesized that the use of SI during CPR would reduce the 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 (ie, 180 s versus 120 s), with 80% power and a 2-tailed α -error of 0.05.

Data Collection and Analysis

The 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 ECO₂ were measured and analyzed by using Flow Tool Physiologic Waveform Viewer (Philips Healthcare, Wallingford, CT). The data are presented as mean±standard deviation for normally distributed continuous variables and median (interquartile range) when the distribution was skewed. Kaplan-Meier survival graphs were used and the proportions of surviving piglets to 4 hours after resuscitation of the 2 intervention groups were compared by *z* test. Data during the resuscitation from the intervention groups were compared by using the Student *t* test for parametric and the Mann-Whitney *U* test for non-parametric comparisons of continuous variables, and Fisher 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 the Student *t* test. Hemodynamic parameters were compared by using 1-way analysis of variance and 2-way repeated-measures analysis of variance 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, TX).

Results

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

Resuscitation

Time to ROSC was significantly decreased in the SI group with 38 (23–44) s in comparison with 143 (84–303) s in the 3:1 group (*P*=0.0008). In the SI group, significantly more piglets survived to 4 hours after resuscitation than in the 3:1 group (7/8 [87.5%] versus 3/8 [37.5%], respectively; *P*=0.038; Figure 3).

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

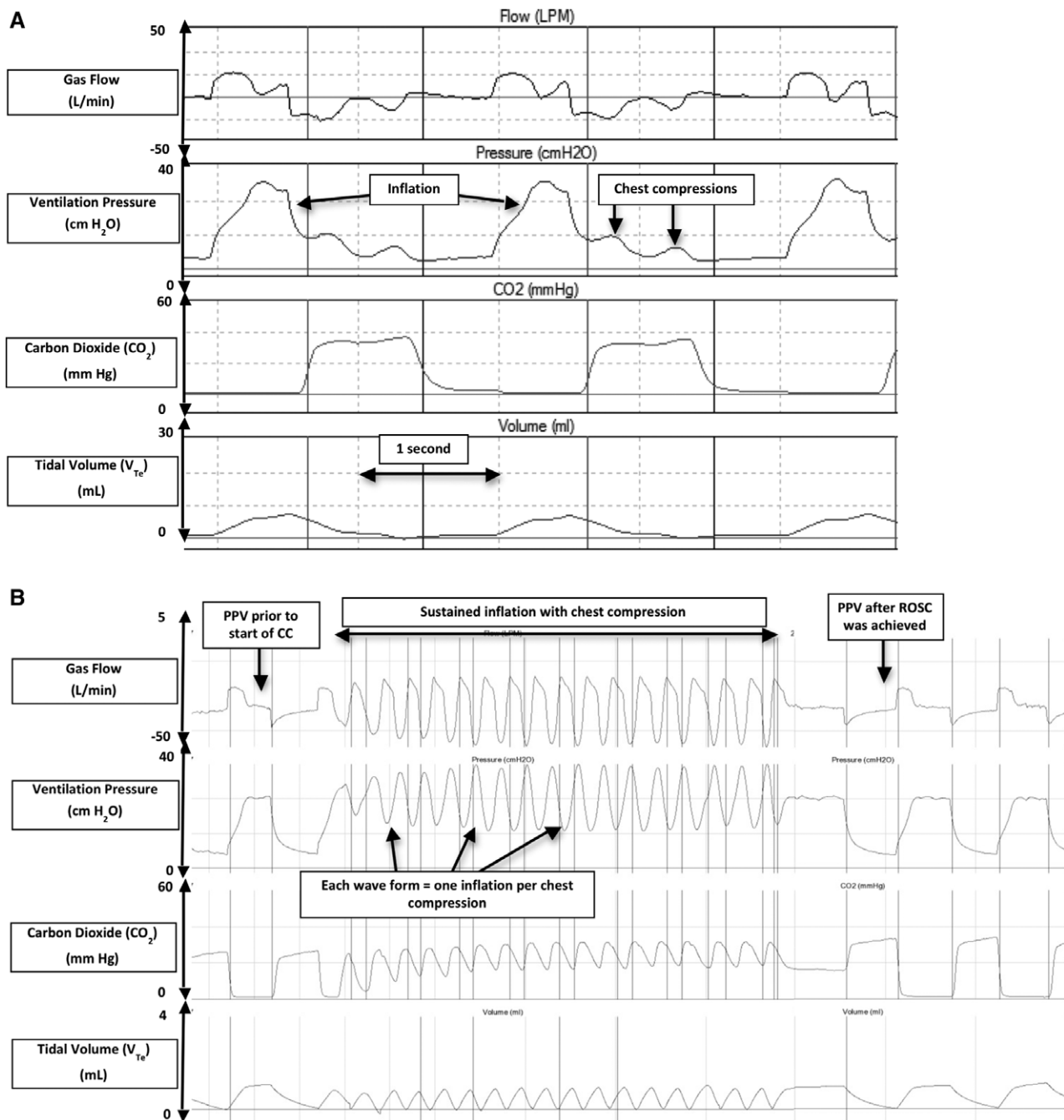


Figure 2. Respiratory waveforms during CPR in the 3:1 (A) and SI groups (B; gas flow (LPM=L/min), airway pressure, ECO_2 , and tidal volume). CPR indicates cardiopulmonary resuscitation; ECO_2 , exhaled CO_2 ; and SI, sustained inflation.

During CPR, the SI group had 119 (119–121) inflations/min until ROSC was achieved in comparison with 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 in comparison with the 3:1 group 119 (119–121) versus 90 (89–93) CCs/min ($P<0.001$), respectively.

Hemodynamic Parameters During CCs

PAP and MAP were significantly higher in the SI group than in 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 than in the 3:1 group ($47\pm 27\%$ versus $14\pm 23\%$ 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 the 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 CCs

V_T was significantly higher in the 3:1 group versus the SI group (Table 3). However, in comparison with the 3:1 group,

Table 1. Characteristics of Newborn Piglets at Baseline, at Commencement of CPR, and Once ROSC Was Restored

	3:1 Group (n=8)	SI Group (n=8)	Sham-operated Group (n=4)
Baseline characteristics			
Age, days	2±1	2±1	2±1
Weight, g	1800±107	1800±107	1675±125
Male/female	7/1	6/2	4/0
Heart rate, bpm	237±42	222±29	214±17
Arterial pH	7.35±0.07	7.37±0.06	7.41±0.08
Arterial pCO ₂ , mm Hg	47±5*	46±4	38±7
Lactate, mmol/L	3.9±1.2	4.1±0.6	4.5±1.5
Arterial hemoglobin, g/L	83.4±11.4	84.6±12.4	77.3±23.5
Characteristics at commencement of CPR			
Arterial pH	6.92±0.12	6.98±0.07	7.37±0.08
Arterial pCO ₂ , 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 pCO ₂ , 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

CPR indicates cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; and SI, sustained inflation.

*P values <0.05 vs sham-operated.

the SI group had a significant increase in minute ventilation, secondary to a 2-fold increase in the number of inflations per minute (Table 3). ECO₂, 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

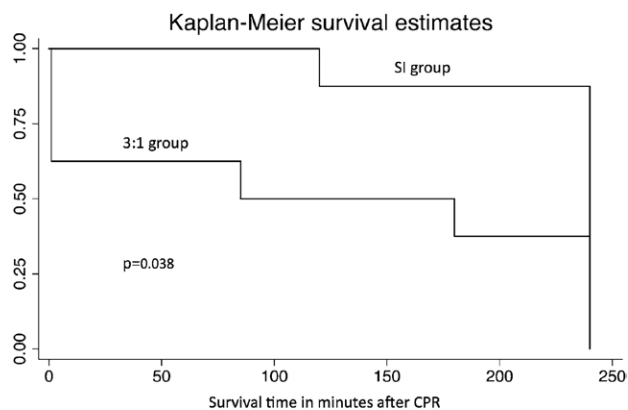


Figure 3. Kaplan-Meier survival graph for the 2 intervention groups after CPR in minutes. CC indicates chest compressions; CPR, cardiopulmonary resuscitation; PPV, positive pressure ventilation; and ROSC, return of spontaneous circulation.

Table 2. Mean Pulmonary and Systemic Arterial Pressures and Central Venous Pressure Over the Duration of Chest Compressions

	3:1 Group (n=8)	SI Group (n=8)	P Value
PAP, mm Hg	31±7	41±7	0.038
MAP, mm Hg	31±5	51±10	0.001
CVP, mm Hg	23±12	22±10	NS
MAP/PAP ratio	0.98±0.1	0.82±0.2	NS

CVP indicates central venous pressure; MAP, mean systemic arterial pressure; NS, not significant; PAP, mean pulmonary artery pressure; and SI, sustained inflation.

cardiac output in comparison with the sham-operated piglets (Table 4). The common carotid arterial and superior mesenteric arterial, but not renal, blood flows and MAP of both the SI and 3:1 groups were lower than those of the 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 versus 7.25±0.17 and 5.8±3.3 mmol/L, respectively.

Discussion

Current resuscitation guidelines recommend a 3:1 C:V ratio, but the most effective C:V ratio in newborns remains controversial.⁴ Recent neonatal piglet cardiac arrest studies compared various C:V ratios (3:1 versus 9:2 versus 15:2) and did not report any difference in ROSC, mortality, oxygen delivery, hemodynamics, or epinephrine administration.^{15,16} In addition, current resuscitation guidelines recommend 120 events/min, which comprise 90 CCs and 30 inflations.⁴ A recent mathematical study suggests that the most effective CC frequency during CPR depends on body size and weight.¹⁷ For newborn infants, CC rates >120/min may be more beneficial and improve survival.¹⁷ To our knowledge, no study has examined the differences of CCs during SI and compared this with the current standard 3:1 C:V ratio. In the current study, we delivered 120 CCs/min during SI, which passively delivered an adequate V_T. The results of this study can be summarized as follows: (1) CCs with SI significantly reduced time to ROSC, mortality (Figure 3), epinephrine administration, and improved systemic and regional hemodynamic recovery (Table 2, Figure 4); (2) minute ventilation, and therefore alveolar oxygen delivery, was significantly increased in the SI group (Table 3); (3) CCs during SI forced V_T out of the chest, and the passive chest recoil allowed air to be drawn back into the lungs (Figure 2B). We speculate that (1) a significant increase in MAP (and therefore possibly higher coronary artery pressure; Table 2), (2) faster recovery of systemic and regional blood flows (Figure 4), and (3) 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 circulation,²² whereas the thoracic pump theory states that antegrade blood flow is a result of phasic increases in intrathoracic pressure.^{5,9,23,24} In the

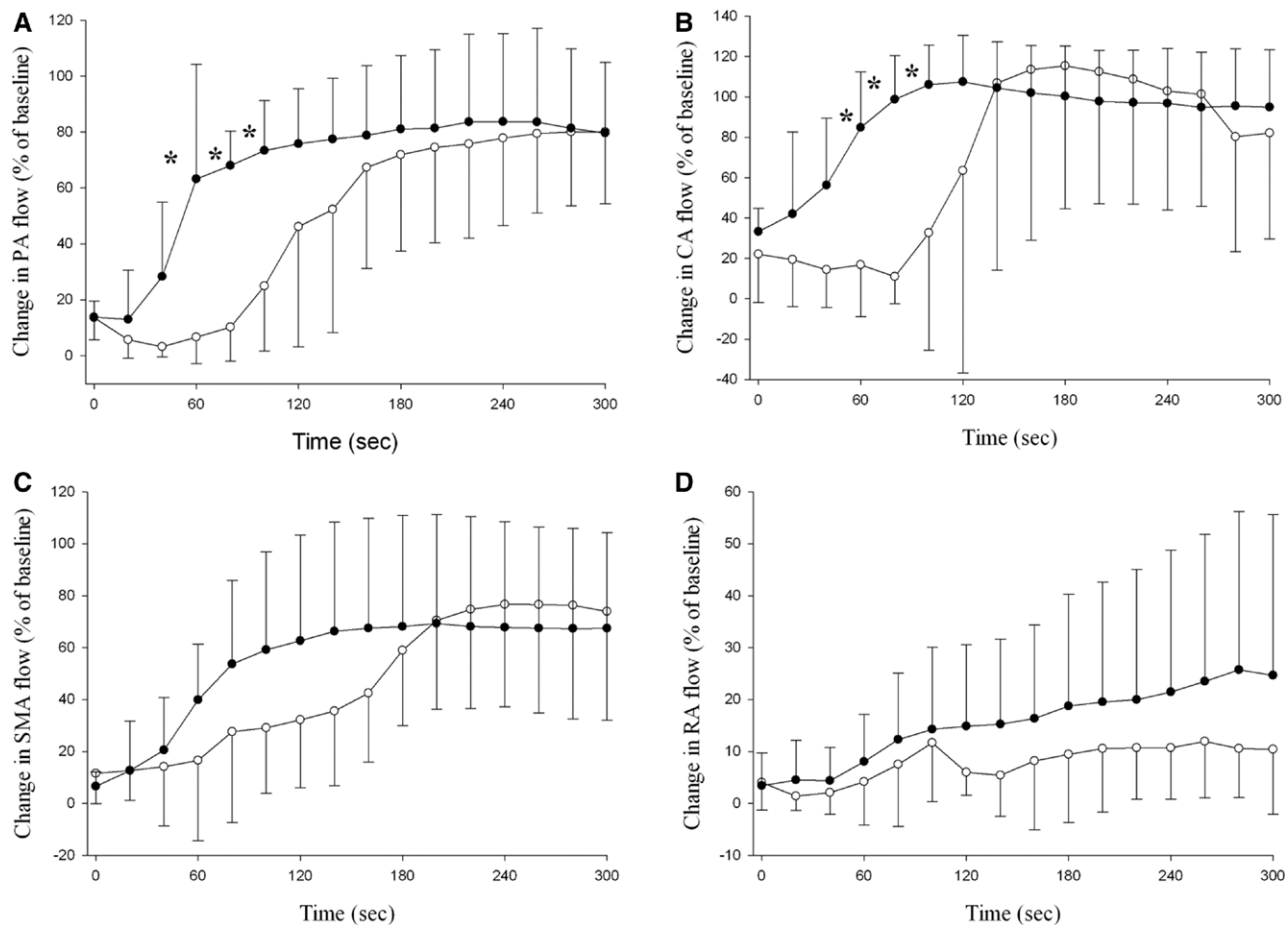


Figure 4. Mean (standard deviation) percentage changes from normoxic baseline of blood flow in the pulmonary artery (PA; **A**), the common carotid artery (CA; **B**), the superior mesenteric artery (SMA; **C**), and the renal artery (RA; **D**) in 20-se intervals during CPR in the SI group (●) and the 3:1 group (○). CPR indicates cardiopulmonary resuscitation; and SI, sustained inflation. **P*<0.05 vs 3:1 group at specific time.

current study, continuous CCs 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 CCs and ventilation generates higher intrathoracic and vascular pressure and enhances myocardial and cerebral perfusion.^{9,10,19,20,25–27} Similar observations in regard to increased blood pressure and carotid blood flow during simultaneous CCs and ventilation have been reported in a human trial.¹⁰ In contrast, interrupting CCs

to deliver manual inflations resulted in substantial decreases in the aortic diastolic pressures and coronary perfusion pressures.²⁴ Interestingly, studies in infant piglets were unable to demonstrate an increase in intrathoracic pressure or enhanced myocardial and cerebral perfusion during uninterrupted CCs.^{21,28} However, our model differentiates substantially from Berkowitz et al²¹ and Hou et al.²⁸ Berkowitz and Hou delivered 60 CCs/min in addition to 60 inflations/min. Our studies used 120 CCs/min, which is twice as many as Berkowitz and Hou used 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 in comparison with the 60 cm H₂O in the Berkowitz and Hou studies.^{21,28} The increased peak inflation pressures might have impaired blood flow. In addition, the delivered V_T in our study was ≈14 mL/kg. Berkowitz and Hou used a peak inflation pressure of 60 cm H₂O for their rescue breaths, which potentially delivered even higher V_Ts and might have caused increased lung tissue injury in the experimental group in Hou's study.²⁸ 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 with the Berkowitz and Hou studies, in which 60 inflations/min were delivered. The V_T in our study was potentially limited to the force used to deliver CCs. Current

Table 3. Respiratory Parameters Over the Duration of Chest Compressions

	3:1 Group (n=6)	SI Group (n=6)	P Value
Tidal volume, mL/kg	21.1±3.5	14.5±2.6	0.0039
Minute ventilation, mL·kg ⁻¹ ·min ⁻¹	623±116	936±201	0.0080
Exhaled CO ₂ , mm Hg	12±10	32±10	0.0065
Peak inspiratory flow, L/min	6.7±0.8	8.3±0.9	0.0086
Peak expiratory flow, L/min	-10.0±2.3	-11.7±1.6	NS
Peak inflation pressure, cm H ₂ O	30.4±0.6	43.2±2.3	0.0001
Positive end-expiratory pressure, cm H ₂ O	4.3±1.2	19.5±2.7	0.0001

NS indicates not significant; and SI, sustained inflation.

Table 4. Hemodynamic Parameters of Newborn Piglets at 4 Hours After Cardiopulmonary Resuscitation

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

Values are mean±standard deviation. SI indicates sustained inflation.

*P values <0.05 vs sham-operated.

resuscitation guidelines recommend 120 events/min, which comprise of 90 CCs and 30 inflations. In the SI group, we used 120 CCs/min, which may have contributed to the increased survival and improved hemodynamic parameters. In addition, animal studies have demonstrated that any maneuver that increases intrathoracic pressure can increase carotid blood flow.^{9,27} Chandra et al⁹ used total airway occlusion during CCs to significantly increase carotid blood flow. In the current experiment, we applied SIs, which have been shown to increase intrathoracic pressures. In addition, animal experiments demonstrated that 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 delivery.^{11,29} Furthermore, a recent study in near-term asphyxiated lambs reported that a single SI of 30 s immediately after birth improved the speed of circulatory recovery and lung compliance.²⁹ We combined continuous CCs with SI to maximize the increase in intrathoracic pressure, which significantly improved minute ventilation and regional and systematic hemodynamics. Improved lung aeration results in marked increases in pulmonary blood flow.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.^{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 CCs are interrupted after every third CC to deliver 1 inflation (Figure 2A), which would result in a decrease in intrathoracic pressure.⁵ The purpose of inflations during CPR is to deliver an adequate V_T to facilitate gas exchange. In addition, each inflation increases intrathoracic pressure, which augments antegrade blood flow.⁵ Recent studies measuring respiratory function in the delivery room demonstrated that V_T in the initial stabilization period varies considerably in newborn infants.^{30,31} However, no study has measured the delivered V_T during neonatal CPR to understand

the effect of CCs on lung aeration and V_T delivery. In the current study, we demonstrated that air is forced out of the chest during CCs, and an adequate V_T is delivered during the passive chest recoil (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 models⁷; instead, ventilation was passively achieved during CCs. This is a novel finding that has not been reported previously. The current resuscitation guidelines recommend 30 inflations/min in comparison with the 120 inflations/min used in the current study. Our approach increases the number of inflations per minute by a 4-fold, thus resulting in a significantly increase in minute ventilation. In addition, ECO_2 was significantly increased in the SI group, indicating increased alveolar ventilation, pulmonary perfusion (right cardiac output), and CO_2 production attributable to metabolism.^{32,33}

Administration of 100% oxygen is recommended during CPR and can be reduced once an adequate heart rate and oxygen saturation are achieved.³ 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.^{34–36} In the current study, only 3/8 piglets in the SI group required 100% oxygen during CPR in comparison with 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.³⁷

Animal studies during asphyxia-mediated arrest have demonstrated that epinephrine increases systemic vascular resistance, coronary artery perfusion pressure, and blood flow to the myocardium.³⁸ However, the optimal dose and route to administer epinephrine in newborn infants remains controversial.⁴ In the current study, no piglet in the SI group required epinephrine in comparison with 7/8 in the 3:1 group owing 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 significantly increased PAP, MAP, PA, and regional blood flows, minute ventilation, and higher oxygen delivery, as well, may have contributed to less epinephrine administration in the SI group. Further, Schmittinger et al³⁹ recently demonstrated histological features of stress-induced cardiotoxicity correlated with doses of epinephrine administration, thus cautioning about the 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 CCs and SI in future clinical neonatal resuscitation trials. The current model is one in which the piglets have already undergone fetal to neonatal transition, and the piglets are sedated/anesthetized. In addition, the piglets in our model were all intubated by the use of a tightly secured endotracheal tube to prevent any endotracheal tube leak; this is different from clinical situations 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 posttransitional neonate during asphyxial episodes are qualitatively similar.³² Further, in the current study, the ductus arteriosus was ligated in all piglets to help ensure that cardiac output could be accurately assessed by PA blood flow. This is a limitation of translation to delivery room resuscitations, because this method will contribute to a decrease in vascular shunting. This warrants further studies with the use of animal models with patent ductus arteriosus. Of note, giving 100% oxygen after 30 s of CCs and the administration of epinephrine at 60 s after CCs was started and continued every minute are not in line with the current resuscitation guidelines.¹⁴ This might have influenced our results; however, the piglets randomly assigned to the SI group did not require a single dose of epinephrine in comparison with 7/8 in the 3:1 group to achieve ROSC. The current resuscitation guidelines recommend a peak inflation pressure of 20 to 25 cm H₂O during positive pressure ventilation in the delivery room,⁴ but higher opening pressures may be needed until functional residual capacity is established. In the current study, a peak inflation pressure of 30 cm H₂O resulted in large delivered V_T values, which has been shown to cause lung injury to the premature lung.⁴⁰ Because 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 the assessment of cerebral hemodynamics and brain injury.

Conclusions

Simultaneous CCs and SI 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

Drs Schmölzer and Cheung contributed to conception and design. Drs Schmölzer, LaBossiere, and Lee, S. Cowan, S. Qin, and Drs O'Reilly, Bigam, and Cheung contributed to the collection and assembly of data, the analysis and interpretation of the data, the drafting of the article, critical revision of the article for important intellectual content, and the final approval of the article.

Sources of Funding

We thank the Laerdal Foundation for Acute Medicine, Norway for their support of the current study. We would like to acknowledge Respironics (Philips) and Fisher & Paykel for their support. Dr Schmölzer is the recipient of a Banting Postdoctoral Fellowship, Canadian Institutes of Health Research and an Alberta Innovates - Health Solution Clinical Fellowship. The study was supported in part by an operating grant from the Canadian Institutes of Health Research (MOP53116 to Dr Cheung).

Disclosures

None.

References

- Wyckoff M, Perlman J. Cardiopulmonary resuscitation in very low birth weight infants. *Pediatrics*. 2000;106:618–620.
- Wyckoff MH, Salhab WA, Heyne RJ, Kendrick DE, Stoll BJ, Laptook AR; National Institute of Child Health and Human Development Neonatal Research Network. Outcome of extremely low birth weight infants who received delivery room cardiopulmonary resuscitation. *J Pediatr*. 2012;160:239–244.e2.
- Kapadia V, Wyckoff MH. Chest compressions for bradycardia or asystole in neonates. *Clin Perinatol*. 2012;39:833–842.
- Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, Guinsburg R, Hazinski MF, Morley C, Richmond S, Simon WM, Singhal N, Szyld E, Tamura M, Velaphi S; Neonatal Resuscitation Chapter Collaborators. Part 11: Neonatal Resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*. 2010;122(16 suppl 2):S516–S538.
- Rudikoff MT, Maughan WL, Effron M, Freund P, Weisfeldt ML. Mechanisms of blood flow during cardiopulmonary resuscitation. *Circulation*. 1980;61:345–352.
- Berg RA, Hilwig RW, Kern KB, Ewy GA. “Bystander” chest compressions and assisted ventilation independently improve outcome from piglet asphyxial pulseless “cardiac arrest”. *Circulation*. 2000;101:1743–1748.
- Hallstrom A, Cobb L, Johnson E, Copass M. Cardiopulmonary resuscitation by chest compression alone or with mouth-to-mouth ventilation. *N Engl J Med*. 2000;342:1546–1553.
- Berg RA, Hilwig RW, Kern KB, Babar I, Ewy GA. Simulated mouth-to-mouth ventilation and chest compressions (bystander cardiopulmonary resuscitation) improves outcome in a swine model of prehospital pediatric asphyxial cardiac arrest. *Crit Care Med*. 1999;27:1893–1899.
- Chandra N, Weisfeldt ML, Tsitlik J, Vaghaiwalla F, Snyder LD, Hoffecker M, Rudikoff MT. Augmentation of carotid flow during cardiopulmonary resuscitation by ventilation at high airway pressure simultaneous with chest compression. *Am J Cardiol*. 1981;48:1053–1063.
- Chandra N, Rudikoff M, Weisfeldt ML. Simultaneous chest compression and ventilation at high airway pressure during cardiopulmonary resuscitation. *Lancet*. 1980;1:175–178.
- Sobotka KS, Hooper SB, Allison BJ, Te Pas AB, Davis PG, Morley CJ, Moss TJ. An initial sustained inflation improves the respiratory and cardiovascular transition at birth in preterm lambs. *Pediatr Res*. 2011;70:56–60.
- Cheung PY, Gill RS, Bigam DL. A swine model of neonatal asphyxia. *J Vis Exp*. 2011;56:e3166.
- Gill RS, Manouchehri N, Liu JQ, Lee TF, Cho WJ, Thiesen A, Churchill T, Bigam D, Cheung PY. Cyclosporine treatment improves cardiac function and systemic hemodynamics during resuscitation in a newborn piglet model of asphyxia: a dose-response study. *Crit Care Med*. 2012;40:1237–1244.
- Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, Hazinski MF, Halamek LP, Kumar P, Little G, McGowan JE, Nightengale B, Ramirez MM, Ringer S, Simon WM, Weiner GM, Wyckoff M, Zaichkin J. Part 15: Neonatal Resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18 suppl 3):S909–S919.
- Solevåg AL, Dannevig I, Wyckoff M, Saugstad OD, Nakstad B. Return of spontaneous circulation with a compression:ventilation ratio of 15:2 versus 3:1 in newborn pigs with cardiac arrest due to asphyxia. *Arch Dis Child Fetal Neonatal Ed*. 2011;96:F417–F421.
- Solevåg AL, Dannevig I, Wyckoff M, Saugstad OD, Nakstad B. Extended series of cardiac compressions during CPR in a swine model of perinatal asphyxia. *Resuscitation*. 2010;81:1571–1576.
- Babbs CF, Meyer A, Nadkarni V. Neonatal CPR: room at the top—a mathematical study of optimal chest compression frequency versus body size. *Resuscitation*. 2009;80:1280–1284.
- Falck AJ, Escobedo MB, Baillargeon JG, Villard LG, Gunkel JH. Proficiency of pediatric residents in performing neonatal endotracheal intubation. *Pediatrics*. 2003;112(6 pt 1):1242–1247.
- Chandra NC, Beyar R, Halperin HR, Tsitlik JE, Wurmb E, Rayburn B, Guerci AD, Weisfeldt ML. Vital organ perfusion during assisted circulation by manipulation of intrathoracic pressure. *Circulation*. 1991;84:279–286.
- Koehler RC, Chandra N, Guerci AD, Tsitlik J, Traystman RJ, Rogers MC, Weisfeldt ML. Augmentation of cerebral perfusion by simultaneous chest compression and lung inflation with abdominal binding after cardiac arrest in dogs. *Circulation*. 1983;67:266–275.
- Berkowitz ID, Chantarojanasiri T, Koehler RC, Schlei CL, Dean JM, Michael JR, Rogers MC, Traystman RJ. Blood flow during cardiopulmonary resuscitation with simultaneous compression and ventilation in infant pigs. *Pediatr Res*. 1989;26:558–564.
- Higano ST, Oh JK, Ewy GA, Seward JB. The mechanism of blood flow during closed chest cardiac massage in humans: transesophageal echocardiographic observations. *Mayo Clin Proc*. 1990;65:1432–1440.

23. Halperin HR, Guerci AD, Chandra N, Herskowitz A, Tsitlik JE, Niskanen RA, Wurmb E, Weisfeldt ML. Vest inflation without simultaneous ventilation during cardiac arrest in dogs: improved survival from prolonged cardiopulmonary resuscitation. *Circulation*. 1986;74:1407–1415.
24. Berg RA, Sanders AB, Kern KB, Hilwig RW, Heidenreich JW, Porter ME, Ewy GA. Adverse hemodynamic effects of interrupting chest compressions for rescue breathing during cardiopulmonary resuscitation for ventricular fibrillation cardiac arrest. *Circulation*. 2001;104:2465–2470.
25. Ewy GA, Zuercher M, Hilwig RW, Sanders AB, Berg RA, Otto CW, Hayes MM, Kern KB. Improved neurological outcome with continuous chest compressions compared with 30:2 compressions-to-ventilations cardiopulmonary resuscitation in a realistic swine model of out-of-hospital cardiac arrest. *Circulation*. 2007;116:2525–2530.
26. Halperin HR, Tsitlik JE, Guerci AD, Mellits ED, Levin HR, Shi AY, Chandra N, Weisfeldt ML. Determinants of blood flow to vital organs during cardiopulmonary resuscitation in dogs. *Circulation*. 1986;73:539–550.
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. *Circulation*. 1983;67:258–265.
28. Hou SH, Lue HC, Chu SH. Comparison of conventional and simultaneous compression-ventilation cardiopulmonary resuscitation in piglets. *Jpn Circ J*. 1994;58:426–432.
29. Klingenberg C, Sobotka KS, Ong T, Allison BJ, Schmölzer GM, Moss TJM, Polglase GR, Dawson JA, Davis PG, Hooper SB. Effect of sustained inflation duration; resuscitation of near-term asphyxiated lambs. *Arch Dis Child Fetal Neonatal Ed*. 2013;98:F222–F227.
30. Schmölzer GM, Kamlin OC, O'Donnell CP, Dawson JA, Morley CJ, Davis PG. Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room. *Arch Dis Child Fetal Neonatal Ed*. 2010;95:F393–F397.
31. Poulton DA, Schmölzer GM, Morley CJ, Davis PG. Assessment of chest rise during mask ventilation of preterm infants in the delivery room. *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. *Pediatr Res*. 2011;69(5 pt 1):401–405.
33. Falk JL, Rackow EC, Weil MH. End-tidal carbon dioxide concentration during cardiopulmonary resuscitation. *N Engl J Med*. 1988;318:607–611.
34. Haase E, Bigam DL, Nakonechny QB, Jewell LD, Korbitt G, Cheung PY. Resuscitation with 100% oxygen causes intestinal glutathione oxidation and reoxygenation injury in asphyxiated newborn piglets. *Ann Surg*. 2004;240:364–373.
35. Cheung PY, Obaid L, Emara M, Brierley Y, Johnson ST, Chan GS, Jewell L, Korbitt G, Bigam DL. Cardio-renal recovery of hypoxic newborn pigs after 18%, 21% and 100% reoxygenation. *Intensive Care Med*. 2008;34:1114–1121.
36. Sabir H, Jary S, Tooley J, Liu X, Thoresen M. Increased inspired oxygen in the first hours of life is associated with adverse outcome in newborns treated for perinatal asphyxia with therapeutic hypothermia. *J Pediatr*. 2012;161:409–416.
37. Saugstad OD, Ramji S, Vento M. Oxygen for newborn resuscitation: how much is enough? *Pediatrics*. 2006;118:789–792.
38. Weiner GM, Niermeyer S. Medications in neonatal resuscitation: epinephrine and the search for better alternative strategies. *Clin Perinatol*. 2012;39:843–855.
39. Schmittinger CA, Dünser MW, Torgersen C, Luckner G, Lorenz I, Schmid S, Joannidis M, Moser P, Hasibeder WR, Halabi M, Steger CM. Histologic pathologies of the myocardium in septic shock: a prospective observational study. *Shock*. 2013;39:329–335.
40. Hillman NH, Moss TJ, Kallapur SG, Bachurski C, Pillow JJ, Polglase GR, Nitsos I, Kramer BW, Jobe AH. Brief, large tidal volume ventilation initiates lung injury and a systemic response in fetal sheep. *Am J Respir Crit Care Med*. 2007;176:575–581.

CLINICAL PERSPECTIVE

Delivery room cardiopulmonary resuscitations are an infrequent event in newborn infants and associated with high rates of neurodevelopmental impairment and mortality. The poor prognosis associated with delivery room resuscitations raises questions as to whether specifically tailored neonatal cardiopulmonary resuscitations could improve outcomes. Current neonatal resuscitation guidelines recommend a ratio of 90 chest compressions and 30 ventilations per minute; however, the most effective ratio remains controversial. In our porcine model of neonatal hypoxia-asphyxia, we were able to passively ventilate the lung while providing chest compressions. To achieve passive ventilation, we applied airway pressure of 30 cm H₂O, which was sustained for the duration of the chest compressions. This novel approach significantly improved the return of spontaneous circulation and survival in newborn piglets. We observed improved lung aeration, which resulted in marked increases in pulmonary blood flow. An increase in oxygenated blood flow returning from the lungs restores cardiac function, resulting in increased systemic and pulmonary blood pressure and carotic blood flow during resuscitation. With the use of this new technique, significantly fewer piglets required supplemental oxygen and none required intravenous epinephrine administration. This may be of clinical relevance because hyperoxia can lead to the generation of oxygen-free radicals, a major cause in reperfusion injury after asphyxia. Our results are of considerable clinical relevance, because improved respiratory and hemodynamic parameters potentially minimize morbidity and mortality in newborn infants.