Protocol

SURV1VE-Trial

Sustained inflation and chest comp**r**ession **v**ersus 3:**1** chest compression to **v**entilation ratio during cardiopulmonary resuscitation of asphyxiated n**e**wborns – a cluster randomized controlled trial

Protocol:	Protocol SURV1VE Phase II
Trial phase	Phase II
Protocol date (version):	**Version 4.0, December 1st 2020**
Study sites:	Multi-centre; Multi-national

Declaration of Commitment

Name of investigator	
Institution	

Clinical trial

Trial title	**SURV1VE-Trial - Su**stained inflation and chest comp**r**ession **v**ersus 3:**1** chest compression to **v**entilation ratio during cardiopulmonary resuscitation of asphyxiated n**e**wborns – a cluster randomized control trial
Inclusion criteria	All infants (preterm and term infants) requiring chest compression at birth
Exclusion criteria	Congenital anomalies, Parents decline to consent for data use
Recruitment period (months)	24 months

Strategy for the determination of recruitment figures

How many neonates fulfilling entry criteria will be approximately eligible?	
Approximately how many patients will be recruited during the entire trial *(anticipated 2 year recruitment period)*?	

Will there be any other ongoing clinical trials/projects competing for the same patients

☐ Yes

☐ No

If yes: How will this affect recruitment for the above-named clinical trial?

Note: Reported recruitment will be checked if funding is provided (pre-trial visits). If inconsistencies exist between the estimated and verified numbers, the principal investigator will be asked to address this issue.

Commitment to Participate

I hereby agree to participate in the above-named clinical trial and support the trial by recruiting patients.

_____

Date/Signature

Conflicts of Interest

I hereby declare that I have no conflict interest, neither personal nor commercial, with regard to the above-mentioned clinical trial and the investigational drugs that will be used.

_____

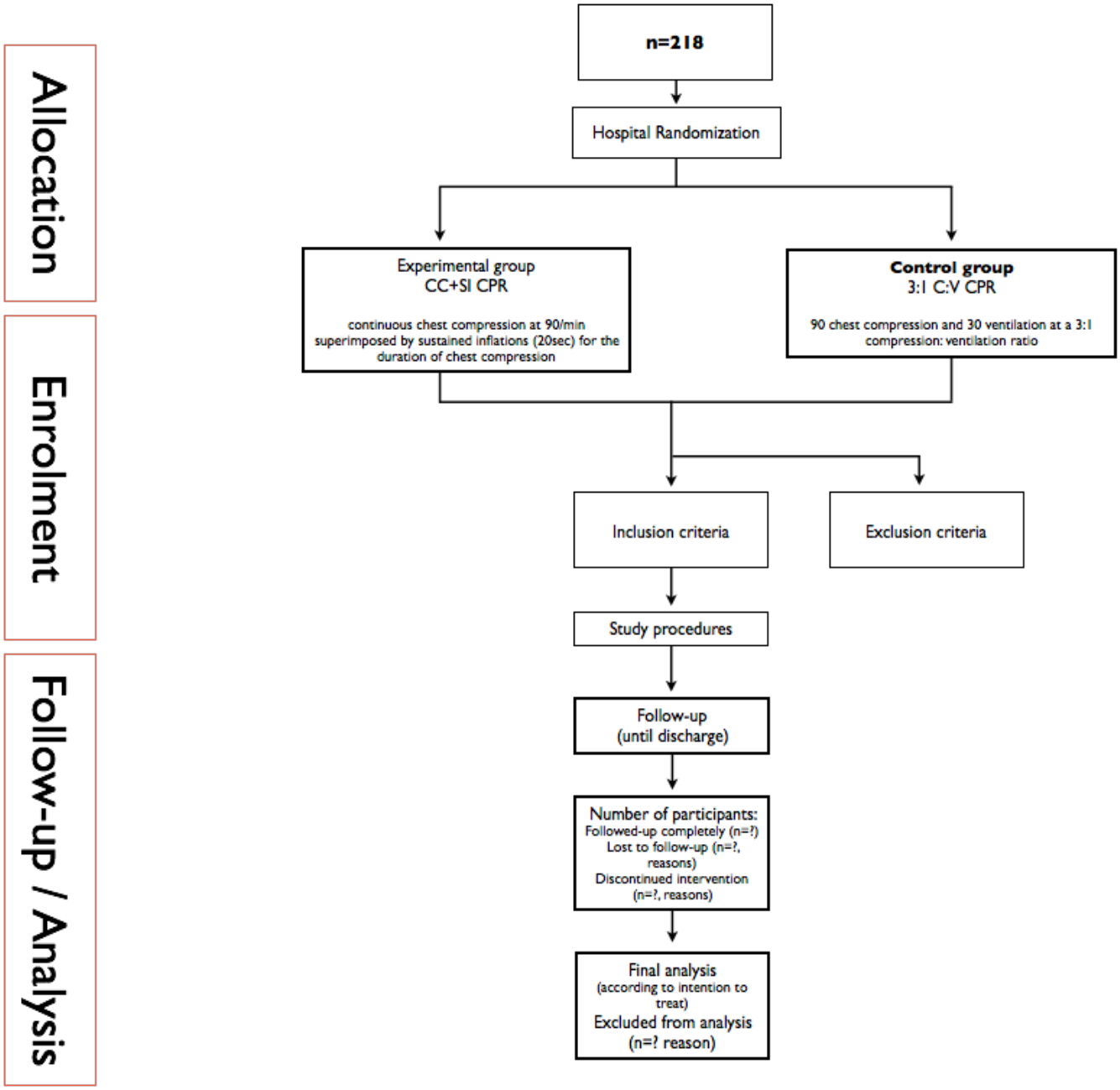
Date/Signature

Protocol Summary

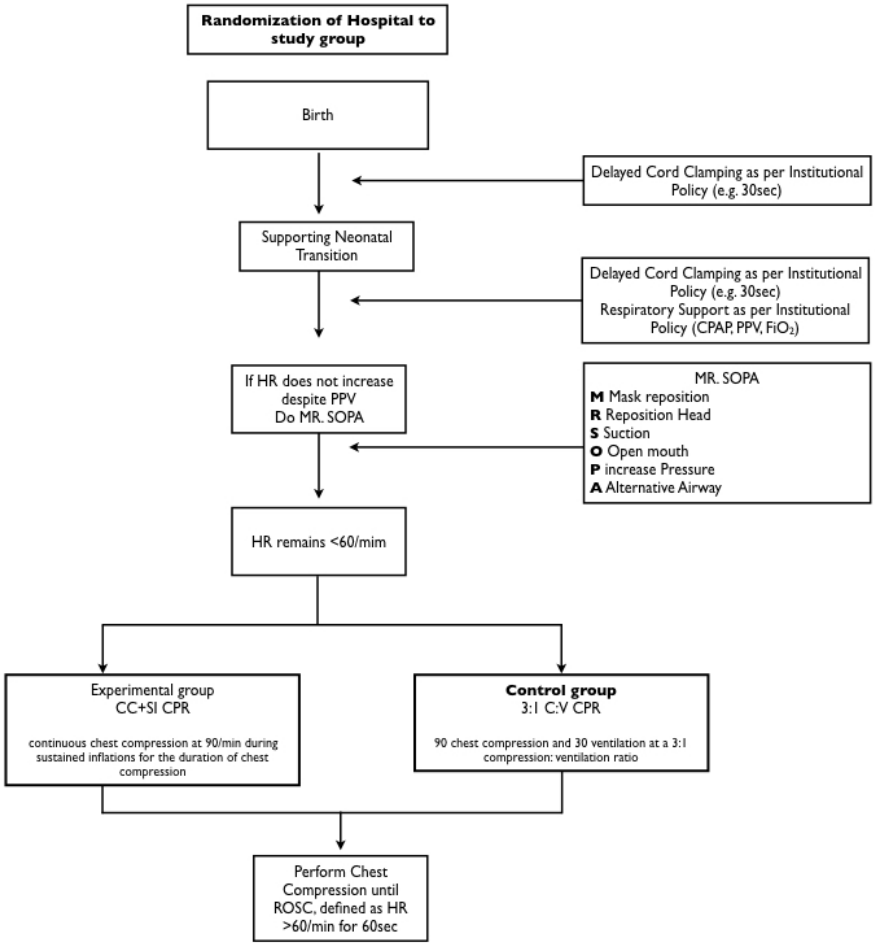
Study Title	SURV1VE-Trial - Sustained inflation and chest compression versus 3:1 chest compression to ventilation ratio during cardiopulmonary resuscitation of asphyxiated newborns – a cluster randomized control trial
Population	Infants (preterm >28 weeks' gestation and term) requiring chest compression in the delivery room.
Primary Objective	Chest Compression during sustained inflation (CC+SI) will improve short- and long-term outcomes in preterm and term newborns
Primary Hypothesis	By using CC+SI during cardiopulmonary resuscitation (CPR) the time needed to achieve return of spontaneous circulation (ROSC) compared to the current 3:1 compression to ventilation (C:V) will be reduced in asphyxiated newborns.
Design and Sample Size	This prospective multi-national randomized controlled trial (RCT) is a two-arm parallel design of two alternative courses of treatment. 218 infants – 109 control / 109 intervention
Inclusion Criteria	Infants (preterm and term) requiring chest compression in the delivery room.
Exclusion Criteria	a) Congenital abnormality b) Condition that might have an adverse effect on breathing or ventilation (e.g. congenital diaphragmatic hernia) c) Congenital heart disease requiring intervention in the neonatal period) d) Parents' refusal to give consent to this study
Efficacy Endpoints	Primary: • Time to achieve return of spontaneous circulation defined as a heart rate of >60/min for 60sec **Secondary:** • All mortality prior to discharge from hospital • Delivery room interventions (use of epinephrine) • Admission temperature • Use of therapeutic cooling • Mechanical ventilation • Use of inotropes

	• Infection/sepsis • Necrotizing enterocolitis • Pneumothorax • Bronchoplumonary dysplasia • Retinopathy of prematurity • Brain injury as indicated by abnormal neuroimaging • Seizure • 18-24 months neuro-developmental outcomes
Safety Evaluations	Adverse events
Statistical Methodology	Interim analyses will be conducted when 10%, 25% and 50% of participants complete primary outcome. The final analysis will be conducted after the study is completed, unblinded, and the database is released for analysis. All analyses will be performed using IBM SPSS Statistics Ver. 24 (IBM Corp.) and SAS version 9.4 (SAS Institute Inc.) or later.
Clinical Centers	Multi-national sites (including Canada, Austria, Norway, Germany, Spain, Poland, Italy, The Netherlands, Ireland, United Kingdom, Australia and China), further sites are invited
Enrollment Period	2 years
Study Duration	3 years
Webpage	http://surv1ve.org
ClinicalTrials.Gov Trial	NCT02858583

Study flow diagram



Intervention flow diagram



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List of abbreviations

CC	- Chest compression
DR	- Delivery room
CPR	- Cardiopulmonary resuscitation
SI	- Sustained inflation
CC+SI	- Chest compression during sustained inflation
ROSC	- Return of spontaneous circulation
C:V ratio	- Compression to ventilation ratio
DBP	- Diastolic blood pressure
CCaV	- Continuous chest compression with asynchronous ventilations
V_T	- Tidal volume
RN	- Registered Neonatal Nurse
RRT	- Registered Respiratory Therapist
NNP	- Neonatal Nurse Practitioner
PIP	- Peak inflation pressure
PEEP	- Peep expiratory pressure
ECO_2	- Exhaled carbon dioxide
eCRF	- electronic Case Report Forms
SD	- Standard deviation
IQR	- Interquartile range
SAE	- Serious adverse event
DSMB	- Data and Safety Monitoring Board
GCP	- Good Clinical Practice
NIRS	-Near Infrared Spectroscopy
aEEG	-amplitude integrated electroencephalography

Background

The majority of newborn infants successfully make the transition from fetal to neonatal life without any help[1]. However, an estimated 10% of newborns need help to establish effective ventilation, which remains the most critical step of neonatal resuscitation. Fortunately, the need for chest compression (CC) or medications in the delivery room (DR) is rare. Although, only about 0.1% of term infants and up to 15% of preterm infants[2,3] receive these interventions, this will result in approximately 1 million newborn deaths annually worldwide. A recent cohort study at a level III center with a trained resuscitation team showed that only 6 per 10,000 infants received epinephrine[4]. However, the same study showed that those infants who received epinephrine during resuscitation had a high incidence of mortality (41%) and short-term neurologic morbidity (57% hypoxic-ischemic encephalopathy and seizures)[4]. A recent review of newborns who received prolonged CC and epinephrine but had no signs of life at 10 minutes following birth noted 83% mortality, with 93% of survivors suffering moderate-to-severe disability[5]. The poor prognosis associated with receiving CC alone or with medications in the DR raises questions as to whether improved cardiopulmonary resuscitation (CPR) methods specifically tailored to the newborn could improve outcomes.

The inability to predict which newborns need CPR, and the infrequent use of CPR in the DR have limited neonatologists' ability to perform rigorous clinical studies to determine the best method for delivering CC to newborn infants. The main cause of cardiovascular collapse in most newborns is asphyxia, which makes newborn infants distinctively different to the adult population. The International Liaison Committee on Resuscitation and the American Academy of Pediatrics/American Heart Association Neonatal Resuscitation Program have recognize this difference, however the guidelines almost exclusively rely on data from studies in the adult population or animal studies. Such data may not be wholly applicable to the neonatal population because the most common cause of cardiovascular collapse in the adult is ventricular fibrillation, not asphyxia. Thus, further studies are needed to determine the optimal method for improving hemodynamics and recovery during neonatal resuscitation.

Research question

In newborn infants (preterm infants >28 weeks' gestation and term infants) requiring CPR, does CC during sustained inflation compared to 3:1 compression to ventilation ratio improves return of spontaneous circulation (ROSC)?

Primary objective: To prove that CC during sustained inflation will improve recovery from CPR in preterm and term newborns with faster ROSC than that by 3:1 CPR technique.

Secondary objectives: To examine i) if CC during sustained inflation will improve short- and

long-term outcomes in preterm and term newborns, and ii) the value of feedback devices (e.g. ECO_2, ECG and/or SpO_2) in determining ROSC.

Hypotheses to be tested

Primary hypothesis: By using CC during sustained inflation (CC+SI) during CPR the time needed to achieve ROSC compared to the current 3:1 compression to ventilation (C:V) ratio will be reduced in asphyxiated newborns.

Secondary hypotheses: The benefits associated with CC+SI will i) decrease death; ii) improve short- and long-term outcomes in preterm and term newborns; and iii) feedback devices help to determine ROSC.

Knowledge to date

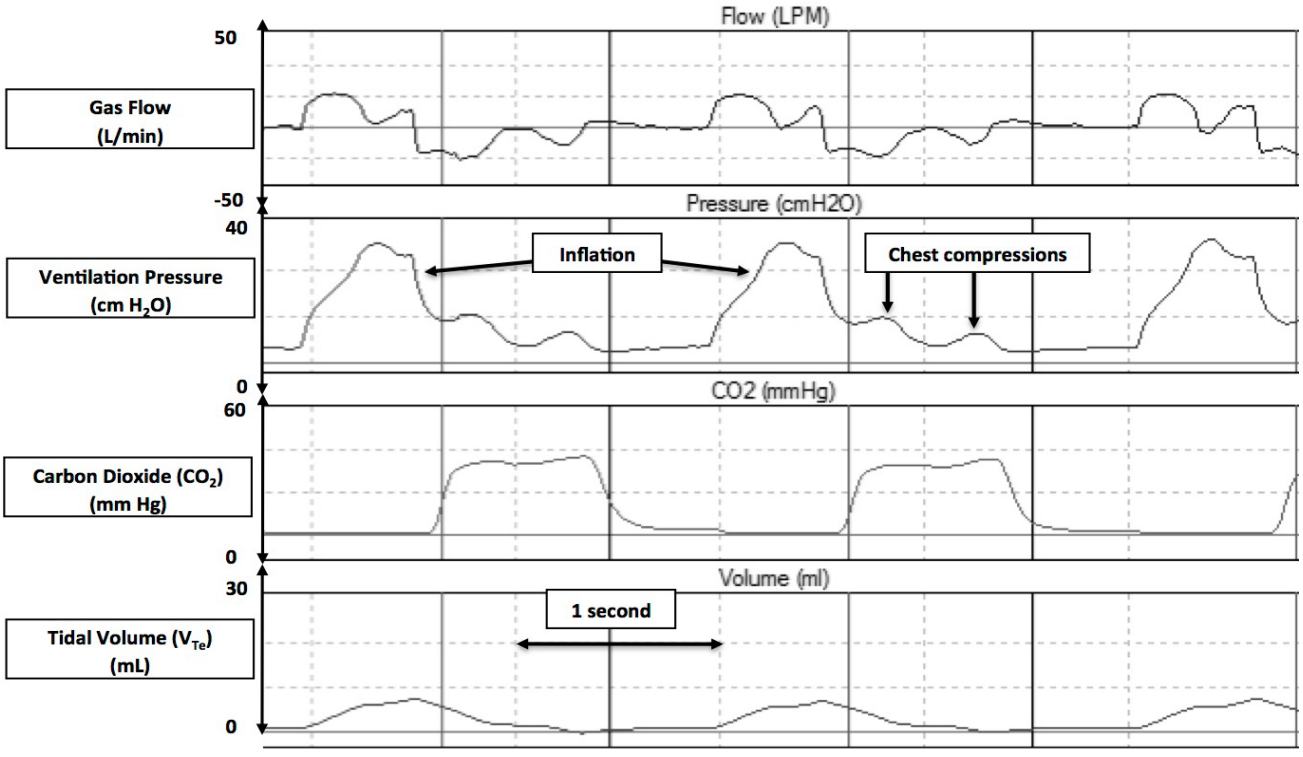
Asphyxia at birth

Asphyxia, a condition of impaired gas exchange with simultaneous hypoxia and hypercapnia leading to a mixed metabolic and respiratory acidosis, is the most common reason that newborns fail to make successful transition[6]. Asphyxia could result from either failure of placental gas exchange before delivery (e.g. abruption, chorioamnionitis), adverse events during delivery (e.g. dystocia/obstructed labor, cord prolapse), or deficient pulmonary gas exchange immediately after birth (e.g. apnea, airway obstruction, respiratory distress syndrome)[6]. Asphyxia depresses myocardial function leading to cardiogenic shock, pulmonary hypertension, mesenteric ischemia/reperfusion, and acute renal failure. Newborn infants either present with severe bradycardia or asystole at birth as a consequence of asphyxia. Current resuscitation guidelines recommend to initiate CC if the heart rate remains <60/min despite adequate ventilation for at least 30 seconds; CC should be then performed at a rate of 90/min and ventilations at a rate of 30/min, i.e. a 3:1 C:V ratio (Figure 1A) to achieve adequate oxygen delivery[1].

Chest compressions serve to mechanically pump the blood through the body until the return of myocardial function[6]. Blood expulsion from the ventricles during CPR is thought to occur by either direct compression of the heart between the sternum and vertebral column (cardiac pump theory), or phasic increases in intrathoracic pressure (thoracic pump theory). The “cardiac pump theory” postulates that CC directly eject blood from the heart into the circulation with each compression[7]. In comparison, the “thoracic pump theory” states that a phasic increase in intrathoracic pressure produced by compression of the chest creates a pressure gradient between the arterial and venous compartment[8-12]. This pressure gradient then serves as the driving force for antegrade blood flow. Optimized CC has been demonstrated to generate 30% of normal organ perfusion, with preferential (>50%) perfusion to the heart and brain[8]. During CC, coronary blood flow occurs during diastole with coronary perfusion pressure determined by

the difference between aortic blood pressure and right atrial pressure[15]. In adult animals and humans, uninterrupted CC and systemic vasoconstrictors such as epinephrine enhance diastolic blood pressure (DBP) during CPR. Studies using sudden cardiac collapse models in 2-3 month old asphyxiated pigs[16] as well as randomized trials during adult cardiac arrest[17] have demonstrated that continuous CC without rescue breaths significantly reduce time to ROSC and increase survival due to improved hemodynamics. These studies led to a change in adult life support guidelines recommending that bystander CPR be performed without rescue breaths and that in lone rescuer advanced CPR, CC should be uninterrupted for the first few minutes[18]. In both adult and pediatric advanced life support, continuous CC with asynchronous ventilations are recommended after a secure airway has been established[18,19]. In contrast, current neonatal resuscitation guidelines recommend using a coordinated 3:1 C:V ratio if CC are needed, even after the placement of an endotracheal tube. This approach is composed of 90 CC and 30 inflations per minute, with a pause after every 3rd CC to deliver one effective inflation (Figure 1A). This approach may not be optimizing DBP during neonatal CPR as every interruption in CC results in a drop in DBP that needs to be regenerated during the next compression cycle.

Figure 1A: Respiratory waveforms during 3:1 CPR[13]



Rationale for using 3:1 compression to ventilation ratio

The recommendation to use a 3:1 C:V ratio is based on expert opinion, extraction from animal data and consensus rather than strong scientific evidence form studies in newborn infants[20]. Rationales

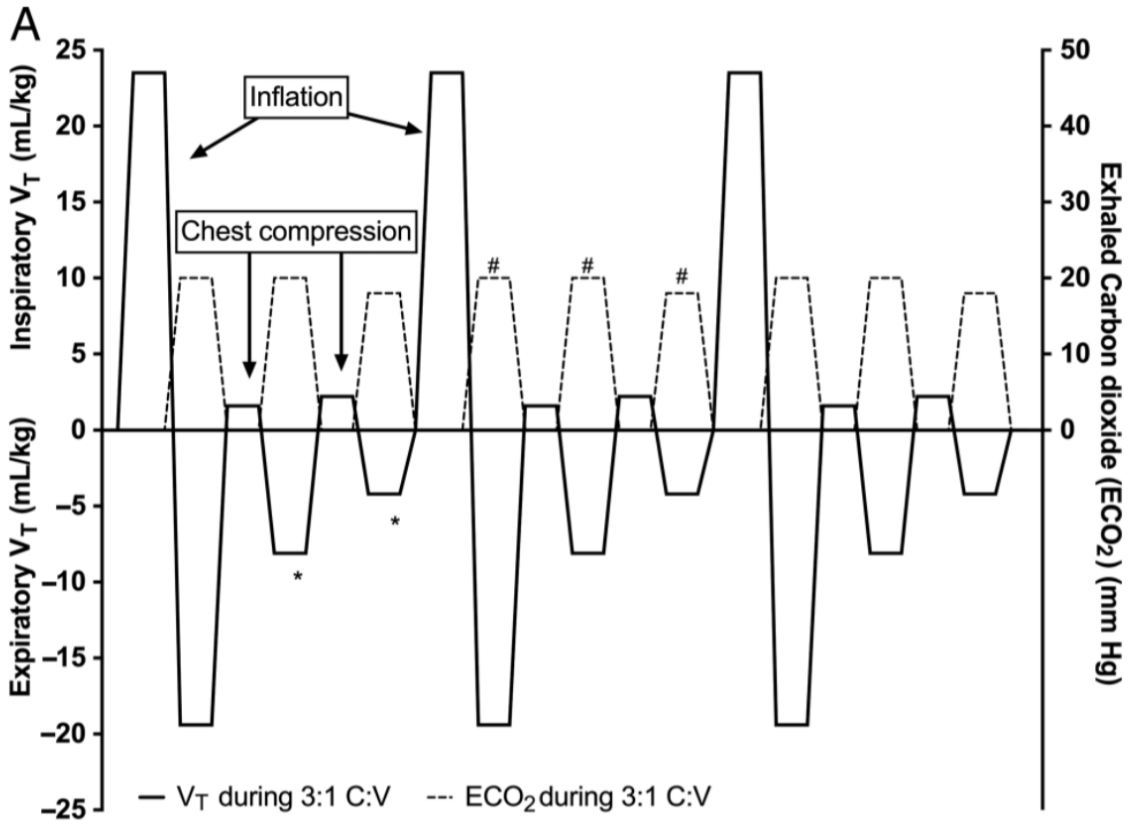
for using a 3:1 C:V ratio include the higher physiological heart rate of 120-160/min and breathing rates of 40-60/min in newborns compared to adults. Furthermore, profound bradycardia or cardiac arrest in newborns is usually caused by hypoxia rather than primary cardiac compromise; therefore, providing ventilation is more likely to be beneficial in neonatal CPR compared to adult CPR[1]. However, the optimal C:V ratio that should be used during neonatal resuscitation to optimize coronary and cerebral perfusion while providing adequate ventilation of an asphyxiated newborn remains unknown[14].

Animal studies using cardiac arrest induced by asphyxia in newborn piglets demonstrated that combining CC with ventilations improves ROSC and neurological outcome at 24 hours compared to ventilations or CC alone[16,21]. *Solevåg et al* performed a study investigating alternating 9 CC and 3 ventilations in asphyxiated piglets with cardiac arrest with the hypothesis that 9 CC would generate higher DBP during CPR than only 3 CC per series[15]. However, increasing the number of CC in a row should not be at the expense of ventilation, hence the ratio of CC to ventilation was maintained at 3:1. The time to ROSC was similar between the two approaches (median time of 150 and 148 sec for 3:1 C:V and 9:3 C:V, respectively). In addition, there were no differences in DBP during CC[15]. Similarly, C:V ratios of 3:1 and 15:2 were compared using the same model[16]. Although the 15:2 C:V ratio provided higher mean CC per minute (75 versus 58 for 3:1), time to ROSC was similar between groups (median time of 195 and 150 sec for 15:2 and 3:1, respectively)[16]. These studies suggest that during neonatal CPR higher C:V ratios do not improve outcomes.

Manikin studies have confirmed higher ventilation rates during simulated CPR using 3:1 C:V compared to higher C:V ratios[17-19]. A more recent neonatal manikin study examined respiratory parameters during neonatal CPR and reported that a 3:1 C:V ratio delivered significantly higher minute ventilation of 191 mL/kg compared to the minute ventilation at 9:3 and 15:2 C:V ratios (140 and 77 mL/kg/min, respectively)[20]. A further manikin study compared 3:1 C:V with continuous CC with asynchronous ventilations (CCaV) using 90 CC and 30 non-synchronized inflations and reported significantly higher minute ventilation in the CCaV group compared to the 3:1 group (221 versus 191 mL/kg/min, respectively)[28]. *Schmölzer et al* compared 3:1 C:V CPR with CCaV in a piglet model of neonatal asphyxia and reported similar minute ventilation (387 versus 275 mL/kg)[21]. However, there was a trend towards a reduced time to ROSC (143 and 114 sec for 3:1 and CCaV, respectively), and survival (3/8 and 6/8, respectively) in the CCaV group. The same manikin and animal study[28,21] also reported similar tidal volume (V_T) delivery between 3:1 C:V and CCaV (manikin study V_T 6.4 and 5.6 mL/kg, respectively[28] and animal study V_T 14.7 versus 11.0 mL/kg[21]). In a secondary analysis of the study by *Schmölzer et al*[21], *Li et al* reported that during 3:1 C:V a cumulated loss of V_T of 4.5 mL/kg occurs for each 3:1 C:V cycle (Figure 2A)[22]. Similarly, during CCaV a cumulated loss of V_T of 9.1 mL/kg for each cycle of three CC and one inflation was observed[22]. This is concerning as a loss in V_T could cause lung decruitment, which could hamper oxygenation and therefore ROSC. Further, an argument for synchronized CPR is the potential interference of non-synchronized CC with V_T delivery, hence

impairment of oxygen delivery. However, the study by *Schmölzer et al* observed that a comparable 29% and 25% of manual inflations were affected during CC using CCaV or 3:1 C:V CPR[21], respectively. These studies suggest no advantages (e.g. oxygen delivery, V_T or minute ventilation) of using CCaV compared to 3:1 C:V.

Figure 2A: Inspiratory and expiratory tidal volume (V_T) during 3:1 C:V CPR[22]

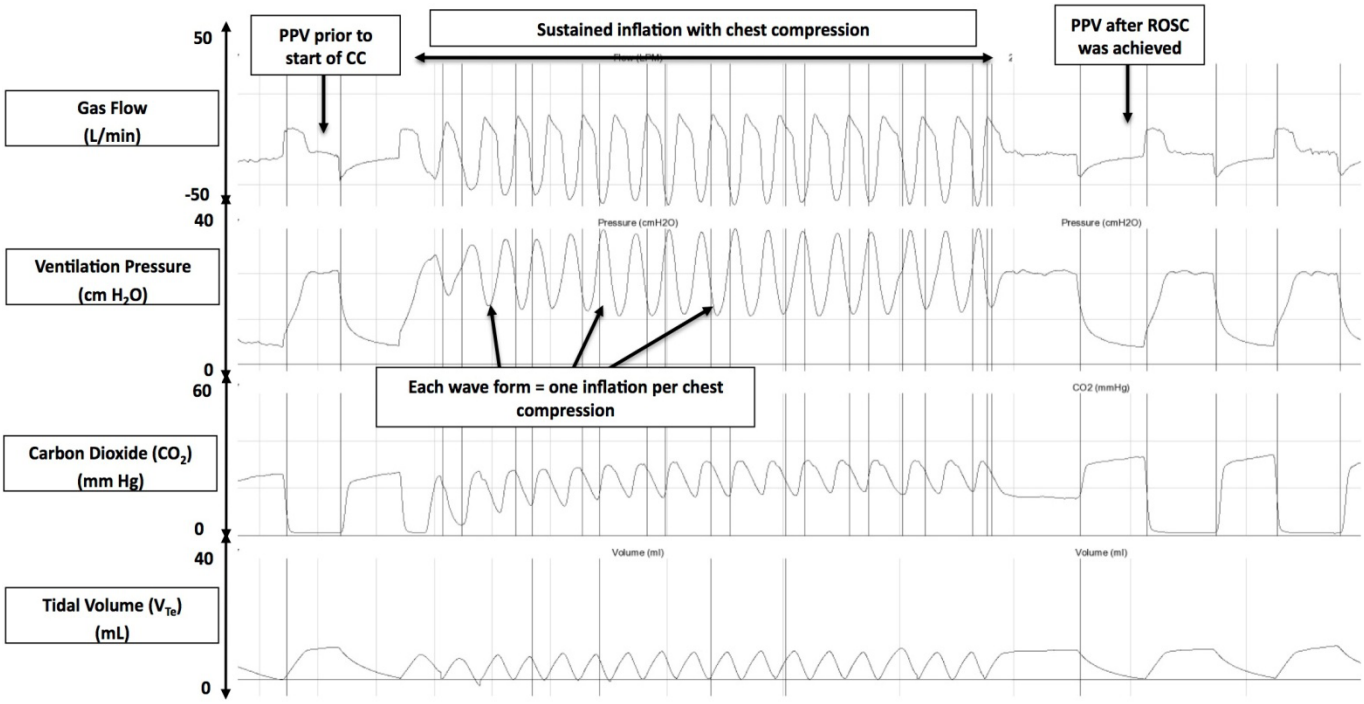


Rational for using CC+SI

Reoxgenation and adequate blood flow are the cornerstones of neonatal CPR. Any effective resuscitative manoeuvre should increase blood flow and optimize oxygen delivery. In addition to standard CPR, manoeuvres that raise intrathoracic pressure can significantly increase carotid blood flow during CPR[9,23]. *Chandra et al* provided ventilation at high airway pressure while simultaneously performing CC in an animal model and demonstrated increased carotid flow without compromising oxygenation[9]. Further, studies in preterm lambs have demonstrated that a sustained inflation (SI) also increases intrathoracic pressure without impeding blood flow[24]. An experimental study using a ventricular fibrillation model of adult cardiac arrest demonstrated that emphasis on CC over ventilation increases neurologically intact survival in pigs[25]. In the resuscitation of asphyxiated newborn piglets,

Schmölzer et al recently reported that passive ventilation during CC, achieved by superimposing CC with a SI (CC+SI) (Figure 1B), significantly improved hemodynamics, minute ventilation, and time to ROSC compared to the currently recommended approach of using a 3:1 C:V ratio (mean arterial pressure: 51 versus 31 mmHg; pulmonary arterial pressure: 41 versus 31 mmHg; mean minute ventilation: 936 versus 623 mL/kg; median time to ROSC: 38 versus 143 sec, respectively)[13]. However, the study by *Schmölzer et al* used a CC rate of 120/min (in the CC+SI group), which is higher than the currently recommended CC rate of 90/min, which could have also added to the improved outcomes.

Figure 1B: Respiratory waveforms during CC+SI CPR[13]



A recent mathematical model suggests that higher CC rates than the currently recommended 90 CC/min could optimize systemic perfusion[26]. This model further suggests that the most effective CC rate depends upon body size and weight, which would translate to 180 CC/min for term infants and even higher rates for preterm infants[26]. However, a recent simulation study comparing various CC rates (e.g. 90/min versus 120/min) reported faster fatigue with increasing CC rates[27]. Overall, using CC rates of 90/min was the least fatiguing and the most preferred method of neonatal CPR compared to using CC rates of 120/min[27]. This is further supported by a study by *Solevåg et al* who quantified the force used during CC and reported that fatigue occurs faster with increasing CC rates[28]. These studies suggest that a rate of 90/min will be the least fatiguing CC rate. Further, a recent randomized animal trial

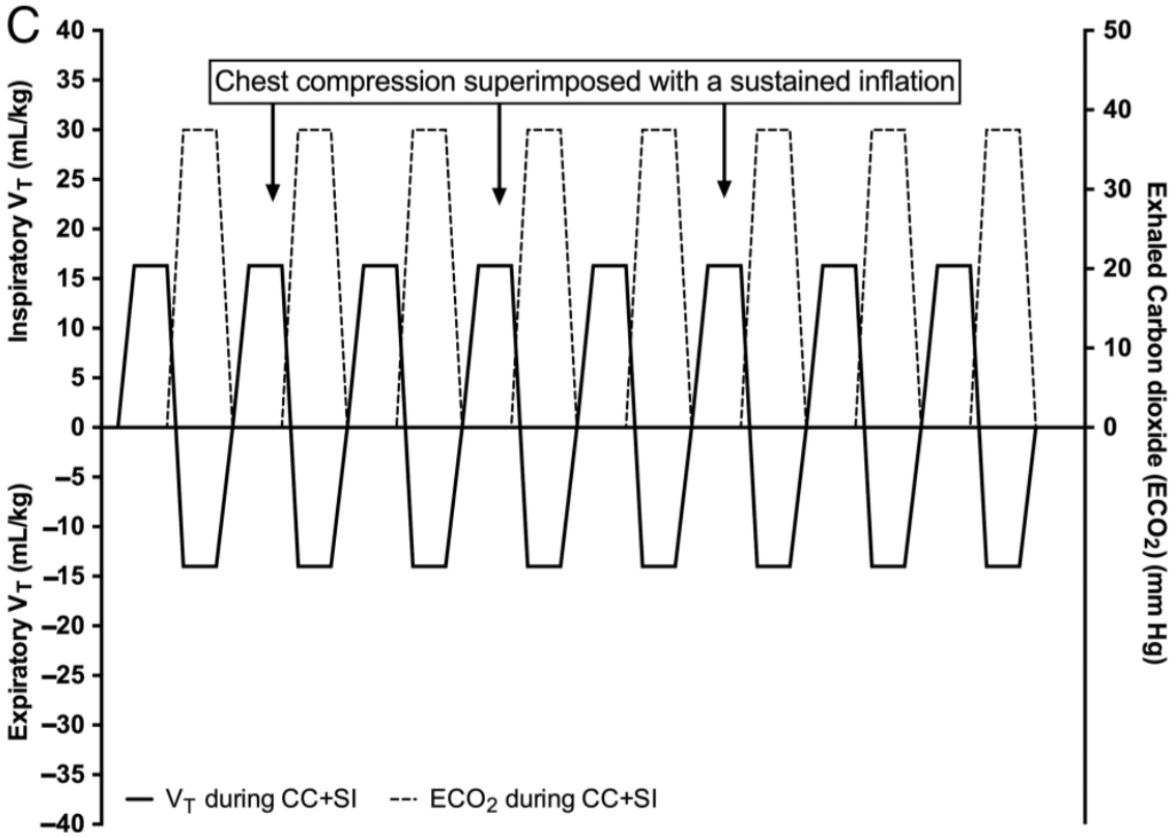
compared CC+SI using CC rates of 90/min versus 120/min and reported similar time to ROSC, survival rates, and respiratory parameters during CPR[29]. During CC carotid blood flow, mean arterial pressure, and % change in ejection fraction and cardiac output were higher in the CC+SI 90/min group compared to CC+SI 120/min[29]. This further supports that higher CC rates do not improve systemic perfusion and that the current recommendation of 90 CC per minute is sufficient to achieve systemic perfusion. A further randomized animal trial comparing SI+CC 90/min with 3:1 C:V ratio (in review, Schmölzer last author) showed a significant reduction in median (IQR) time to ROSC 34 (28-156) sec versus 210 (72-300) sec (p=0.05), less oxygen; 3/8 versus 8/8 required 100% oxygen during CPR (p=0.03), and 3/8 versus 6/8 piglets received epinephrine (p=0.32) in the SI+CC 90/min group. In addition, improved respiratory and hemodynamic parameters were observed in the SI+CC 90/min group versus the 3:1 C:V ratio group. A recent pilot trial in preterm infants <32 weeks gestation showed similar results (in review, Schmölzer first author). Overall, the mean (SD) time to ROSC was significantly shorter in the CC+SI group with 31 (9) sec compared to 138 (72) sec in the 3:1 C:V group (p=0.011). Overall, 0/5 in the CC+SI group and 1/5 in the 3:1 C:V group received epinephrine.

Providing adequate ventilation to achieve reoxgenation is a further cornerstone of neonatal CPR. Current best practice is to provide 90 CC and 30 ventilations that are coordinated with a pause in CC to deliver an inflation[1]. The purpose of inflations during CC is to deliver an adequate V_T to facilitate gas exchange. However, delivery of an adequate V_T during CPR remains difficult. Several DR studies reported that mask ventilation is the most difficult task during neonatal CPR. V_T delivery could be compromised due to mask leak or airway obstruction[30-38], causing inadequate oxygen delivery to the asphyxiated newborn. A recent case report by *Li et al* reported a large mask leak during mask ventilation in the DR, which resulted in severe bradycardia and the need for neonatal CC[39]. In addition, once CC were started mask leak further increased[39]. This is further supported by manikin studies, which reported decreased expiratory V_T once CC were started[20,40,41]. *Binder et al* examined human or monitor feedback during simulated neonatal CPR using a leak-free manikin and reported lower expiratory V_T in all groups compared with mask ventilation alone[41]. These studies suggest a decrease in expiratory V_T once CCs are initiated. A loss in expiratory V_T could cause lung decruitment, which could hamper oxygenation and therefore ROSC. This has been recently confirmed in an animal model of neonatal CPR. In a secondary analysis of the study by *Schmölzer et al*[21], *Li et al* reported that during a significant loss of expiratory V_T compared to inspiratory V_T over each 3:1 C:V cycle (mean total inspiratory V_T was 27.2mL/kg and mean total expiratory V_T 31.7mL/kg = a loss of 4.5mL/kg per 3:1 C:V cycle) (Figure 2A)[22]. In contrast, no V_T loss was observed in CC+SI. Instead a continued lung recruitment and establishment of functional residual capacity was observed (mean total inspired V_T was 16.3mL/kg and mean total expiratory was 14mL/kg = a gain of 2.3mL/kg/CC+SI cycle) (Figure 2B)[22]. This improvement in V_T delivery may lead to better alveolar oxygen delivery and lung aeration. More importantly, the initial study by *Schmölzer et al*[21] and secondary analysis by *Li et al*[22] describe passive V_T delivery during each chest compression

cycle. Similar observations have been reported by *Tsui et al*[42] in children under the age of 17 years undergoing any surgery requiring general anesthesia and endotracheal intubation. Tsui et al compared V_T after induction of general anesthesia before and after intubation by applying a downward force on the chest, which was not greater than the patient's weight in seven infants[42]. Overall, median (IQR) V_T generated before and after intubation was 2.4 (0.8-4.0) and 2.0 (0.4-3.6) mL/kg, respectively[42]. Although, *Tsui et al* only applied gentle chest pressure, they were able to achieve ~33% of an infants physiological V_T of 5-7mL/kg. During CC the mean applied force is ~10kg (3-4 times the weight of the newborn infant)[28], which would result in adequate V_T delivery during CC+SI. Further, *Solevåg et al* determined the distending pressure needed to achieve sufficient V_T delivery using different models (manikin and cadaver piglets) during CC+SI{Solevag:2017hd}. Distending pressure and V_T correlated in cadaver piglets ($r=0.83$, $p<0.001$), manikin ($r=0.98$, $p<0.001$), and combined data ($r=0.49$, $p<0.001$). V_T was delivered during chest recoil during CC in both models. In cadaver piglets a distending pressure ~ 25cmH_2O was needed to achieve an adequate V_T. This study suggests that chest recoil generates V_T depending on an adequate distending pressure, and that a pressure of ~25cmH_2O will be needed to achieve adequate V_T delivery. In a recent pilot trial comparing CC+SI versus 3:1 C:V CPR in 10 preterm infants <32 weeks gestation (5 in each group) *Schmölzer et al* used a distending pressure of 24cmH_2O (local hospital policy during neonatal resuscitation) and showed adequate V_T and significantly higher minute ventilation in the CC+SI group versus 3:1 C:V group ($p<0.001$) (under review, Schmölzer first author). These data suggest that CC+SI has the potential to improve ventilation and oxygen delivery during neonatal CPR.

Successful resuscitation from cardiac arrest or severe bradycardia requires the delivery of high-quality CC while providing adequate ventilation. However, no study has examined different chest compression techniques during neonatal resuscitation in asphyxiated newborn infants.

Figure 2B: Inspiratory and expiratory tidal volume (V_T) during CC+SI CPR[22]



Methodology

Ethics

This multi-center cluster randomized clinical trial will be reviewed by the appropriate Research Ethics Office at all participating sites. We will request a deferred consent model at all sites (see parental consent paragraph for details). Written consent will be sought from the parents of these infants as soon as possible after the birth so that acquired data could be utilized for research[35].

In the trial, participating centres will **change their local hospital policy** to either 3:1 C:V or CC+SI as per randomization to enrol for one year. To enrol the next 30 infants, participating centres **will change their local hospital policy** to the other arm with CC+SI or 3:1 C:V. After completion of enrollment, every centre will change to their original hospital policy. **This approach will assure that all eligible infants are enrolled** as the **local hospital policy** will be changed to match the study intervention. The order in which centres will start will be chosen randomly.

Inclusion criteria

All infants (term or preterm infants >28 weeks' gestation) requiring CC in the delivery room will be eligible for the trial.

Exclusion criteria

Infants will be excluded if they have a congenital abnormality or condition that might have an adverse effect on breathing or ventilation (e.g. congenital diaphragmatic hernia), or congenital heart disease requiring intervention in the neonatal period. Infants will be also excluded if their parents refuse to give consent to this study.

Patient discontinuation and withdrawal

The participant's parents are free to withdraw the participant from the intervention or from the SURV1VE trial entirely at any time, and this will not have any consequences for the participant's further treatment. When possible, the parents will be asked if they will allow their infant to participate in the remaining follow-up assessments, and allow their infants' already collected data to be used in a database, a registry, and/or a publication.

The attending clinician can withdraw the participant from the trial at any time. The reasons shall be documented. There are no pre-specified criteria for discontinuation of participants from the trial. The discontinuation of participants in the trial will not result in replacement with new participants.

Randomization

At the beginning of the trial participating sites will be randomized. Centers will be equally allocated to either CC+SI group ("intervention group") or 3:1 C:V group ("control group") for the first year. For the second year, after a wash out period of 2 months, centers in the intervention group will be changed to control and vice versa.

Sample Size and Power calculation

Our **primary outcome measure** will be time to achieve ROSC. We hypothesize that the time to achieve ROSC will be reduced in the "CC+SI group". A sample size of 208 infants, 104 in each group, would be sufficient to detect a clinically important 33% reduction in time to achieve ROSC using Cox proportional hazards regression with 80% power and a 2-tailed alpha error of 0.05. This 33% reduction represents 282 sec versus 420 sec of CC (based on the database of 30 term infants requiring CC in 2014 and 2015 at the Royal Alexandra Hospital, Edmonton). To account for cluster randomization, the

sample size is multiplied by design effect of 1.045, so the total sample size is 218 infants, 109 in each group.

Blinding

There will be no blinding during the recruitment phase. Each hospital is allocated to one treatment arm and therefore the CC technique used at each particular site is known to the clinical team. The outcome assessor will be unaware of the group allocation. This blinding will be maintained until the data is locked for the final analysis and un-blinded.

Technique of Resuscitation

Infants will only be eligible and randomized if they require chest compressions. The methods described below also describe resuscitation interventions for infants prior to the start of chest compressions.

Constitution of the Resuscitation Team

The members of the resuscitation team will be site specific (for example in Edmonton it consists of a Registered Neonatal Nurse (RN), Respiratory Therapist (RT), Pediatric Resident or Neonatal Sub-specialty Resident (Fellow) or Neonatal Nurse Practitioner (NNP) and/or Neonatologist). The most senior team member will act as the team leader, who will manage the protocol and guide the intervention during the trial.

Description of general interventions

Term infants

The initial steps of the resuscitation will be according to the current neonatal resuscitation guidelines[1]. Delayed cord clamping should be performed as per local hospital policy (standard hospital practice guideline) at participating sites where eligible. Afterwards, dry and stimulate the infant, and open the airway. If heart rate is <100/min, the infant is gasping or has apnea, start positive pressure ventilation. At the same time consider attaching a pulse oximeter and also consider applying electrocardiography. If heart rate remains <100/min, perform MR. SOPA (**M**ask is tightly applied to the face, **R**e-position the head into the “sniffing” orientation, **S**uction the nares and the pharynx, **O**pen the mouth, **P**ressure of PPV can be increased to a max of 40 cm H_2O, **A**lternate airway (endotracheal tube or Laryngeal Mask Airway). If heart rate is <60/min or remains <60 despite **all steps** of MR. SOPA including alternate airway, start chest compressions and increase to 100% oxygen.

Preterm infants

The initial steps of the resuscitation will be according to the current neonatal resuscitation guidelines[1]. Delayed cord clamping should be performed as per local hospital policy (standard hospital practice guideline) at participating sites where eligible. Immediately afterwards, preterm infants (according to local hospital policy - standard hospital practice guideline) will be either placed (without drying) in a polyethylene bag under radiant heat[44] or dried and placed under radiant heat.

A pulse oximeter will be used to monitor oxygen saturation immediately after birth and oxygen delivery will be guided by published norm values for oxygen saturation in preterm infants[45].

If heart rate is <100/min, the infant is gasping or has apnea, start positive pressure ventilation. Also consider applying electrocardiography at that time. If heart rate remains <100/min, perform MR. SOPA (**M**ask is tightly applied to the face, **R**e-position the head into the "sniffing" orientation, **S**uction the nares and the pharynx, **O**pen the mouth, **P**ressure of PPV can be increased to a max of 40 cm H_2O, **A**lternate airway (endotracheal tube or Laryngeal Mask Airway). If heart rate is <60/min or remains <60 despite all steps of MR. SOPA start chest compression and increase to 100% oxygen.

Mask Ventilation

The clinical team will determine if an infant requires mask ventilation. If mask ventilation is required, it should be provided with a T-Piece device (e.g. Fisher & Paykel, Auckland, New Zealand or Giraffe Warmer, GE Health Care, Burnaby, BC, Canada), and appropriate face mask with default settings for peak inflation pressure (PIP) of 25 cmH_2O, a peep expiratory pressure (PEEP) of 5 cm H_2O, and a gas flow rate of 8-10L/min using a ventilation rate of 40-60 inflations/min. Initial respiratory support can include initial sustained inflations (instead of positive pressure ventilation alone) as per local hospital policy (standard hospital practice guideline).

Cardiopulmonary Resuscitation

If heart rate is <60/min or remains <60/min despite all steps of MR. SOPA start chest compressions. Prior to the start of CC intubation should be considered. However, in cases of intubation failure it is possible to start CC during mask ventilation. Compressions will be performed using the 2-thumb encircling technique as recommended by current resuscitation guidelines[46]. Epinephrine will be administered according to current resuscitation guidelines either via umbilical vein catheter (0.01 mg/kg per dose – first line) or via endotracheal tube (0.05 mg/kg to 0.1 mg/kg) or every three to five minutes as needed[44]. Chest compressions and epinephrine will be continued until ROSC.

Determination of ROSC

ROSC will defined as an increase in heart rate >60/min for 60sec determined by auscultation of the heart. Return of spontaneous circulation will be assessed after 60sec of a heart rate of >60/min.

The current neonatal resuscitation guidelines do not recommend feedback devices (e.g. exhaled carbon dioxide (ECO_2) monitors, electrocardiography (ECG), or pulse oximetry for detection of ROSC[1]. A secondary objective of the study will be to examine if either feedback device ECO_2, ECG or pulse oximetry can be used for detection of ROSC. Participating centres (e.g. Edmonton, Graz, Winnipeg, Ulm, San Diego) are using either ECO_2 monitors, ECG, and/or pulse oximetry routinely during neonatal resuscitation[35,47-49].

Interventions

"3:1 C:V group"

If the PIP has been increased >30 cm H_2O during MR.SOPA, the PIP should be decreased to 30 cmH_2O prior start of chest compression. Infants randomized into the "*3:1 C:V* group" will receive CC at a rate of 90/min and ventilations at a rate of 30 /min in a 3:1 C:V ratio as recommended by the current resuscitation guidelines[1] (study flow diagram). During CC, the inflations should be delivered using a PIP of 25-30 cmH_2O (As per local hospital policy /standard hospital practice guideline). Heart rate should be reevaluated every 60sec according to current neonatal resuscitation guidelines[1].

"CC+SI group"

If the PIP has been increased >30 cm H_2O during MR.SOPA, the PIP should be decreased to 30 cmH_2O prior start of chest compression. Infants randomized into the "CC+SI group" will receive a SI with a PIP 25-30 cmH_2O while receiving CC. CC will be performed at a rate of 90/min. The SI will be delivered over a period of 20 seconds. This will be followed by PEEP of 5-8 cm water as per local hospital policy (standard hospital practice guideline) for one second. Then the next SI for 20sec is started while CCs are continued. Again after 20sec there will be a 1sec pause with PEEP, which will be followed by another SI for 20sec with continuous CC. After 3x20sec SI+CC (total of 60sec) an assessment of heart rate should be performed. If heart rate is >60/min continue with standard care as per local hospital policy (standard hospital practice guideline). If heart rate remains <60/min continue with CC+SI for another 60sec (3x20sec SI+CC (total of 60sec) at which time a further assessment should be performed. If heart rate remains <60/min continue with CC+SI. If CPR is ongoing for 5 minutes using SI+CC, the clinical team must convert to the standard method of care using 3:1 C:V ratio.

Discontinuing Resuscitation

Deciding how long resuscitative efforts should continue in any of the study infants will be solely at the discretion of the clinical team in accordance with the current neonatal resuscitation guidelines[1] and per local hospital policy (standard hospital practice guideline) at every participating site.

Recording of physiological parameters

Participating sites who have the capability to record physiological parameters and/or video during neonatal resuscitations can include this if time permits prior to delivery[38,48-51]. Secondary objectives of the study will be recording physiological parameters during neonatal resuscitation to i) determine if either feedback device exhaled carbon dioxide (ECO_2), Electrocardiograph (ECG), or pulse oximetery (SpO_2) can be used for detection of ROSC, ii) examine changes of physiological parameters during neonatal resuscitation, and iii) examine respiratory function.

18-24 months follow-up

SI+CC might result in improved pCO_2 during CPR. A more favourable pCO_2 might be neuro-protective, and we hypothesize that SI+CC infants will have a better neurodevelopmental outcome compared to infants randomized to 3:1 C:V. Most infants who receive chest compressions are routinely assessed for neurodevelopmental outcomes at 18-24 months of age in the outpatient clinic in the study hospital. A Bayley III assessment (reference) will be performed by a psychologist or other professional with the relevant competence at the study site. This participant data will be collected at the 18-24 month follow up visit if this is part of routine care; it is not mandatory to collect.

Outcome measures

Primary outcome

Time to achieve ROSC is defined as a heart rate of >60/min for 60sec determined by auscultation of the heart. Return of spontaneous circulation will be assessed after 60sec of a heart rate of >60/min.

Secondary outcomes

Secondary outcomes amongst others will include neonatal mortality (Neonatal death <28 days) and morbidities, for example, rates of brain injury (reported either via magnetic resonance imaging (MRI) or head ultrasound), changes in regional cerebral oxygen saturation using near-infrared spectroscopy (NIRS) monitoring started in the DR and discontinued when clinical stabilization is achieved, results of amplitude-integrated electroencephalograpy (aEEG) monitoring until normalization of background

patterns and occurrence of sleep-wake cycling, DR interventions (including the use of epinephrine), admission temperature, use of therapeutic cooling, mechanical ventilation, pneumothorax, use of inotropes, infection/sepsis, intraventricular hemorrhages, necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity and long-term neurodevelopmental outcomes. We will also assess the value of ECO_2, ECG and/or SpO_2 in determining ROSC as described previously.

Outcome assessment tools

Mortality: All causes of mortality will be recorded. Cerebral injury will be assessed with either cerebral ultrasound or cerebral MRI if performed prior to discharge. If an infant dies prior to any neuro-imaging, a request for autopsy should be made. Autopsy could include imaging alone or full autopsy. Morbidity: Case history until discharge or term age (for preterm infants). Secondary outcome parameters: Case history and output from feedback devices.

Compliance with the Protocol

The clinical investigation will be conducted in compliance with this protocol. Modifications to the protocol will not be implemented without agreement from the Principal Investigators and relevant ethics committee approval are obtained.

Investigators are not allowed to deviate from the protocol except as specified above. Any major or safety related deviations will be recorded, analyzed and the ethics committees notified. If an investigator refuses to comply with the protocol he/she will be disqualified.

Data collection

Infants will be recruited over a period of 26 months. Approximately another six months will be required to collect hospital data on all infants enrolled. Resuscitation data will be collected on a standard form (Neonatal Resuscitation Record) that will form part of each infant's hospital record. The Neonatal Resuscitation Record should be completed by the clinical team attending the resuscitation. Other medical data on each infant will be collected on an electronic Case Report Form (eCRF). The eCRF will be designed in collaboration with Women and Children's Health Research Institute, University of Alberta, Edmonton, Canada. Data will be entered into REDCap database from each site within one week after discharge or death of an infant. Long-term follow-up will be entered within two weeks after examination. All information entered into REDCap database will be used for analysis.

Data analysis

The Clinical Research Informatics Core and Biostatistics Core of the Women and Children's Health Research Institute, at the University of Alberta, will do data management and analysis. Additional information about the storage, management and analysis of study data is available.

All analyses will be carried out according to the intention-to-treat principle. Statistical analyses will be performed using IBM SPSS Statistics Ver. 24 (IBM Corp.) and SAS version 9.4 (SAS Institute Inc.) or later.

Interim Analysis

Interim safety analysis will be performed at 10%, 25% and 50% of enrolment to review the primary outcome, ROSC, and severe adverse events (SAEs).

Thus, three interim analyses will be performed at 22 patients (11 patients per group), 54 (27 patients per group), and 110 (55 patients per group) to evaluate the efficacy of the intervention. At each interim analysis posterior probability of SI+CC arm to reduce time to ROSC by 10% or more compared to the control arm will be calculated. If this probability is less than 0.5, the trial will be stopped for futility. If the posterior probability is greater than 0.98, the Data and Safety Monitoring Board will consider the trial to be stopped for superiority. Since no statistical tests will be performed at interim analyses, type I error (alpha) does not need adjustment.

Final Analysis

Primary Analysis

The primary outcome is the time to achieve ROSC defined as a heart rate of >60/min for 60sec. Data will be analyzed on an intention-to treat basis and will include all randomized participants. A per protocol analysis will also be conducted using the data from the actual allocation of participating infants. A survival analysis will be used to analyze the difference in time to ROSC between intervention and control groups. To account for cluster randomization, Cox proportional hazards regression with time to ROSC as an outcome and allocation group as an independent variable will be created. Centers will be entered as clusters in the model and the statistical significance of the allocation group variable will be evaluated. The analysis will be 2-sided and p-value < 0.05 will be considered statistically significant.

Secondary Analysis

The data will be presented as mean (standard deviation, SD) for normally distributed continuous variables and median (interquartile range, IQR) when the distribution is skewed. The clinical characteristics and outcome parameters will be compared using Student's t-test for parametric and

Mann-Whitney *U*-test for nonparametric comparisons of continuous variables, and χ^2 for categorical variables. All *p*-values will be 2-sided and $p < 0.05$ will be considered statistically significant.

Assessment of safety

Adverse and Serious Adverse Events

Infants who require CPR in the DR are a very seriously ill patient group. Most adverse events may be of a serious nature with or without the SURV1VE-trial intervention, and both intervention groups are expected to have a very high proportion of serious adverse events (SAEs). Serious adverse events to be recorded are therefore mortality within the DR (e.g. did not achieve ROSC or did achieve ROSC but care was withdrawn), and within the NICU (any mortality).

Given the global pandemic, all physical distancing, Personal Protective Equipment requirements and other requirements outlined by the local health authority will be strictly adhered to by study staff during consenting procedures. The consenting process is the only extra contact for the SURV1VE study.

Parents will be made aware of this extra contact by a clinical staff member prior to contact with a research team member. Only once verbal consent is received from the parents will research staff begin the consent process.

Expected adverse events

Adverse events we expect to be related to the application of the treatment guideline include: No ROSC leading to death, accidental displacement of the endotracheal tube or extubation, accidental displacement of venous or arterial catheters, use of Nitric Oxide for pulmonary hypertension, sepsis, pneumothorax, and intraventricular hemorrhage (grades 1-4)[52].

Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will monitor the study to: (1) protect all study patients, (2) safeguard the interests of all study patients, (3) monitor the overall conduct of the trial, (4) advise the investigators in order to protect the integrity of the trial, and (5) supervise the conduct and analysis of all interim analyses. To its end the DSMB will receive regular reports from the trial on any injuries or adverse events, any developments that jeopardize the continued success of the trial, and data by which to accomplish the evaluation of pre-determined early stopping rules. Serious Adverse Events to be reported (mortality) will be sent within 72 hours to the DSMB; reports of other/less serious adverse events and recruitment will be sent monthly; demographics and adverse events (including pneumothorax, and intraventricular hemorrhage grade 3 or higher according to Papile[52]) will be included with the interim and final safety and efficacy analyses. The DSMB will perform interim safety analysis at

10%, 25% and 50% of enrolment to review the primary outcome of ROSC, and SAEs. At the discretion of the DSMB further interim analyses can be requested.

Members of the DSMB are Myra Wyckoff (current Chair of the International Liaison Committee on Resuscitation (ILCOR), Neil Finer (Professor Emeritus, University of California San Diego), and Maryna Yaskina (Statistician, Biostatistics Unit, Women and Children's Health Research Institute, University of Alberta, Edmonton, Canada).

Suspension or premature termination of the clinical investigation

The sponsor/principal investigator and the ethics committees can make decisions about trial discontinuation. If the trial is terminated or suspended the parents of all trial participants will be informed and appropriate follow-up will be assured. If sponsor/principal investigator terminates or suspends the trial the relevant ethics committees will be provided with a detailed written explanation of the termination or suspension.

The sponsor/principal investigator can, upon completion of the analysis of the reason(s) for a suspension, decide to lift the suspension when the necessary corrective actions have been implemented. The investigators and ethics committees will be notified and provided with the relevant data supporting the decision.

Stopping rules

The DSMB will review the data at interim analyses at 10%, 25% and 50%. Predefined stopping rules will include:

1) An increased mortality in the SI+CC group by 25% compared to the 3:1 C:V group at the predefined interim analysis at 10%, 25% and 50%.
2) Increase in rate of morbidities including pneumothorax, intraventricular hemorrhage or the combination, in the SI+CC group by 25% compared to the 3:1 C:V group at the predefined interim analysis at 10%, 25% and 50%.
3) Bayesian posterior probability of SI+CC group being better than the control is less than 0.5 or greater than 0.98. (Posterior probability of SI+CC arm to reduce time to ROSC by 10% or more compared to the control arm will be calculated. If this probability is less than 0.5, the trial will be stopped for futility. If the posterior probability is greater than 0.98, DSMB will consider the trial to be stopped for superiority. Since no statistical tests will be performed at interim analyses, type I error (alpha) does not need adjustment).

Opt-out Rule

In any cases were CPR is ongoing for 5 minutes, the clinical team must convert to the standard method of care using the 3:1 C:V ratio.

Ethical Considerations

The SURV1VE-trial will be conducted in compliance with the guidelines of the Declaration of Helsinki in its latest form, the International Conference on Harmonization of Good Clinical Practice Guidelines. In case of modifications in the study protocol that are not merely of a formal nature but contain changes pertinent to the study participants, a renewed vote of the relevant ethics committees will be obtained. If applicable, the patients (parents) will be informed in the patient information and consent form about changes in the terms and conditions of the trial. The SURV1VE-trial will only start the randomization of participants after approvals from the relevant ethics committees have been obtained.

Parental consent

We aim to use a deferred consent approach as per Tri-Council Policy Statement in Human Research guidelines for research in "Individual Medical Emergencies". For these infants, retrospective consent will be sought from the parents as soon as possible after birth to use the data obtained. For this important study to be feasible, and enroll a representative sample, a deferred consent is important, as obtaining consent prior to delivery can be difficult.

Guidelines for a deferred consent as laid down by Tri-Council Policy Statement state that, any study wishes to use deferred consent needs:

a) “A serious threat to the prospective participant requires immediate intervention.” Infants participating in this trial will have cardiac arrest (or severe bradycardia), which in most cases is unforeseen prior to delivery; hence these infants will all need CPR and using chest compression will be therapeutic. However, only the 3:1 C:V ratio method (3:1 C:V group) is routinely used in all participating sites. It would not be feasible for a neonatal CPR study to ask permission prior to delivery from every parent delivering within the participating sites.

b) “either no standard efficacious care exists or the research offers a realistic possibility of direct benefit to the participant in comparison with standard care.”

   The currently used approach of a 3:1 C:V ratio is extrapolated from animal studies and human adult studies. So far only one small pilot trial (Schmölzer PI) has examined CC in newborn infants. The available animal evidence and limited neonatal data suggest that the interventional approach has the potential to improve standards of care.

c) "either the risk is not greater than that involved in standard efficacious care, or it is clearly justified by the prospect for direct benefits to the participant." Resuscitation is therapeutic and the currently available animal evidence and limited neonatal data suggest that the interventional approach has no higher risk of harm compared to the current standard of care (3:1 C:V group).

d) "the prospective participant is unconscious or lacks capacity to understand the risks, methods and purposes of the research project." A woman in labor cannot give a valid informed consent to a research study. The parents are not considered to be capable of receiving and understanding information about the trial immediately following the birth of a severely compromised child. Thus, the parents will be informed as soon as possible after stabilization of the infant about the study and asked to consent to the use of data that have been collected on their child.

e) "third party authorization cannot be secured in sufficient time, despite diligent and documented efforts to do so;" The parents will be informed as soon as possible after birth/resuscitation/ROSC/death about the study and asked to consent to the use of data that have been collected on their child.

f) "No relevant prior directive by the participant is known to exist."

There is an increasing use of the deferred consent approach within DR research. In fact, the PI of this application has ample experience with using deferred consent during neonatal resuscitation studies[47,53]. This study fulfills the criteria for a deferred consent in Europe, Canada and the United States. It also complies with the ethical requirements laid down by the National Health and Medical Research Council Australia for the ethical conduct of trials in neonatal intensive care research.

Data management

Data handling and archiving

Source data will be registered in the participant's medical records/CRF and into the eCRF. A common web-based eCRF will be devised to enable a central database (Women and Children's Health Research Institute, University of Alberta, Edmonton, Canada). Data entry into the central database and handling of medical records is the responsibility of the investigators. After the establishment of a 'clean file', the database will be locked; The data will be locked after completion of patient recruitment and data entry. After long-term follow-up data entry this portion of the database will locked. Data will be stored for statistical analysis at the Biostatistics Unit, Women and Children's Health Research Institute, University of Alberta, Edmonton, Canada. The trial database will hereafter be kept according to the respective national laws. After the end of trial, the data will be archived for 25 years according to good clinical

practice guidelines. At each trial-site the data flow will be monitored according to the GCP principles by a locally appointed external monitoring committee. After completion of statistical data analysis, data will be pseudo-anonymized and stored at the University of Alberta, Edmonton, Canada.

Data protection

The investigator(s) permits trial-related monitoring, audits, and regulatory inspection(s) by providing direct access to the source data and other relevant documents. Trial data will be handled according to regulations of the data protection agency in the respective countries.

Quality assurance

The trial will be carried out in accordance with the Declaration of Helsinki in its latest form and the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines.

Monitoring

The chief investigator consents to data evaluation being performed by the person in charge of monitoring in accordance with the monitoring plan, in order to ensure satisfactory data collection and adherence to the study protocol. Furthermore, the chief investigator states that he/she is willing to cooperate with this person and shall provide this person with all required information whenever necessary. This includes access to all documents related to the trial, including study-relevant medical files of patients in original form. The tasks of the investigator include maintenance of these patients' medical files as comprehensively as possible; this includes information concerning medical history, accompanying diseases, inclusion in the trial, data about visits, results of investigations, dispensing of medication, and adverse events. The monitor will also be permitted to perform data evaluation and draw comparisons with the relevant medical files in accordance with the standard operating procedures and ICH-GCP guidelines at predetermined intervals, in order to ensure adherence to the study protocol and continuous registration of data. All original medical reports required as sources for the information given in the CRF or the database shall be inspected. The study participants will have given their consent to such inspection by signing the consent form. The person in charge of monitoring is obliged to treat all information as confidential and to preserve the basic claims of the study participants in respect of integrity and protection of their privacy.

Publication plan

The trial will be registered on ClinicalTrials.gov (NCT02858583) prior to the randomization of the first participant. Attempts will be sought to publish protocol, all results, positive, neutral, as well as negative, in peer-reviewed international journals. Authorship will be determined according to the International Committee of Medical Journal Editors. Attempts will be made to publish a list of all investigators with their contributions in all publications.

Potential Significance

Morbidity and mortality rates are extremely high for newborns requiring CC. We believe the combination of simultaneous CC and SI during CPR has the potential to significantly improve ROSC and survival. In addition, we believe that combining CC and SI might lead to improved pCO_2, which has been demonstrated to be neuro-protective. This would be of considerable clinical relevance because improved respiratory and hemodynamic parameters potentially minimize morbidity and mortality in newborn infants. In addition, this will be the first randomized control trial to examine chest compression in the newborn period.

References

1. Perlman JM, Wyllie JP, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, et al. Part 7: Neonatal Resuscitation: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation 2015;132:S204–41.

2. Wyckoff MH, Perlman JM. Cardiopulmonary resuscitation in very low birth weight infants. Pediatrics 2000;106:618–20.

3. Soraisham AS, Lodha AK, Singhal N, Aziz K, Yang J, Lee SK, et al. Neonatal outcomes following extensive cardiopulmonary resuscitation in the delivery room for infants born at less than 33 weeks gestational age. Resuscitation 2014;85:238–43.

4. Barber CA, Wyckoff MH. Use and efficacy of endotracheal versus intravenous epinephrine during neonatal cardiopulmonary resuscitation in the delivery room. Pediatrics 2006;118:1028–34.

5. Harrington DJ, Redman CW, Moulden M, Greenwood CE. The long-term outcome in surviving infants with Apgar zero at 10 minutes: a systematic review of the literature and hospital-based cohort. American Journal of Obstetrics and Gynecology 2007;196:463.e1–463.e5.

6. Kapadia V, Wyckoff MH. Chest Compressions for Bradycardia or Asystole in Neonates. Clin Perinatol 2012;39:833–42.

7. 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;65:1432–40.

8. Berg RA, Sanders AB, Kern KB, Hilwig RW, Heidenreich JW, Porter ME, et al. Adverse Hemodynamic Effects of Interrupting Chest Compressions for Rescue Breathing During Cardiopulmonary Resuscitation for Ventricular Fibrillation Cardiac Arrest. Circulation 2001;104:2465–70.

9. Chandra N, Weisfeldt ML, Tsitlik J, Vaghaiwalla F, Snyder LD, Hoffecker M, et al. Augmentation of carotid flow during cardiopulmonary resuscitation by ventilation at high airway pressure simultaneous with chest compression. Am J Cardiol 1981;48:1053–63.

10. Halperin HH, Tsitlik J, Guerci AD, Mellits ED, Levin HR, Shi AY, et al. Determinants of blood flow to vital organs during cardiopulmonary resuscitation in dogs. Circulation 1986;73:539–50.

11. Rudikoff M, Maughan WL, Effron M, Freund P, Weisfeldt ML. Mechanisms of blood flow during cardiopulmonary resuscitation. Circulation 1980;61:345–52.

12. Hevesi ZG, Thrush DN, Downs JB, Smith RA. Cardiopulmonary resuscitation: effect of CPAP on gas exchange during chest compressions. Anesthesiology 1999;90:1078–83.

13. Schmölzer GM, O'Reilly M, LaBossiere J, Lee T-F, Cowan S, Qin S, et al. Cardiopulmonary resuscitation with chest compressions during sustained inflations: a new technique of neonatal resuscitation that improves recovery and survival in a neonatal porcine model. Circulation 2013;128:2495–503.

14. Wyckoff MH, Berg RA. Optimizing chest compressions during delivery-room resuscitation.

Semin Fetal Neonatal Med 2008;13:410–5.

15. Solevåg AL, Wyckoff MH, Dannevig I, Saugstad OD, Nakstad B. Extended series of cardiac compressions during CPR in a swine model of perinatal asphyxia. Resuscitation 2010;81:1571–6.

16. Solevåg AL, Wyckoff MH, Dannevig I, 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 2011;96:F417–21.

17. Hemway RJ, Christman C, Perlman JM. The 3: 1 is superior to a 15: 2 ratio in a newborn manikin model in terms of quality of chest compressions and number of ventilations. Arch Dis Child 2012;

18. Srikantan SK, Berg RA, Cox T, Tice L, Nadkarni V. Effect of one-rescuer compression/ventilation ratios on cardiopulmonary resuscitation in infant, pediatric, and adult manikins. Pediatric Critical Care Medicine 2005;6:293–7.

19. Whyte SD, Sinha AK, Wyllie JP. Neonatal resuscitation--a practical assessment. Resuscitation 1999;40:21–5.

20. Solevåg AL, Madland JM, Gjærum E, Nakstad B. Minute ventilation at different compression to ventilation ratios, different ventilation rates, and continuous chest compressions with asynchronous ventilation in a newborn manikin. Scand J Trauma Resusc Emerg Med 2012;20:73.

21. Schmölzer GM, O'Reilly M, LaBossiere J, Lee T-F, Cowan S, Nicoll J, et al. 3:1 compression to ventilation ratio versus continuous chest compression with asynchronous ventilation in a porcine model of neonatal resuscitation. Resuscitation 2014;85:270–5.

22. Li ES-S, Cheung P-Y, O'Reilly M, Schmölzer GM. Change in tidal volume during cardiopulmonary resuscitation in newborn piglets. Arch Dis Child Fetal Neonatal 2015;100:F530–3.

23. Chandra N, Rudikoff M, Weisfeldt M. SIMULTANEOUS CHEST COMPRESSION AND VENTILATION AT HIGH AIRWAY PRESSURE DURING CARDIOPULMONARY RESUSCITATION. The Lancet 1980;315:175–8.

24. Sobotka KS, Hooper SB, Allison BJ, Pas te A, Davis PG, Morley CJ, et al. An initial sustained inflation improves the respiratory and cardiovascular transition at birth in preterm lambs. Pediatr Res 2011;70:56–60.

25. Kern KB, Hilwig RW, Berg RA, Sanders AB, Ewy GA. Importance of continuous chest compressions during cardiopulmonary resuscitation: improved outcome during a simulated single lay-rescuer scenario. Circulation 2002;105:645–9.

26. Babbs C, Meyer A, Nadkarni V. Neonatal CPR: room at the top--a mathematical study of optimal chest compression frequency versus body size. Resuscitation 2009;80:1280–4.

27. Li ES-S, Cheung P-Y, O'Reilly M, Aziz K, Schmölzer GM. Rescuer fatigue during simulated neonatal cardiopulmonary resuscitation. J Perinatol 2015;35:142–5.

28. Solevåg AL, Cheung P-Y, Li ES-S, Aziz K, O'Reilly M, Fu B, et al. Quantifying force application to a newborn manikin during simulated cardiopulmonary resuscitation. J Matern Fetal Neonatal

Med 2015;:1–3.

29. Li ES-S, Cheung P-Y, Lee T-F, Lu M, O'Reilly M, Schmölzer GM. Return of spontaneous Circulation Is Not Affected by Different Chest Compression Rates Superimposed with Sustained Inflations during Cardiopulmonary Resuscitation in Newborn Piglets. PLoS ONE 2016;11:e0157249–14.

30. Schmölzer GM, Dawson JA, Kamlin COF, O'Donnell CP, Morley CJ, Davis PG. Airway obstruction and gas leak during mask ventilation of preterm infants in the delivery room. Arch Dis Child Fetal Neonatal 2011;96:F254–7.

31. Schmölzer GM, Kamlin COF, 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 2010;95:F393–7.

32. Poulton DA, Schmölzer GM, Morley CJ, Davis PG. Assessment of chest rise during mask ventilation of preterm infants in the delivery room. Resuscitation 2011;82:175–9.

33. Finer N, Rich W, Wang C, Leone TA. Airway Obstruction During Mask Ventilation of Very Low Birth Weight Infants During Neonatal Resuscitation. Pediatrics 2009;123:865–9.

34. Schilleman K, van der Pot CJM, Hooper SB, Lopriore E, Walther FJ, Pas te A. Evaluating manual inflations and breathing during mask ventilation in preterm infants at birth. J Pediatr 2013;162:457–63.

35. Cheung D, Mian QN, Cheung P-Y, Reilly MOA, Aziz K, van Os S, et al. Mask ventilation with two different face masks in the delivery room for preterm infants: a randomized controlled trial. 2015;:1–5.

36. Dawson JA, Schmölzer GM, Kamlin COF, Pas te A, O'Donnell CP, Donath S, et al. Oxygenation with T-piece versus self-inflating bag for ventilation of extremely preterm infants at birth: a randomized controlled trial. J Pediatr 2011;158:912–918.e1–2.

37. Schmölzer GM, Kamlin COF, Dawson JA, Pas te A, Morley CJ, Davis PG. Respiratory monitoring of neonatal resuscitation. Arch Dis Child Fetal Neonatal 2010;95:F295–303.

38. van Os S, Cheung P-Y, Pichler G, Aziz K, O'Reilly M, Schmölzer GM. Exhaled carbon dioxide can be used to guide respiratory support in the delivery room. Acta Paediatrica 2014;103:796–806.

39. Li ES-S, Cheung P-Y, Pichler G, Aziz K, Schmölzer GM. Respiratory function and near infrared spectroscopy recording during cardiopulmonary resuscitation in an extremely preterm newborn. Neonatology 2014;105:200–4.

40. Roehr C-C, Schmölzer GM, Thio M, Dawson JA, Dold SK, Schmalisch G, et al. How ABBA may help improve neonatal resuscitation training: auditory prompts to enable coordination of manual inflations and chest compressions. J Paediatr Child Health 2014;50:444–8.

41. Binder-Heschl C, Schmölzer GM, O'Reilly M, Schwaberger B, Pichler G. Human or monitor feedback to improve mask ventilation during simulated neonatal cardiopulmonary resuscitation. Arch Dis Child Fetal Neonatal 2014;99:F120–3.

42. Tsui BCH, Horne S, Tsui J, Corry GN. Generation of tidal volume via gentle chest pressure in children over one year old. Resuscitation 2015;92:148–53.

43. Aziz K, Chadwick M, Downton G, Baker M, Andrews W. The development and implementation of a multidisciplinary neonatal resuscitation team in a Canadian perinatal centre. Resuscitation 2005;66:45–51.

44. Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, et al. Part 15: neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122:S909–19.

45. Dawson JA, Kamlin COF, Vento M, Wong C, Cole TJ, Donath S, et al. Defining the reference range for oxygen saturation for infants after birth. Pediatrics 2010;125:e1340–7.

46. Wyckoff MH, Aziz K, Escobedo MB, Kapadia V, Kattwinkel J, Perlman JM, et al. Part 13: Neonatal Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. American Heart Association, Inc; 2015. pages S543–60.

47. Pichler G, Urlesberger B, Baik N, Schwaberger B, Binder-Heschl C, Avian A, et al. Cerebral Oxygen Saturation to Guide Oxygen Delivery in Preterm Neonates for the Immediate Transition after Birth: A 2-Center Randomized Controlled Pilot Feasibility Trial. J Pediatr 2015;

48. Fuchs H, Lindner W, Buschko A, Almazam M, Hummler HD, Schmid MB. Brain oxygenation monitoring during neonatal resuscitation of very low birth weight infants. J Perinatol 2011;32:356–62.

49. Fuchs H, Lindner W, Buschko A, Trischberger T, Schmid M, Hummler HD. Cerebral oxygenation in very low birth weight infants supported with sustained lung inflations after birth. Pediatr Res 2011;70:176–80.

50. Kang LJ, Cheung P-Y, Pichler G, O'Reilly M, Aziz K, Schmölzer GM. Monitoring Lung Aeration during Respiratory Support in Preterm Infants at Birth. PLoS ONE 2014;9:e102729.

51. Pichler G, Zotter H, Binder-Heschl C, Avian A, Schmölzer GM, Morris N, et al. aEEG and NIRS during transition and resuscitation after birth: Promising additional tools; an observational study. Resuscitation 2013;84:974–8.

52. Papile L-A, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529–34.

53. Schmölzer GM, Morley CJ, Wong C, Dawson JA, Kamlin COF, Donath S, et al. Respiratory function monitor guidance of mask ventilation in the delivery room: a feasibility study. J Pediatr 2012;160:377–381.e2.

Statistical Analysis Plan

Based on JAMA. 2017; 318(23):2337-2343. doi:10.1001/jama.2017.18556

Trial:
SURV1VE-Trial

Sustained inflation and chest comp**r**ession **v**ersus 3:**1** chest compression to **v**entilation ratio during cardiopulmonary resuscitation of asphyxiated n**e**wborns – a cluster randomized controlled trial

Trial Registration: ClinicalTrials.gov Identifier: NCT02858583

PI: Georg Schmölzer, MD, PhD

Co-PI:
Po-Yin Cheung
Anne Solevåg
Gerhard Pichler

Protocol Number: Version 4.0

Protocol Date: December 1st 2020

Abbreviations

Abbreviation	Definition
CC	Chest Compression
DR	Delivery room
CPR	Cardiopulmonary resuscitation
ROSC	Return of spontaneous circulation
CC+SI	Chest compression with sustained inflation
3:1 C:V	Compression to ventilation ratio

Section 1: Administrative Information

1.1 SAP revisions

Protocol version	Updated SAP version no.	Section number changed	Description of and reason for change	Date changed

1.2 Roles and responsibility

5 Names, affiliations, and roles of SAP contributors

Contributor	Affiliation	Role of Contributor
Georg Schmölzer	University of Alberta	PI

1.3 Signatures

Author of SURV1VE-Trial Study SAP:

Name (print):	Dr. Maryna Yaskina
Signature:	
Date (dd-mmm-yyyy):	

Principal Investigator of the SURV1VE-Trial: **Su**stained inflation and chest comp**r**ession **v**ersus 3:**1** chest compression to **v**entilation ratio during cardiopulmonary resuscitation of asphyxiated n**e**wborns – a cluster randomized controlled trial

Name (print):	DDr. Georg Schmölzer
Signature:	
Date (dd-mmm-yyyy):	19-Oct-2022

Section 2: Introduction

2.1 Background and rationale

The majority of newborn infants successfully make the transition from fetal to neonatal life without any help[1]. However, an estimated 10% of newborns need help to establish effective ventilation, which remains the most critical step of neonatal resuscitation. Fortunately, the need for chest compression (CC) or medications in the delivery room (DR) is rare. Although, only about 0.1% of term infants and up to 15% of preterm infants[2,3] receive these interventions, this will result in approximately 1 million newborn deaths annually worldwide. A recent cohort study at a level III center with a trained resuscitation team showed that only 6 per 10,000 infants received epinephrine[4]. However, the same study showed that those infants who received epinephrine during resuscitation had a high incidence of mortality (41%) and short-term neurologic morbidity (57% hypoxic-ischemic encephalopathy and seizures)[4]. A recent review of newborns who received prolonged CC and epinephrine but had no signs of life at 10 minutes following birth noted 83% mortality, with 93% of survivors suffering moderate-to-severe disability[5]. The poor prognosis associated with receiving CC alone or with medications in the DR raises

questions as to whether improved cardiopulmonary resuscitation (CPR) methods specifically tailored to the newborn could improve outcomes.

The inability to predict which newborns need CPR, and the infrequent use of CPR in the DR have limited neonatologists' ability to perform rigorous clinical studies to determine the best method for delivering CC to newborn infants. The main cause of cardiovascular collapse in most newborns is asphyxia, which makes newborn infants distinctively different to the adult population. The International Liaison Committee on Resuscitation and the American Academy of Pediatrics/American Heart Association Neonatal Resuscitation Program have recognized this difference, however the guidelines almost exclusively rely on data from studies in the adult population or animal studies. Such data may not be wholly applicable to the neonatal population because the most common cause of cardiovascular collapse in the adult is ventricular fibrillation, not asphyxia. Thus, further studies are needed to determine the optimal method for improving hemodynamics and recovery during neonatal resuscitation.

Rationale for using 3:1 compression to ventilation ratio

The recommendation to use a 3:1 C:V ratio is based on expert opinion, extraction from animal data and consensus rather than strong scientific evidence form studies in newborn infants[20]. Rationales for using a 3:1 C:V ratio include the higher physiological heart rate of 120-160/min and breathing rates of 40-60/min in newborns compared to adults. Furthermore, profound bradycardia or cardiac arrest in newborns is usually caused by hypoxia rather than primary cardiac compromise; therefore, providing ventilation is more likely to be beneficial in neonatal CPR compared to adult CPR[1]. However, the optimal C:V ratio that should be used during neonatal resuscitation to optimize coronary and cerebral perfusion while providing adequate ventilation of an asphyxiated newborn remains unknown[14].

Animal studies using cardiac arrest induced by asphyxia in newborn piglets demonstrated that combining CC with ventilations improves ROSC and neurological outcome at 24 hours compared to ventilations or CC alone[16,21]. *Solevåg et al* performed a study investigating alternating 9 CC and 3 ventilations in asphyxiated piglets with cardiac arrest with the hypothesis that 9 CC would generate higher DBP during CPR than only 3 CC per series[15]. However, increasing the number of CC in a row should not be at the expense of ventilation, hence the ratio of CC to ventilation was maintained at 3:1. The time to ROSC was similar between the two approaches (median time of 150 and 148 sec for 3:1 C:V and 9:3 C:V, respectively). In addition, there were no differences in DBP during CC[15]. Similarly, C:V ratios of 3:1 and 15:2 were compared using the same model[16]. Although the 15:2 C:V ratio provided higher mean CC per minute (75 versus 58 for 3:1), time to ROSC was similar between groups (median time of 195 and 150 sec for 15:2 and 3:1, respectively)[16]. These studies suggest that during neonatal CPR higher C:V ratios do not improve outcomes.

Manikin studies have confirmed higher ventilation rates during simulated CPR using 3:1 C:V compared to higher C:V ratios[17-19]. A more recent neonatal manikin study examined respiratory parameters during neonatal CPR and reported that a 3:1 C:V ratio delivered significantly higher minute ventilation of 191 mL/kg compared to the minute ventilation at 9:3 and 15:2 C:V ratios (140 and 77 mL/kg/min, respectively)[20]. A further manikin study compared 3:1 C:V with continuous CC with asynchronous ventilations (CCaV) using 90 CC and 30 non-synchronized inflations and reported significantly higher minute ventilation in the CCaV group compared to the 3:1 group (221 versus 191 mL/kg/min, respectively)[28]. *Schmölzer et al* compared 3:1 C:V CPR with CCaV in a piglet model of neonatal asphyxia and reported similar minute ventilation (387 versus 275 mL/kg)[21]. However, there was a trend towards a reduced time to ROSC (143 and 114 sec for 3:1 and CCaV, respectively), and survival (3/8 and 6/8, respectively) in the CCaV group. The same manikin and animal study[28,21]

also reported similar tidal volume (V_T) delivery between 3:1 C:V and CCaV (manikin study V_T 6.4 and 5.6 mL/kg, respectively[28] and animal study V_T 14.7 versus 11.0 mL/kg[21]). In a secondary analysis of the study by *Schmölzer et al*[21], *Li et al* reported that during 3:1 C:V a cumulated loss of V_T of 4.5 mL/kg occurs for each 3:1 C:V cycle[22]. Similarly, during CCaV a cumulated loss of V_T of 9.1 mL/kg for each cycle of three CC and one inflation was observed[22]. This is concerning as a loss in V_T could cause lung decruitment, which could hamper oxygenation and therefore ROSC. Further, an argument for synchronized CPR is the potential interference of non-synchronized CC with V_T delivery, hence impairment of oxygen delivery. However, the study by *Schmölzer et al* observed that a comparable 29% and 25% of manual inflations were affected during CC using CCaV or 3:1 C:V CPR[21], respectively. These studies suggest no advantages (e.g. oxygen delivery, V_T or minute ventilation) of using CCaV compared to 3:1 C:V.

Rational for using CC+SI

Reoxgenation and adequate blood flow are the cornerstones of neonatal CPR. Any effective resuscitative manoeuvre should increase blood flow and optimize oxygen delivery. In addition to standard CPR, manoeuvres that raise intrathoracic pressure can significantly increase carotid blood flow during CPR[9,23]. *Chandra et al* provided ventilation at high airway pressure while simultaneously performing CC in an animal model and demonstrated increased carotid flow without compromising oxygenation[9]. Further, studies in preterm lambs have demonstrated that a sustained inflation (SI) also increases intrathoracic pressure without impeding blood flow[24]. An experimental study using a ventricular fibrillation model of adult cardiac arrest demonstrated that emphasis on CC over ventilation increases neurologically intact survival in pigs[25]. In the resuscitation of asphyxiated newborn piglets, *Schmölzer et al* recently reported that passive ventilation during CC, achieved by superimposing CC with a SI (CC+SI), significantly improved hemodynamics, minute ventilation, and time to ROSC compared to the currently recommended approach of using a 3:1 C:V ratio (mean arterial pressure: 51 versus 31 mmHg; pulmonary arterial pressure: 41 versus 31 mmHg; mean minute ventilation: 936 versus 623 mL/kg; median time to ROSC: 38 versus 143 sec, respectively)[13]. However, the study by *Schmölzer et al* used a CC rate of 120/min (in the CC+SI group), which is higher than the currently recommended CC rate of 90/min, which could have also added to the improved outcomes.

A recent mathematical model suggests that higher CC rates than the currently recommended 90 CC/min could optimize systemic perfusion[26]. This model further suggests that the most effective CC rate depends upon body size and weight, which would translate to 180 CC/min for term infants and even higher rates for preterm infants[26]. However, a recent simulation study comparing various CC rates (e.g. 90/min versus 120/min) reported faster fatigue with increasing CC rates[27]. Overall, using CC rates of 90/min was the least fatiguing and the most preferred method of neonatal CPR compared to using CC rates of 120/min[27]. This is further supported by a study by *Solevåg et al* who quantified the force used during CC and reported that fatigue occurs faster with increasing CC rates[28]. These studies suggest that a rate of 90/min will be the least fatiguing CC rate. Further, a recent randomized animal trial compared CC+SI using CC rates of 90/min versus 120/min and reported similar time to ROSC, survival rates, and respiratory parameters during CPR[29]. During CC carotid blood flow, mean arterial pressure, and % change in ejection fraction and cardiac output were higher in the CC+SI 90/min group compared to CC+SI 120/min[29]. This further supports that higher CC rates do not improve systemic perfusion and that the current recommendation of 90 CC per minute is sufficient to achieve systemic perfusion. A further randomized animal trial comparing SI+CC 90/min with 3:1 C:V ratio (in review, Schmölzer last author) showed a significant reduction in median (IQR) time to ROSC 34 (28-156) sec versus 210 (72-

300) sec (p=0.05), less oxygen; 3/8 versus 8/8 required 100% oxygen during CPR (p=0.03), and 3/8 versus 6/8 piglets received epinephrine (p=0.32) in the SI+CC 90/min group. In addition, improved respiratory and hemodynamic parameters were observed in the SI+CC 90/min group versus the 3:1 C:V ratio group. A recent pilot trial in preterm infants <32 weeks gestation showed similar results (in review, Schmölzer first author). Overall, the mean (SD) time to ROSC was significantly shorter in the CC+SI group with 31 (9) sec compared to 138 (72) sec in the 3:1 C:V group (p=0.011). Overall, 0/5 in the CC+SI group and 1/5 in the 3:1 C:V group received epinephrine.

Providing adequate ventilation to achieve reoxgenation is a further cornerstone of neonatal CPR. Current best practice is to provide 90 CC and 30 ventilations that are coordinated with a pause in CC to deliver an inflation[1]. The purpose of inflations during CC is to deliver an adequate V_T to facilitate gas exchange. However, delivery of an adequate V_T during CPR remains difficult. Several DR studies reported that mask ventilation is the most difficult task during neonatal CPR. V_T delivery could be compromised due to mask leak or airway obstruction[30-38], causing inadequate oxygen delivery to the asphyxiated newborn. A recent case report by *Li et al* reported a large mask leak during mask ventilation in the DR, which resulted in severe bradycardia and the need for neonatal CC[39]. In addition, once CC were started mask leak further increased[39]. This is further supported by manikin studies, which reported decreased expiratory V_T once CC were started[20,40,41]. *Binder et al* examined human or monitor feedback during simulated neonatal CPR using a leak-free manikin and reported lower expiratory V_T in all groups compared with mask ventilation alone[41]. These studies suggest a decrease in expiratory V_T once CCs are initiated. A loss in expiratory V_T could cause lung decruitment, which could hamper oxygenation and therefore ROSC. This has been recently confirmed in an animal model of neonatal CPR. In a secondary analysis of the study by *Schmölzer et al*[21], *Li et al* reported that during a significant loss of expiratory V_T compared to inspiratory V_T over each 3:1 C:V cycle (mean total inspiratory V_T was 27.2mL/kg and mean total expiratory V_T 31.7mL/kg = a loss of 4.5mL/kg per 3:1 C:V cycle)[22]. In contrast, no V_T loss was observed in CC+SI. Instead a continued lung recruitment and establishment of functional residual capacity was observed (mean total inspired V_T was 16.3mL/kg and mean total expiratory was 14mL/kg = a gain of 2.3mL/kg/CC+SI cycle)[22]. This improvement in V_T delivery may lead to better alveolar oxygen delivery and lung aeration. More importantly, the initial study by *Schmölzer et al*[21] and secondary analysis by *Li et al*[22] describe passive V_T delivery during each chest compression cycle. Similar observations have been reported by *Tsui et al*[42] in children under the age of 17 years undergoing any surgery requiring general anesthesia and endotracheal intubation. Tsui et al compared V_T after induction of general anesthesia before and after intubation by applying a downward force on the chest, which was not greater than the patient's weight in seven infants[42]. Overall, median (IQR) V_T generated before and after intubation was 2.4 (0.8-4.0) and 2.0 (0.4-3.6) mL/kg, respectively[42]. Although, *Tsui et al* only applied gentle chest pressure, they were able to achieve ~33% of an infants physiological V_T of 5-7mL/kg. During CC the mean applied force is ~10kg (3-4 times the weight of the newborn infant)[28], which would result in adequate V_T delivery during CC+SI. Further, *Solevåg et al* determined the distending pressure needed to achieve sufficient V_T delivery using different models (manikin and cadaver piglets) during CC+SI{Solevag:2017hd}. Distending pressure and V_T correlated in cadaver piglets (r=0.83, p<0.001), manikin (r=0.98, p<0.001), and combined data (r=0.49, p<0.001). V_T was delivered during chest recoil during CC in both models. In cadaver piglets a distending pressure ~ 25cmH_2O was needed to achieve an adequate V_T. This study suggests that chest recoil generates V_T depending on an adequate distending pressure, and that a pressure of ~25cmH_2O will be needed to achieve adequate V_T delivery. In a recent pilot trial comparing CC+SI versus 3:1 C:V CPR in 10 preterm infants <32 weeks gestation (5 in each group) *Schmölzer et al* used a distending pressure of 24cmH_2O (local hospital policy during neonatal resuscitation) and showed adequate V_T

and significantly higher minute ventilation in the CC+SI group versus 3:1 C:V group ($p<0.001$) (under review, Schmölzer first author). These data suggest that CC+SI has the potential to improve ventilation and oxygen delivery during neonatal CPR.

Rationale

The null hypothesis for this study is that the time to return of spontaneous circulation (ROSC) will be no different by using either chest compression with sustained inflation (CC+SI) or 3:1 compression to ventilation ratio (C:V) during CPR of newborn infants.

2.2 Objectives

Primary objective: To prove that CC during sustained inflation will improve recovery from CPR in preterm and term newborns with faster ROSC than that by 3:1 CPR technique.

Secondary objectives: To examine i) if CC during sustained inflation will improve short- and long-term outcomes in preterm and term newborns, and ii) the value of feedback devices (e.g. ECO_2, ECG and/or SpO_2) in determining ROSC.

Section 3: Study Methods

3.1 Trial design

This study will be a cluster-crossover design, unmasked randomized controlled trial comparing two chest compression techniques during CPR. Participants will be randomized to receive either CC+SI or 3:1 C:V ratio during CPR with 1:1 ratio.

3.2 Randomization

In the trial, participating centres will change their local hospital policy to either CC+SI or 3:1 C:V ratio during CPR to enrol as many infants as possible.
Description of study randomization procedure (REDCap, phone, internet) and allocation ratio.

3.3 Sample size

Our **primary outcome measure** will be time to achieve ROSC. We hypothesize that the time to achieve ROSC will be reduced in the “CC+SI group”. A sample size of 208 infants, 104 in each group, would be sufficient to detect a clinically important 33% reduction in time to achieve ROSC using Cox proportional hazards regression with 80% power and a 2-tailed alpha error of 0.05. This 33% reduction represents 282 sec versus 420 sec of CC (based on the database of 30 term infants requiring CC in 2014 and 2015 at the Royal Alexandra Hospital, Edmonton). To account for cluster randomization, the sample size is multiplied by design effect of 1.045, so the total sample size is 218 infants, 109 in each group.

3.4 Framework

Comparisons for the trial will be conducted under a superiority framework.

3.5 Statistical interim analyses and stopping guidance

Interim Analysis

Interim safety analysis will be performed at 10%, 25% and 50% of enrolment to review the primary outcome, ROSC, and severe adverse events (SAEs). Thus, three interim analyses will be performed at 22 patients (11 patients per group), 54 (27 patients per group), and 110 (55 patients per group) to evaluate the efficacy of the intervention. At each interim analysis, posterior probability of SI+CC arm to reduce time to ROSC by 10% or more compared to the control arm will be calculated. If this probability is less than 0.5, the trial will be stopped for futility. If the posterior probability is greater than 0.98, the Data and Safety Monitoring Board will consider the trial to be stopped for superiority. Since no statistical tests will be performed at interim analyses, type I error (alpha) does not need adjustment.

Stopping rules

The DSMB will review the data at interim analyses at 10%, 25% and 50%. Predefined stopping rules will include:

4) An increased mortality in the SI+CC group by 25% compared to the 3:1 C:V group at the predefined interim analysis at 10%, 25% and 50%.
5) Increase in rate of morbidities including pneumothorax, intraventricular hemorrhage or the combination, in the SI+CC group by 25% compared to the 3:1 C:V group at the predefined interim analysis at 10%, 25% and 50%.
6) Bayesian posterior probability of SI+CC group being better than the control is less than 0.5 or greater than 0.98. (Posterior probability of SI+CC arm to reduce time to ROSC by 10% or more compared to the control arm will be calculated. If this probability is less than 0.5, the trial will be stopped for futility. If the posterior probability is greater than 0.98, DSMB will consider the trial to be stopped for superiority. Since no statistical tests will be performed at interim analyses, type I error (alpha) does not need adjustment).

3.6 Timing of final analysis

The final analysis for the SURV1VE-Trial will take place in one stage. The main report of the trial will be prepared after hospital data of every patient have been completed and all data has been collected, cleaned and the database has been "closed".

3.7 Timing of outcome assessments

The Schedule of Activities is given in the Planned recruitment rate section of the trial protocol. Outcome data will be collected throughout hospital stay and at follow-up and entered in the REDCap data base.

Section 4: Statistical Principles

4.1 Confidence intervals and P values

A two-sided level of 0.05 will be used to declare significance.

4.2 Adjustments for multiplicity

No multiplicity

4.3 Confidence intervals to be reported

A 95% confidence interval will be reported around estimates of the treatment effects of the primary and secondary outcomes.

4.4 Adherence and protocol deviations

4.4.1 Adherence

Adherence will be determined by completion of MEASURE at TIME POINT. Non-adherence will be a dichotomous variable defined as ...

4.4.1 Protocol deviations

Major protocol deviations are defined as:

1. Enrollment of ineligible patient
2. Failure to obtain informed consent or improper consent procedure
3. Patient randomized but receives none of the study interventions.

Protocol deviations are classified prior to unblinding of treatment. The number (and percentage) of patients with major and minor protocol deviations will be summarised by treatment group with details of type of deviation provided. The patients that are included in the ITT analysis data set will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.

4.5 Analysis populations

All analyses will adhere to the principle of intention-to-treat. The ITT population will include all participants who were randomized in the trial. Additional analyses will be conducted on the per protocol populations. The per protocol population will include all patients who were

adherent to the treatment, i.e. This additional analysis will only be presented if there is a substantial difference in this population compared to the ITT population.

Section 5: Trial Population

5.1 Eligibility

We will use the CONSORT extension for cluster trials flow diagram to provide details of the number of patients screened followed by a breakdown of how many patients were eligible and how many were excluded due to violating our inclusion/exclusion criteria outlined in the trial protocol.

Inclusion criteria

All infants (term or preterm infants >28 weeks' gestation) requiring CC in the delivery room will be eligible for the trial.

Exclusion criteria

Infants will be excluded if they have a congenital abnormality or condition that might have an adverse effect on breathing or ventilation (e.g. congenital diaphragmatic hernia), or congenital heart disease requiring intervention in the neonatal period. Infants will be also excluded if their parents refuse to give consent to this study.

The inclusion criteria are designed to be pragmatic and provide useful knowledge translation for most of the patient population in the future. Infants who meet study criteria will be enrolled. Sex, race, and ethnicity are not part of the exclusion criteria for this trial, and as such it should represent the combined demographics of all centers involved. A deferred consent approach as per Tri-Council Policy Statement in Human Research guidelines for research in "Individual Medical Emergencies" will be sought for all centres for data collection.

5.2 Recruitment

A CONSORT extension for cluster trials flow diagram will be used to summarise the number of patients were assessed for eligibility at screening for both trials.

- eligible at screening
- ineligible at screening*
- eligible and randomised
- eligible but not randomised*
- received the randomised allocation
- did not receive the randomised allocation*

- lost to follow-up*
- discontinued the intervention*
- randomised and included in the primary analysis
- randomised and excluded from the primary analysis*

*reasons will be provided.

5.3 Withdrawal/follow-up

5.3.1 Timing of withdrawal/lost to follow-up

Timing of withdrawal and lost to follow up data will be presented in CONSORT extension for cluster trials diagram format with numbers and reasons for withdrawal and/or exclusion from analysis given at each stage.

5.3.2 Presentation of withdrawal data

The numbers (with reasons) of losses to follow-up (drop-outs and withdrawals) over the course of the trial will be summarised by treatment arm.

5.4 Baseline patient characteristics

Patients will be described with respect to the following baseline variables:

- gestational age
- birth weight
- sex
- Apgar scores at 1, 5, and 10 minutes
- Caesarean section
- Cord pH
- Cord pCO_2
- Cord base excess

The demographic and clinical variables at baseline will be presented using the appropriate descriptive statistics, namely: means, standard deviations, medians and interquartile ranges for continuous variables, and frequency with proportions for discrete variables. These variables will be summarized by treatment group.

Section 6: Analysis

6.1 Outcome definitions List

Primary Efficacy Outcome:

The Primary Efficacy Endpoint will be time to achieve ROSC which is defined as a heart rate of >60/min for 60sec determined by auscultation of the heart. Return of spontaneous circulation will be assessed after 60sec of a heart rate of >60/min.

Secondary Efficacy Outcomes:

1. All-cause in-hospital mortality
2. Severe brain injury

Exploratory Outcomes

See list below

Safety Outcomes:

1. Mortality
2. Pneumothorax
3. Intraventricular hemorrhage grade 3 or higher

#	Outcome	Variable Name	Description
	Gestation in weeks	b_gaw	Continuous Outcome
	Birth weight	d_bw	Continuous Outcome
	Gender (Sex)	d_g	Binary outcome 1=male 0=Female
	Multiple Birth	d_mb	Binary outcome 1=Yes 0=No
	Apgar at 1 Minute	d_a1	Continuous Outcome
	Apgar at 5 Minute	d_a5	Continuous Outcome
	Apgar at 10 Minute	d_a10	Continuous Outcome
	Mode of Delivery	c_mod	Outcome 1=Vaginal, 2=Instrumental 3=Caesarean Section
	Meconium present	c_mp	Binary outcome 1=Yes 0=No
	Antenatal Steroids	c_as c_ams	Binary outcome 1=Yes 0=No
	Antenatal magnesium Sulphate	c_as c_ams	Binary outcome 1=Yes 0=No
	1. Presenting Antenatal Problems (choice=Premature Ruptures of Membranes (PROM))" "2. Presenting Antenatal Problems (choice=Pregnancy Induced Hypertension (PIH))" "3. Presenting Antenatal Problems (choice=Antepartum Hemorrhage (APH))" "4. Presenting Antenatal Problems (choice=Gestational Diabetes (GDM))" "5. Presenting Antenatal Problems (choice=Intrauterine Growth Restriction (IUGR)- less than 10th percentile)" "6. Presenting Antenatal Problems (choice=Fetal Distress)"	c_pap___1 c_pap___2 c_pap___3 c_pap___4 c_pap___5 c_pap___6 c_pap___7 c_pap___8 c_pap___10 c_pap_oth	Each is a binary outcome 1=Yes 0=No, please combine to 1 outcome and present as list n(%)

	"7. Presenting Antenatal Problems (choice=Chorioamnionitis)" "8. Presenting Antenatal Problems (choice=Shoulder Dystocia)" "10. Presenting Antenatal Problems (choice=Other)"		
	Fetal Heart Rate Abnormality	c_fhra	Binary outcome 1=Yes 0=No
	Intrapartum Fever > 38∞ Celsius	c_ipf	Binary outcome 1=Yes 0=No
	Delayed Cord Clamping	e_dcc	Binary outcome 1=Yes 0=No
	Cord Milking	e_cm_yn	Binary outcome 1=Yes 0=No
	Duration of Delayed Cord Clamping	e_ddcc	Continuous outcome in sec please
	Number of Times Cord Milked	e_ntcm	Continuous outcome
	FiO2 at Start of Resuscitation	e_opsr	Continuous Outcome
	Maximum FiO2 during Resuscitation	e_mpor	Continuous Outcome
	Method of determining bradycardia/asystole (choice=Auscultation) Method of determining bradycardia/asystole (choice=Palpation) Method of determining bradycardia/asystole (choice=ECG) Method of determining bradycardia/asystole (choice=Pulse Oximetry) Method of determining bradycardia/asystole (choice=Ultrasound)	e_meth_dba___1 e_meth_dba___2 e_meth_dba___3 e_meth_dba___4 e_meth_dba___5	Each is a binary outcome 1=Yes 0=No, please combine to 1 outcome and present as list n(%)

	Compression Methods used (=group)	e_cm	This is the group variable
	What pressure was used to deliver the SI?	e_si	Continuous Outcome
	Intubation prior to Chest Compression	e_icc	Binary outcome 1=Yes 0=No
	Time to ROSC (Primary outcome)	e_dur_cc	Continuous Outcome
	Technique switched to 3:1 C:V for Compressions required longer than 5 minutes	e_tcc	Yes, No, Site Randomization is 3:1 C:V
	ROSC	e_rosc	Binary outcome 1=Yes 0=No
	Subsequent need for Chest Compressions after ROSC initially achieved	e_sccrosc	No, Yes, Infant did not achieve ROSC
	Subject Alive at end of Resuscitation	e_sar	Binary outcome 1=Yes 0=No
	Epinephrine	e_e_yn	Binary outcome 1=Yes 0=No
	Endotracheal Epinephrine	e_ee	Binary outcome 1=Yes 0=No
	Number of Doses Endotracheal Epinephrine	e_dette	Continuous Outcome
	Intravenous Epinephrine	e_ie	Binary outcome 1=Yes 0=No
	Number of Doses Intravenous Epinephrine	e_ndive	Continuous Outcome
	UVC Epinephrine	e_uvce	Binary outcome 1=Yes 0=No
	Number of Doses UVC Epinephrine	e_nduvce	Continuous Outcome
	Intraosseous Epinephrine	e_ioe	Binary outcome 1=Yes 0=No
	Number of Doses Intraosseous Epinephrine	e_ndioe	Continuous Outcome
	Volume Expander	e_ve	Binary outcome 1=Yes 0=No

	Red Packed Blood Cells	e_prbc	Binary outcome 1=Yes 0=No
	pH (combine sample 1 and 2)	f_ph1 & f_ph2	Continuous Outcome
	pCO2 (combine sample 1 and 2)	f_pco21 & f_pco23	Continuous Outcome
	BE (combine sample 1 and 2)	f_be1 & f_be2	Continuous Outcome
	Lactate (combine sample 1 and 2)	f_l1 & f_l2	Continuous Outcome
	Glucose	f_glu	Continuous Outcome
	Seizures	f_s	Binary outcome 1=Yes 0=No
	Pneumothorax During NICU Admission	g_pnicua	Binary outcome 1=Yes 0=No
	Hours after birth	g_hpd	Continuous Outcome in hours please
	Location of Pneumothorax	g_lop	Left, Right, Bilateral
	Inotropes	g_it	Binary outcome 1=Yes 0=No
	Initiation of Passive Cooling in the Delivery Room	e_ipcdr	Binary outcome 1=Yes 0=No
	Initiation of Active Cooling in the Delivery Room	e_iacdr	Binary outcome 1=Yes 0=No
	Active Cooling in NICU	g_acnicu	Binary outcome 1=Yes 0=No
	Duration of Cooling	g_doc	Continuous Outcome in hours please
	Death during NICU Admission	h_dnicua	Binary outcome 1=Yes 0=No
	Overall Death should combine Subject Alive at end of Resuscitation and Did the infant die during NICU Admission		Both are Binary outcomes but Did the infant die during NICU Admission is a negative one (so the yes and no is reversed).
	Reason for Death	h_rfd	Should be a list of diagnoses

	Intraventricular Hemorrhage (IVH)	g_ivh	Binary outcome 1=Yes 0=No
	Grade of IVH	g_g_ivh	Papile Grade 3 or Papile Grade 4
	Periventricular Leukomalacia	g_pvl	Binary outcome 1=Yes 0=No
	Amplitude EEG (aEEG) performed	f_aeeg	Binary outcome 1=Yes 0=No
	aEEG Pattern after Stabilization/1h (choice=Normal)	f_aeeg1___1	Binary outcome 1=Yes 0=No
	laEEG Pattern after Stabilization/1h (choice=Moderate aEEG Depression)	f_aeeg1___2	Binary outcome 1=Yes 0=No
	aEEG Pattern after Stabilization/1h (choice=Severe aEEG Depression)	f_aeeg1___3	Binary outcome 1=Yes 0=No
	Combine the three above to one variable		Would be a three column list
	aEEG Pattern at 3 hours of age (choice=Normal)	f_aeeg3___1	Binary outcome 1=Yes 0=No
	aEEG Pattern at 3 hours of age (choice=Moderate aEEG Depression)	f_aeeg3___2	Binary outcome 1=Yes 0=No
	aEEG Pattern at 3 hours of age (choice=Severe aEEG Depression)	f_aeeg3___3	Binary outcome 1=Yes 0=No
	Combine the three above to one variable		Would be a three column list
	aEEG Pattern at 5 hours of age (choice=Normal)"	f_aeeg5___1	Binary outcome 1=Yes 0=No
	aEEG Pattern at 5 hours of age (choice=Moderate aEEG Depression)"	f_aeeg5___2	Binary outcome 1=Yes 0=No
	aEEG Pattern at 5 hours of age (choice=Severe aEEG Depression)	f_aeeg5___3	Binary outcome 1=Yes 0=No
	Combine the three above to one variable		Would be a three column list
	MRI findings	g_mri_r	Should be a list of diagnoses

	Days of hospitalisation (= duration between day of birth and Day of discharge to home or transfer to other hospital/ Level 2 NICU	Difference between b_dob and h_dod	Continuous outcome in days please

6.2 Analysis methods

6.2.1 Analysis methods used

Primary analysis

The primary outcome is the time to achieve ROSC defined as a heart rate of >60/min for 60sec. Data will be analyzed on an intention-to treat basis and will include all randomized participants. A per protocol analysis will also be conducted using the data from the actual allocation of participating infants. A survival analysis will be used to analyze the difference in time to ROSC between intervention and control groups. To account for cluster randomization, Cox proportional hazards regression with time to ROSC as an outcome and allocation group as an independent variable will be created. Centers will be entered as clusters in the model and the statistical significance of the allocation group variable will be evaluated. The analysis will be 2-sided and p-value < 0.05 will be considered statistically significant.

Secondary analysis

The data will be presented as mean (standard deviation, SD) for normally distributed continuous variables and median (interquartile range, IQR) when the distribution is skewed. The clinical characteristics and outcome parameters will be compared using Student's t-test for parametric and Mann-Whitney U-test for nonparametric comparisons of continuous variables, and χ^2 for categorical variables. All p-values will be 2-sided and p <0.05 will be considered statistically significant.

Exploratory analysis

Analysis of pre-specified secondary outcomes adjusted for relevant co-variates will be considered exploratory.

Safety outcomes

Analysis will be considered exploratory.

6.2.2 Adjustment for covariates

Due to the very small sample size, no adjustments will be performed.

6.2.3 Sensitivity analyses

None.

6.3 Subgroups

No subgroup analysis

6.4 Missing data

Since the intervention is performed in the delivery room, very low proportion of missing data is expected.

6.5 Additional analyses

None.

6.6 Harms

Severe adverse events will be coded using MedDRA and each SAE will be counted once only for a given participant. Severity, frequency and relationship of SAEs to study intervention will be presented. We will compare SAEs related to the oxygen administration using a chi-square test. A two-sided p-value of 0.05 or lower will be considered to indicate statistical significance for each safety outcome.

6.7 Statistical software

The statistical software SAS (SAS Institute Inc., Cary, NC, USA) and R (R Core Team, Vienna, Austria) will be used for the analysis.

REFERENCES

1. Perlman JM, Wyllie JP, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, et al. Part 7: Neonatal Resuscitation: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation 2015;132:S204–41.

2. Wyckoff MH, Perlman JM. Cardiopulmonary resuscitation in very low birth weight infants. Pediatrics 2000;106:618–20.

3. Soraisham AS, Lodha AK, Singhal N, Aziz K, Yang J, Lee SK, et al. Neonatal outcomes following extensive cardiopulmonary resuscitation in the delivery room for infants born at less than 33 weeks gestational age. Resuscitation 2014;85:238–43.

4. Barber CA, Wyckoff MH. Use and efficacy of endotracheal versus intravenous epinephrine during neonatal cardiopulmonary

resuscitation in the delivery room. Pediatrics 2006;118:1028–34.

5. Harrington DJ, Redman CW, Moulden M, Greenwood CE. The long-term outcome in surviving infants with Apgar zero at 10 minutes: a systematic review of the literature and hospital-based cohort. American Journal of Obstetrics and Gynecology 2007;196:463.e1–463.e5.

6. Kapadia V, Wyckoff MH. Chest Compressions for Bradycardia or Asystole in Neonates. Clin Perinatol 2012;39:833–42.

7. 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;65:1432–40.

8. Berg RA, Sanders AB, Kern KB, Hilwig RW, Heidenreich JW, Porter ME, et al. Adverse Hemodynamic Effects of Interrupting Chest Compressions for Rescue Breathing During Cardiopulmonary Resuscitation for Ventricular Fibrillation Cardiac Arrest. Circulation 2001;104:2465–70.

9. Chandra N, Weisfeldt ML, Tsitlik J, Vaghaiwalla F, Snyder LD, Hoffecker M, et al. Augmentation of carotid flow during cardiopulmonary resuscitation by ventilation at high airway pressure simultaneous with chest compression. Am J Cardiol 1981;48:1053–63.

10. Halperin HH, Tsitlik J, Guerci AD, Mellits ED, Levin HR, Shi AY, et al. Determinants of blood flow to vital organs during cardiopulmonary resuscitation in dogs. Circulation 1986;73:539–50.

11. Rudikoff M, Maughan WL, Effron M, Freund P, Weisfeldt ML. Mechanisms of blood flow during cardiopulmonary resuscitation. Circulation 1980;61:345–52.

12. Hevesi ZG, Thrush DN, Downs JB, Smith RA. Cardiopulmonary resuscitation: effect of CPAP on gas exchange during chest compressions. Anesthesiology 1999;90:1078–83.

13. Schmölzer GM, O'Reilly M, LaBossiere J, Lee T-F, Cowan S, Qin S, et al. Cardiopulmonary resuscitation with chest compressions during sustained inflations: a new technique of neonatal resuscitation that improves recovery and survival in a neonatal porcine model. Circulation 2013;128:2495–503.

14. Wyckoff MH, Berg RA. Optimizing chest compressions during delivery-room resuscitation. Semin Fetal Neonatal Med 2008;13:410–5.

15. Solevåg AL, Wyckoff MH, Dannevig I, Saugstad OD, Nakstad B. Extended series of cardiac compressions during CPR in a swine model of perinatal asphyxia. Resuscitation 2010;81:1571–6.

16. Solevåg AL, Wyckoff MH, Dannevig I, 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 2011;96:F417–21.

17. Hemway RJ, Christman C, Perlman JM. The 3: 1 is superior to a 15: 2 ratio in a newborn manikin model in terms of quality of chest compressions and number of ventilations. Arch Dis Child 2012;

18. Srikantan SK, Berg RA, Cox T, Tice L, Nadkarni V. Effect of one-rescuer compression/ventilation ratios on cardiopulmonary resuscitation in infant, pediatric, and adult manikins. Pediatric Critical Care Medicine 2005;6:293–7.

19. Whyte SD, Sinha AK, Wyllie JP. Neonatal resuscitation--a practical assessment. Resuscitation 1999;40:21–5.

20. Solevåg AL, Madland JM, Gjærum E, Nakstad B. Minute ventilation at different compression to ventilation ratios, different ventilation rates, and continuous chest compressions with asynchronous ventilation in a newborn manikin. Scand J Trauma Resusc Emerg Med 2012;20:73.

21. Schmölzer GM, O'Reilly M, LaBossiere J, Lee T-F, Cowan S, Nicoll J, et al. 3:1 compression to ventilation ratio versus continuous chest compression with asynchronous ventilation in a porcine model of neonatal resuscitation. Resuscitation 2014;85:270–5.

22. Li ES-S, Cheung P-Y, O'Reilly M, Schmölzer GM. Change in tidal volume during cardiopulmonary resuscitation in newborn piglets. Arch Dis Child Fetal Neonatal 2015;100:F530–3.

23. Chandra N, Rudikoff M, Weisfeldt M. SIMULTANEOUS CHEST COMPRESSION AND VENTILATION AT HIGH AIRWAY PRESSURE DURING CARDIOPULMONARY RESUSCITATION. The Lancet 1980;315:175–8.

24. Sobotka KS, Hooper SB, Allison BJ, Pas te A, Davis PG, Morley CJ, et al. An initial sustained inflation improves the respiratory and cardiovascular transition at birth in preterm lambs. Pediatr Res 2011;70:56–60.

25. Kern KB, Hilwig RW, Berg RA, Sanders AB, Ewy GA. Importance of continuous chest compressions during cardiopulmonary resuscitation: improved outcome during a simulated single lay-rescuer scenario. Circulation 2002;105:645–9.

26. Babbs C, Meyer A, Nadkarni V. Neonatal CPR: room at the top--a mathematical study of optimal chest compression frequency versus body size. Resuscitation 2009;80:1280–4.

27. Li ES-S, Cheung P-Y, O'Reilly M, Aziz K, Schmölzer GM. Rescuer fatigue during simulated neonatal cardiopulmonary resuscitation. J Perinatol 2015;35:142–5.

28. Solevåg AL, Cheung P-Y, Li ES-S, Aziz K, O'Reilly M, Fu B, et al. Quantifying force application to a newborn manikin during

simulated cardiopulmonary resuscitation. J Matern Fetal Neonatal Med 2015;:1–3.

29. Li ES-S, Cheung P-Y, Lee T-F, Lu M, O'Reilly M, Schmölzer GM. Return of spontaneous Circulation Is Not Affected by Different Chest Compression Rates Superimposed with Sustained Inflations during Cardiopulmonary Resuscitation in Newborn Piglets. PLoS ONE 2016;11:e0157249–14.

30. Schmölzer GM, Dawson JA, Kamlin COF, O'Donnell CP, Morley CJ, Davis PG. Airway obstruction and gas leak during mask ventilation of preterm infants in the delivery room. Arch Dis Child Fetal Neonatal 2011;96:F254–7.

31. Schmölzer GM, Kamlin COF, 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 2010;95:F393–7.

32. Poulton DA, Schmölzer GM, Morley CJ, Davis PG. Assessment of chest rise during mask ventilation of preterm infants in the delivery room. Resuscitation 2011;82:175–9.

33. Finer N, Rich W, Wang C, Leone TA. Airway Obstruction During Mask Ventilation of Very Low Birth Weight Infants During Neonatal Resuscitation. Pediatrics 2009;123:865–9.

34. Schilleman K, van der Pot CJM, Hooper SB, Lopriore E, Walther FJ, Pas te A. Evaluating manual inflations and breathing during mask ventilation in preterm infants at birth. J Pediatr 2013;162:457–63.

35. Cheung D, Mian QN, Cheung P-Y, Reilly MOA, Aziz K, van Os S, et al. Mask ventilation with two different face masks in the delivery room for preterm infants: a randomized controlled trial. 2015;:1–5.

36. Dawson JA, Schmölzer GM, Kamlin COF, Pas te A, O'Donnell CP, Donath S, et al. Oxygenation with T-piece versus self-inflating bag for ventilation of extremely preterm infants at birth: a randomized controlled trial. J Pediatr 2011;158:912–918.e1–2.

37. Schmölzer GM, Kamlin COF, Dawson JA, Pas te A, Morley CJ, Davis PG. Respiratory monitoring of neonatal resuscitation. Arch Dis Child Fetal Neonatal 2010;95:F295–303.

38. van Os S, Cheung P-Y, Pichler G, Aziz K, O'Reilly M, Schmölzer GM. Exhaled carbon dioxide can be used to guide respiratory support in the delivery room. Acta Paediatrica 2014;103:796–806.

39. Li ES-S, Cheung P-Y, Pichler G, Aziz K, Schmölzer GM. Respiratory function and near infrared spectroscopy recording during cardiopulmonary resuscitation in an extremely preterm newborn. Neonatology 2014;105:200–4.

40. Roehr C-C, Schmölzer GM, Thio M, Dawson JA, Dold SK, Schmalisch G, et al. How ABBA may help improve neonatal

resuscitation training: auditory prompts to enable coordination of manual inflations and chest compressions. J Paediatr Child Health 2014;50:444–8.

41. Binder-Heschl C, Schmölzer GM, O'Reilly M, Schwaberger B, Pichler G. Human or monitor feedback to improve mask ventilation during simulated neonatal cardiopulmonary resuscitation. Arch Dis Child Fetal Neonatal 2014;99:F120–3.

42. Tsui BCH, Horne S, Tsui J, Corry GN. Generation of tidal volume via gentle chest pressure in children over one year old. Resuscitation 2015;92:148–53.