JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 4, NO. 1, 2019

TRANSLATIONAL PERSPECTIVE

Chest Compressions During Sustained Inflation During Cardiopulmonary Resuscitation in Newborn Infants Translating Evidence From Animal Studies to the Bedside

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SUMMARY

Newborn infants receiving chest compressions in the delivery room have a high incidence of mortality (41%) and short-term neurological morbidity (e.g., 57% hypoxic-ischemic encephalopathy and seizures). Furthermore, infants who have no signs of life at 10 min despite chest compressions have 83% mortality, with 93% of survivors experiencing moderate-to-severe disability. The poor prognosis associated with receiving chest compressions in the delivery room raises questions as to whether improved cardiopulmonary resuscitation methods specifically tailored to the newborn could improve outcomes. Combining chest compressions during sustained inflation (CC+SI) has recently been shown to improve morbidity and mortality outcomes during cardiopulmonary resuscitation. Overall, CC+SI accomplishes the following: 1) significantly reduces time to return of spontaneous circulation, mortality, and epinephrine administration, and improves systemic and regional hemodynamic recovery; 2) significantly increases tidal volume and minute ventilation, and therefore alveolar oxygen delivery; 3) allows for passive ventilation during chest compression; and 4) does not increase lung or brain injury markers compared with the current standard of using 3:1 compression:ventilation ratio. A randomized trial comparing CC+SI versus a 3:1 compression:ventilation ratio during cardiopulmonary resuscitation in the delivery room is therefore warranted. (J Am Coll Cardiol Basic Trans Science 2019;4:116–21)

The neonatal resuscitation guidelines recommend initiating chest compressions (CCs) if an infant's heart rate remains <60 beats/min despite adequate ventilation for at least 30 s. CCs should be delivered at a rate of 90/min in sequences of 3 CCs followed by a pause to deliver 1 inflation at a rate of 30/min, which corresponds to a 3:1 compression:ventilation (C:V) ratio (**Figure 1**, Video 1) (Supplemental Appendix A). The 3:1 C:V ratio favors ventilation, as respiratory failure is the primary cause

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The author attests he is in compliance with human studies committees and animal welfare regulations of the authors' institutions and U.S. Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

Manuscript received September 7, 2018; revised manuscript received November 29, 2018, accepted December 20, 2018.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2018.12.004

of asystole or bradycardia in newborn infants. In comparison, during adult cardiopulmonary resuscitation (CPR), a 30:2 C:V ratio is recommended, as the main cause of CPR is cardiovascular collapse.

Overall, ~0.1% of term infants and 5% of preterm infants receive CCs in the delivery room (DR). Infants who receive CCs have a high incidence of mortality (41%) and short-term neurological morbidity (e.g., 57% hypoxic-ischemic encephalopathy and seizures) (Supplemental Appendix A). Furthermore, newborns who received CCs and epinephrine but had no signs of life at 10 min following birth have 83% mortality, with 93% of survivors experiencing moderate-to-severe neurological disability. The poor prognosis associated with receiving CCs in the DR raises questions as to whether improved CPR methods specifically tailored to the newborn could improve outcomes. Therefore, continuing efforts should be made to improve CPR techniques, and alternative methods should be examined. However, the incidence of infants who need CPR at birth is rare and in general unexpected, and therefore randomized clinical trials of alternative CPR methods have not been performed.

CCs IN NEWBORN INFANTS

Newborn infants present with either severe bradycardia or asystole at birth because of severe asphyxia. If the heart rate remains <60 beats/min despite adequate ventilation for at least 30 s, CCs using the 3:1 C:V ratio should be started to achieve adequate oxygen delivery (Supplemental Appendix B). During 3:1 C:V, CCs are delivered at a rate of 90/min in sequences of 3 CCs followed by a pause to deliver 1 inflation at a rate of 30/min. However, this approach may not be optimizing cardiac output during neonatal CPR as every interruption in CC results in a drop in coronary perfusion pressure that needs to be regenerated during the next compression cycle. Schmölzer et al. (1) reported an alternative approach of performing CCs during continuous sustained inflation (SI) (i.e., constant high airway pressure providing CCs [CC+SI]), which resulted in passive ventilation during CCs in asphyxiated piglets. During CC+SI, CCs are delivered continuously, superimposed by a constant high airway pressure (**Figure 1**, Video 1). In addition, CC+SI significantly improved hemodynamic variables, minute ventilation, and time to return of spontaneous circulation (ROSC) compared with the 3:1 C:V CPR (1).

Schmölzer et al. (1) first reported improved recovery in asphyxiated newborn piglets with CC+SI, compared with 3:1 C:V CPR (mean arterial pressure: 51 vs. 31 mm Hg; pulmonary arterial pressure: 41 vs. 31 mm Hg; mean minute ventilation: 936 vs. 623 ml/kg; median time to ROSC: 38 vs. 143 s, respectively). However, CCs were performed at a rate of 120/min in the CC+SI group, which is higher than the currently recommended CC rate of 90/min, which could have added to the improved outcomes (1). Subsequently, the group reported that CC+SI 90/min compared with 3:1 C:V resulted in a reduction in the median (interquartile range) time to ROSC of 34 s (28 to 156 s) versus 210 s (72 to 300 s) ($p = 0.05$), less oxygen (3 of 8 vs. 8 of 8 required 100% oxygen during CPR; $p = 0.03$), and 3 of 8 piglets versus 6 of 8 piglets receiving epinephrine ($p = 0.32$) (2). Furthermore, a recent randomized piglet study compared CC rates of 90/min versus 120/min during CC+SI and reported similar time to ROSC, survival rates, and respiratory parameters (3). More importantly during CCs, carotid blood flow, mean arterial pressure, percent change in ejection fraction, and cardiac output were higher in the CC+SI 90/min group compared with the CC+SI 120/min group. In addition, Vali et al. reported that CC+SI is feasible in a transitional model of near-term lambs. These studies support the use of CC+SI during neonatal CPR and would warrant clinical trials. A small pilot trial in preterm infants <32 weeks' gestation reported a significantly shorter mean time to ROSC in the CC+SI group ($n = 5$; gestational age: 24.6 ± 1.3 weeks) than the 3:1 C:V group ($n = 4$; gestational age: 25.6 ± 2.3 weeks) (31 [9] s vs. 138 [72] s, respectively; $p = 0.011$) (4). Overall, there were no differences in short-term outcomes, including no differences in neonatal brain injury or chronic lung disease. However, there were 2/5 and 0/4 deaths between groups, which might have been due to the small sample size and warrants a larger randomized trial (Supplemental Appendix B).

The data presented suggest that CC+SI has the potential to improve the outcomes of asphyxiated newborn infants. Furthermore, the described novel technique of CC+SI might also be an alternative for pediatric or adult resuscitation. However, until now, no pediatric or adult studies have been performed. Several factors should be examined before a large clinical trial is conducted, however, including: 1) CC, ventilation, and synchrony; 2) adequate tidal volume (V_T) delivery and minute ventilation; 3) distending pressure; and 4) lung or brain injury (Supplemental Appendix B).

ABBREVIATIONS AND ACRONYMS

C:V ratio = compression to ventilation ratio

CC = chest compression

CC+SI = chest compression during sustained inflation

CCaV = continuous chest compression with asynchronous ventilations

CPR = cardiopulmonary resuscitation

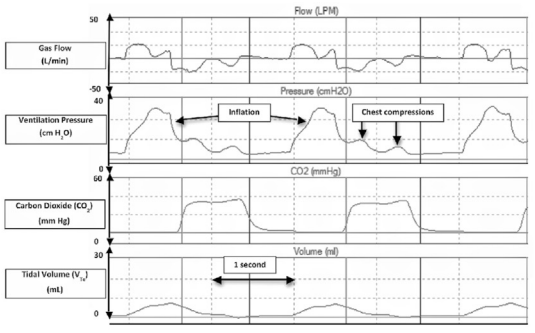
DR = delivery room

ROSC = return of spontaneous circulation

SI = sustained inflation

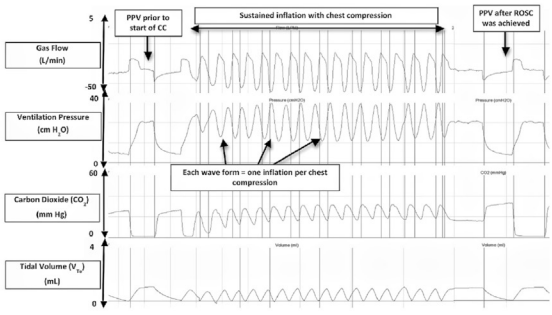
V_T = tidal volume

FIGURE 1 Respiratory Waveforms During 3:1 Compression: Ventilation Ratio and Continuous Chest Compressions During Sustained Inflations and Their Pros and Cons



Pros:
- Synchronization between CC and ventilation

Cons:
- Interruptions of CC to deliver ventilation



Pros:
- Faster time to ROSC
- Improved hemodynamic recovery
- Higher minute ventilation and alveolar oxygen delivery
- Passive ventilation during CC
- No synchronization between CC and ventilation

Cons:
- Hypothetical risk of lung and brain injury

Respiratory wave forms during cardiopulmonary resuscitation using 3:1 Compression:ventilation ratio (left image) and Chest Compression + Sustained Inflation (right image) (Gas flow, airway pressure, expired CO2, and tidal volume). See Video 1.

THE RATE OF CC, VENTILATION, AND SYNCHRONY

A mathematical model calculated that CC rates of 180/min for term infants and even higher rates in preterm infants could optimize systemic perfusion. Although these rates might be optimal in mathematical models, simulation studies reported faster rescuer fatigue with higher CC rates (e.g., 90/min vs. 120/min). Indeed, it is not practical and not infeasible to perform CCs at >120/min. When CC rates of 90/min versus 120/min during CC+SI were compared in asphyxiated newborn piglets, similar time to ROSC, survival rates, and respiratory parameters were reported (3). More importantly during CCs, carotid blood flow, mean arterial pressure, percent change in ejection fraction, and cardiac output were higher in the CC+SI 90/min group compared with the CC+SI 120/min group. This finding contradicts the mathematical model and supports the current recommendation of CCs at a rate of 90/min. Our observations are further supported by Idris et al., who reported that compression rates between 100/min and 120/min in adults experiencing out-of-hospital cardiac arrest were associated with greatest survival to hospital discharge, and higher rates do not improve outcomes (Supplemental Appendix C).

The current resuscitation guidelines recommend 3:1 C:V CPR with one inflation delivered after every third CC. Synchronized CC and ventilation may preclude the theoretical possibility of interfering V_T delivery and oxygenation by nonsynchronized CCs (Supplemental Appendix C). Manikin studies indicate that a 3:1 C:V ratio is favorable in terms of minute ventilation compared with higher C:V ratios (9:3 or 15:2 C:V). Similarly, animal trials comparing 3:1 C:V versus 9:3 or 15:2 C:V reported similar V_Ts but higher minute ventilation with 3:1 C:V. During simulated CPR, continuous CCs with asynchronous ventilations (CCaVs) with 90 CC and 30 nonsynchronized inflations resulted in lower V_T compared with 3:1 C:V. However, CCaV resulted in significantly higher minute ventilation compared with 3:1 C:V CPR (221 vs. 191 ml/kg/min, respectively) most likely due to the higher number of ventilations per minute. A study in asphyxiated piglets randomized to either CCaV or 3:1 C:V reported similar V_T delivery, minute ventilation (275 vs. 387 ml/kg), time to ROSC (114 vs. 143 s), and survival (6 of 8 and 3 of 8), respectively. Although there are concerns that CCaVs potentially interfere with V_T delivery, interference was only observed in ~30% of delivered inflations, which was similar to 3:1 C:V with interference in 25% of inflations. We believe that the observed interference also occurs during

neonatal resuscitation, which could attribute to an increased stress level during real-life resuscitations, and that this deviation from the guidelines is not exceptional.

ADEQUATE V_T DELIVERY

The primary purpose of inflations during CCs 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. Reduced V_T delivery leads to inadequate oxygenation, which often results from mask leak and/or airway obstruction (Supplemental Appendix D). Li et al. recently reported a case in which a large leak during mask ventilation in the DR resulted in severe bradycardia and the need for neonatal CCs. In addition, once CCs were started, the mask leak increased even more. This finding is further supported by manikin studies, which reported decreased expiratory V_T once CCs were started. A similar loss of expiratory V_T was reported by Li et al. (5) in asphyxiated piglets. During 3:1 C:V, a cumulated loss of V_T of 4.5 ml/kg occurred for each 3:1 C:V cycle and, during CCaV, a cumulated loss of V_T of 9.1 ml/kg for each cycle of 3 CCs and 1 inflation was observed. This outcome is concerning because a loss in V_T could cause lung de-recruitment, which might hamper oxygenation and therefore ROSC. In contrast, during CC+SI, a constant lung recruitment and establishment of functional residual capacity was observed (a gain of 2.3 ml/kg per CC+SI cycle) (5). This improvement in V_T may lead to better alveolar oxygen delivery and lung aeration. More importantly, the initial study by Schmölzer et al. (1) and the secondary analysis by Li et al. (5) is the first description of passive ventilation (and V_T delivery) during neonatal CPR. A similar observation was reported during chest recoil after a downward force is applied to the chest in infants undergoing surgery requiring general anesthesia and endotracheal intubation. Overall, the median (interquartile range) V_T generated was 2.4 ml/kg (0.8 to 4.0 ml/kg). Although Tsui et al. only applied gentle chest pressure, they could achieve ~33% of an infants' physiological V_T of 5 to 7 ml/kg. These data suggest that CC+SI would deliver an adequate V_T.

DISTENDING PRESSURE

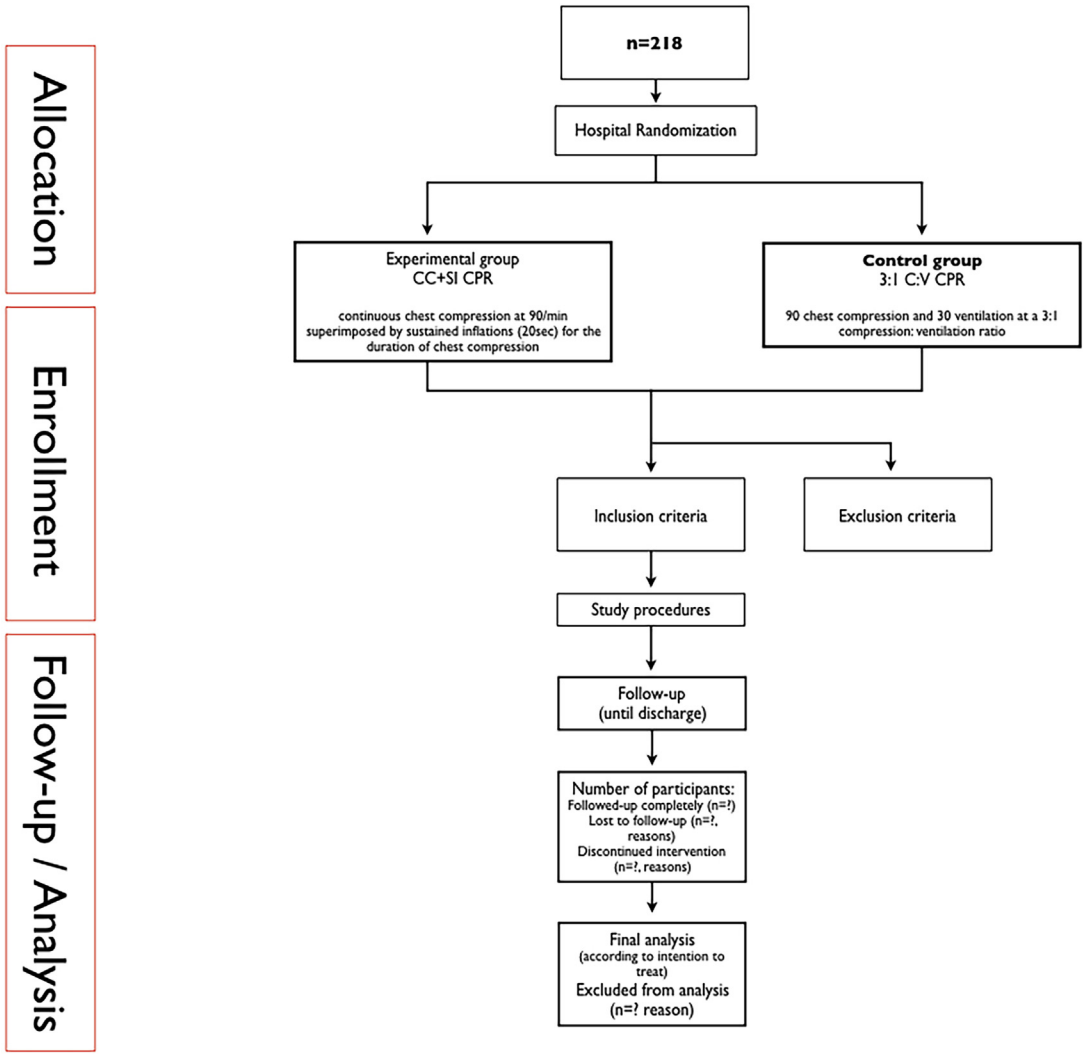
The current neonatal resuscitation guideline recommends an initial distending pressure of 20 to 25 cm H_2O and a potentially higher distending pressure of 30 to 40 cm H_2O in term infants. Although there is ample evidence that a distending pressure of 20 to 25 cm H_2O causes high V_T delivery in preterm infants, no study, to the best of our knowledge, has ever measured V_T delivery during CC in the DR (Supplemental Appendix E). Solevåg et al. determined the distending pressure needed to achieve sufficient V_T during CC+SI using manikins and cadaver piglets. 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 ~25 cm H_2O was needed to achieve an adequate V_T. This study suggests that chest recoil generates a distending pressure-dependent V_T, and that a distending pressure of ~25 cm H_2O is needed to achieve adequate V_T delivery. This is supported by the pilot trial comparing CC+SI and 3:1 C:V in preterm infants <32 weeks' gestation using a distending pressure of 24 cm H_2O (local hospital policy during neonatal resuscitation) (4). The study reported adequate V_T delivery and significantly higher minute ventilation in the CC+SI group compared with the 3:1 C:V group ($p < 0.001$), which suggests that CC+SI has the potential to improve ventilation and oxygenation during neonatal CPR.

LUNG AND BRAIN INJURY

There are concerns that sustained inflations could cause lung or brain injury. Lista et al. reported that premature infants between 25 and 28 weeks' gestation who received a sustained inflation had a higher rate of pneumothorax of 6% compared with 1% in the control group (Supplemental Appendix F). Similarly, meta-analyses suggested a trend toward higher pneumothorax rates when giving a sustained inflation. However, the mechanism for why sustained inflations might result in higher pneumothorax rates remains unknown. None of the animal studies examining CC+SI reported pneumothoraxes during autopsy or increased acute lung inflammation. Furthermore, pro-inflammatory cytokine concentrations in piglets given CC+SI compared with either a sham-operated or standard 3:1 C:V ratio were similar (2). Harling et al. reported similar cytokine levels in bronchoalveolar lavage fluid of preterm infant at 12 h of age, regardless of the 2 s or 5 s sustained inflation.

The main mechanism for brain injury is believed to be impaired venous return. Indeed, Sobotka et al. reported that a single SI causes a blood-brain barrier disruption indicated by increased numbers of blood vessel profiles with plasma protein extravasation in the cerebral cortex. In addition, after resuscitation

FIGURE 2 Study Flow Chart



CC+SI = chest compression during sustained inflation; CPR = cardiopulmonary rescitation; C:V = compression to ventilation ratio.

with a single 30 s SI followed by ventilation in asphyxiated near-term lambs, increases in blood-brain barrier disruption and cerebral vascular leakage have been reported. This raises the possibility that SI may cause neurological injury. However, a recent study by Mustofa et al. reported similar concentrations of pro-inflammatory cytokines during CC+SI and 3:1 C:V CPR in both the thalamus and frontoparietal cortex (Supplemental Appendix G). Overall, these studies suggest that CC+SI during CPR does not increase acute brain and lung injuries more than the currently practiced technique of 3:1 C:V. However, a recent multicenter trial comparing sustained inflation versus positive pressure ventilation (SAIL [Sustained Aeration of Infant Lungs] trial) as initial respiratory support in the DR was terminated after 426 extreme premature infants between 23^{+0} and 26^{+6} were randomized, because of nonstatistically significant increase in mortality within 48 h after birth with an adjusted relative risk of SI versus positive pressure ventilation of 4.73 (95% CI: 1.4 to 16.2). Although this finding is concerning, the proposed SURV1VE trial (Sustained Inflation and Chest Compression Versus 3:1 Chest Compression to Ventilation Ratio During Cardiopulmonary Resuscitation of Asphyxiated Newborns: A Randomized Controlled Trial) will only

include infants >28 weeks' gestation, which are significantly older then the infants enrolled in the SAIL trial. Similarly, our recent pilot trial of CC+SI versus 3:1 in extreme premature infant did report similar mortality rates between CC+SI and 3:1 C:V, which is reassuring (4) (Supplemental Appendix F).

CONCLUSIONS

Morbidity and mortality rates are extremely high for newborns receiving CCs. The presented research describes a clear path from basic science to translation into DRs around the world. Based on the described clinical need, the animal data available, and preliminary human data, a randomized controlled trial is needed. Recruitment for the SURV1VE trial started in January 2018 (**Figure 2**).

ACKNOWLEDGMENT The study investigators thank the public for donating money to their funding agencies.

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KEY WORDS asphyxia, cardiopulmonary resuscitation, delivery room, newborn/infant

APPENDIX For supplemental appendices (which include all of the studies referenced in the article [by name or dcription] throughout the text) and a video, please see the online version of this paper.