Dissertation

Improving cardiopulmonary resuscitation in newborn infants

submitted by

Dr. med. univ.

Marlies KRAINER

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Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz”.

Graz, January 2023 *Marlies Krainer*

Disclosure

Parts of this thesis were published in January 2023 in the journal “Children”:

Four different finger positions and their effects on hemodynamic changes during chest compression in asphyxiated neonatal piglets

Marlies Bruckner[1,2,3], Mattias Neset[1,2], Megan O’Reilly[1,2], Tze-Fun Lee[1,2], Po-Yin Cheung[1,2], Georg M Schmölzer[1,2]

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Author affiliations:
[1] Centre for the Studies of Asphyxia and Resuscitation, Neonatal Research Unit, Edmonton, Alberta, Canada
[2] Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada
[3] Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

All co-authors agree to the inclusion of their published data in the dissertation. Written statements are submitted together with the dissertation.

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This is a list of my published articles, which are cited in this thesis:

1. Bruckner M, Schmölzer GM. Physiologic Changes during Neonatal Transition and the Influence of Respiratory Support. Clin Perinatol. 2021 Dec;48(4):697–709.

2. Bruckner M, Lista G, Saugstad OD, Schmölzer GM. Delivery room management of asphyxiated term and near-term infants. Neonatology. 2021;118(4):487–99.

3. Bruckner M, Kim SY, Shim GH, Neset M, Garcia-Hidalgo C, Lee T-F, et al. Assessment of optimal chest compression depth during neonatal cardiopulmonary resuscitation: a randomised controlled animal trial. Arch Dis Child - Fetal Neonatal Ed. 2022 May 30;107(3):262–8.

4. Bruckner M, O'Reilly M, Lee T-F, Neset M, Cheung P-Y, Schmölzer GM. Effects of varying chest compression depths on carotid blood flow and blood pressure in asphyxiated piglets. Arch Dis Child - Fetal Neonatal Ed. 2021 Feb 4;fetalneonatal-2020-319473.

5. Bruckner M, Neset M, O'Reilly M, Lee T-F, Cheung P-Y, Schmölzer GM. Haemodynamic changes with varying chest compression rates in asphyxiated piglets. Arch Dis Child - Fetal Neonatal Ed. 2022 Feb 8;fetalneonatal-2021-323271.

6. Bruckner M, Neset M, Garcia-Hidalgo C, Lee T, O'Reilly M, Cheung P, et al. Chest Compression Rates of 90/min versus 180/min during Neonatal Cardiopulmonary Resuscitation: A Randomized Controlled Animal Trial. Children. 2022 Nov 28;9(12):1838.

7. Bruckner M, Pichler G, Urlesberger B. NIRS in the fetal to neonatal transition and immediate postnatal period. Semin Fetal Neonatal Med. 2020 Apr;25(2):101079.

8. Ramachandran S, Bruckner M, Wyckoff MH, Schmölzer GM. Chest compressions in newborn infants : a scoping review. Arch Dis Child Fetal Neonatal Ed. 2022 Dec 1;Epub ahead(1):1–9.

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Table of Contents

Abbreviations

bpm	beats per minute
CBF	carotid blood flow
CC	chest compression
CCaV	continuous chest compression with asynchronized ventilation
CC+SI	continuous chest compression during sustained inflation
CO_2	carbon dioxide
CPR	cardiopulmonary resuscitation
$CrSO_2$	cerebral tissue oxygen saturation
C:V ratio	compression:ventilation ratio
ECG	electrocardiogram
HR	heart rate
IVH	intraventricular hemorrhage
KFT	knocking-fingers technique
LV dp/dt max	maximum rate of change of left ventricular pressure
LV dp/dt min	minimum rate of change of left ventricular pressure
OTTT	over-the-head two-thumb encircling technique
pCO_2	partial pressure of carbon dioxide
PEEP	positive end expiratory pressure
PEF	peak expiratory flow
PIF	peak inspiratory flow
PIP	peak inspiratory pressure
PPV	positive pressure ventilation
SpO2	arterial oxygen saturation
TFT	two-finger-technique
TTT	encircling two-thumb-technique
V_T	tidal volume

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Zusammenfassung

Hintergrund In den aktuellen Leitlinien der Neugeborenen Wiederbelebung wird empfohlen zur Durchführung von Thoraxkompressionen (CC) während der kardiopulmonalen Reanimation (CPR) die encircling two-thumb-technique (TTT) zu verwenden. Diese Empfehlungen basieren auf Studien an Simulationspuppen und Expertenmeinungen. Bisher wurde keine Studie veröffentlicht, die verschiedene CC Techniken im Tierversuch untersuchten. Ziel dieser Studie war es hämodynamische und respiratorische Parameter verschiedener CC Techniken während der CPR von asphyxierten neugeborenen Ferkeln miteinander zu vergleichen. Die Hypothese lautete, dass der Blutfluss der Arteria carotis der Ferkel mit der empfohlenen TTT besser ist als mit den anderen CC Techniken.

Methodik Es wurden neugeborene Ferkel im Alter zwischen null und drei Tagen eingeschlossen, welche vom University Swine Research Technology Center, University of Alberta, Canada, bezogen wurden. Die Ferkel wurden anästhesiert, intubiert, invasiv monitorisiert und einer normokapnischen Hypoxie, welche zur Asphyxie führte, ausgesetzt. Schließlich kam es zu Bradykardie und Asystolie. Es wurden vier CC Techniken miteinander verglichen: i) encircling two-thumb-technique (TTT), ii) two-finger-technique (TFT), iii) knocking-fingers technique (KFT) und iv) over-the-head two-thumb encircling technique (OTTT). Jede der vier CC Techniken wurde nacheinander bei jedem Ferkel in zufälliger Reihenfolge für eine Minute pro Technik durchgeführt. Hämodynamische und respiratorische Parameter wurden kontinuierlich gemessen.

Ergebnisse Insgesamt wurden sieben Ferkel mit einem medianen (range) Alter von 3 (1–4) Tagen und einem Gewicht von 2,0 (1,8–2,1) kg eingeschlossen. Zwischen den CC Techniken gab es keine Unterschiede in: Blutfluss der Arteria carotis (ml/min/kg), der prozentualen Änderung des mittleren Blutflusses der Arteria carotis verglichen zum Ausgangswert, Blutdruck, enddiastolischen Volumen oder in der maximalen Anstiegsrate des linksventrikulären Drucks. Der Anstieg des Blutflusses der Arteria carotis pro CC war signifikant schneller mit TTT und OTTT (118 (45) und 121 (46) ml/min/s) im Vergleich zu TFT und KFT (75 (48) und 71 (67) ml /min/s) ($p < 0,001$). Die TFT und KFT Techniken führten zu einer signifikant niedrigeren minimalen Änderungsrate des ventrikulären Drucks (als Ausdruck der linksventrikulären Funktion) im Vergleich zu TTT. (TFT –568 (229) und KFT –578 (180) vs. TTT –1052 (369); $p = 0,012$). Es gab keine Unterschiede zwischen den verschiedenen CC Techniken bezüglich respiratorischer Parameter, der

Gewebssauerstoffsättigung des Gehirns und der aufgewendeten Kompressionskraft und Kompressionstiefe.

Schlussfolgerung Die Verwendung der encircling two-thumb-technique und der over-the-head two-thumb encircling technique führte zu einem schnelleren Anstieg des Blutflusses der Arteria carotis und einer höheren minimalen Änderungsrate des ventrikulären Drucks. Dies deutet auf einen etwas besseren linksventrikulären Auswurf unter der Verwendung dieser beiden Techniken hin. Die Unterschiede resultierten jedoch nicht in einem verbesserten Blutfluss der Arteria carotis. Diese Studie zeigte, dass die Untersuchung verschiedener CC Techniken in neonatalen Tiermodellen machbar ist. Weitere Tierversuche sollten durchgeführt werden um das Outcome verschiedener CC-Techniken zu untersuchen.

Abstract

Background Current neonatal resuscitation guidelines recommend providing chest compressions (CC) with the encircling two-thumb-technique (TTT). These recommendations are based on manikin studies and expert opinion rather than on animal or clinical data. Until now there are no studies investigating different CC techniques in animal experiments published. The aim of the study was to compare hemodynamic and respiratory parameters when providing CC with the TTT, the conventional two-finger-technique (TFT), the knocking-fingers technique (KFT), and the over-the-head two-thumb encircling technique (OTTT) in an asphyxiated neonatal piglet model. We hypothesised that in newborn asphyxiated piglets the TTT compared to the other CC techniques improve carotid blood flow during cardiopulmonary resuscitation (CPR).

Methods We included newborn mixed-breed piglets, between zero and three days of age obtained from the University Swine Research Technology Center, University of Alberta, Canada. Newborn piglets were anesthetized, intubated, instrumented, and exposed to normocapnic hypoxia followed by asphyxia. This led to bradycardia and finally asystole. Each of the four CC techniques (TTT, TFT, KFT, and OTTT) was sequently performed in each piglet in random order. After one minute the CPR with one technique was changed to another one, again for one minute. Hemodynamic and respiratory parameters were continuously measured.

Results A total of seven piglets were included with a median (range) age of 3 (1-4) days old and weight 2.0 (1.8-2.1) kg. There were no differences in the carotid blood flow (ml/min/kg), the percentage changes of mean carotid blood flow to baseline, in blood pressure, end diastolic volume, or maximal rate of rise of left ventricular pressure between the groups. The rise of carotid blood flow per CC was significantly faster with the TTT and OTTT (118 (45) and 121 (46) mL/min/s) compared to the TFT and the KFT (75 (48) and 71 (67) mL/min/s) ($p<0.001$). Using the TFT and the KFT resulted in significantly lower minimum rate of change of ventricular pressure (as an expression of left ventricular function) compared to the TTT (TFT -568 (229) and KFT -578 (180) vs. TTT -1052 (369); $p=0.012$). There were no differences in respiratory parameter, cerebral tissue oxygen saturation, and CC force and depth between the different CC techniques during CPR.

Conclusion Using the encircling two-thumb-technique and the over-the-head two-thumb encircling technique resulted in faster rise of carotid blood flow and higher minimum rate of change of ventricular pressure suggesting a slightly better left ventricular ejection. However,

those differences did not result in improved carotid blood flow. This study demonstrated that investigating different CC techniques in neonatal animal models is feasible. Further animal studies are warranted to investigate the outcome of different CC techniques.

1 Introduction

1.1 Neonatal transition

Within the first minutes after birth every newborn infant has to get through major physiological changes to adapt from intra- to extrauterine environment. Most infants undergo an uneventful immediate transition without the need for medical interventions. However, approximately six to seven million newborn infants per year (5% of all newborn infants) show insufficient breathing with the need for respiratory support in the delivery room(3–5). In addition, approximately two million newborn infants per year (0.1% of term infants, 10-15% of preterm infants) need cardiopulmonary resuscitation (CPR) including chest compressions (CC)(6,7). Failed neonatal transition and ineffective resuscitation could have serious consequences for short- and long term outcome(8).

1.1.1 Changes in respiratory system

In utero, fetal airways and lung are liquid-filled and no gas exchange occurs through the lung. The resistance between the fetal lung/airways and the amniotic sac generate a transpulmonary pressure. This pressure leads to a hyperexpanded state of the fetal lung triggering lung growth development(9). Lung liquid clearance is a complex physiological process and occurs during a 3-phase process with i) airway liquid clearance, ii) liquid accumulation within the lungs' interstitial tissue compartment, and iii) respiratory gas exchange and metabolic homeostasis(10,11).

During the first phase, lung liquid gets absorbed from the airways rapidly to establish functional residual capacity of the lung(10). Contrary to the long accepted assumption, that rising catecholamine levels and sodium uptake across the airway epithelium are responsible for rapid lung liquid clearance, latest findings implicate that the driving force for lung liquid clearance in phase one is respiratory activity and ventilation with adequate lung aeration(12–14). About 95% of lung aeration occurs during inspiration over the first breaths after birth(14). Healthy newborn infants start breathing within the first median(range) 9 (2-33) seconds after birth(15). End-tidal carbon dioxide (CO_2), an indicator for lung aeration and gas exchange, can be detected between the first three to seven breaths with maximum end-tidal CO_2 values one minute after birth in healthy term newborn infants(15,16). With lung aeration also tidal volume

increases significantly over time reaching a plateau at two minutes after birth(15,16). Failed lung aeration leads to inadequate functional residual capacity establishment and impaired gas exchange. This is followed by hypoxia, and soon after bradycardia. As long as the lung is not aerated heart rate (HR) does not increase and might result in the need for CPR with chest compressions in the delivery room. In newborn infants with risk for failed lung aeration (e.g., preterm infants) and/or need for respiratory support, pulse-oximetry should be used to monitor arterial oxygen saturation (SpO_2) levels immediately after birth(4). After birth, SpO_2 increases rapidly from 60% in minute one up to 95% in minute eight, although preterm infants often need a longer time to reach SpO_2 of above 90% compared to term or near-term infants(17,18). However, reference ranges for SpO_2 to monitor lung aeration and guide respiratory support are available in literature and are recommended to use during neonatal resuscitation(17,19–21).

During the second phase of lung liquid clearance, in the interstitial tissue compartment accumulated liquid gets absorbed via the lymphatic and blood vessels over the next four to six hours(10,11). Liquid re-entry might occur during expiration into the airways due to an increased pressure within the intestinal tissue. In infants with impaired gas exchange this can lead to the need for non-invasive positive end-expiratory pressure application to maintain gas exchange(11).

The third phase starts when immediate transition is completed and liquid has been removed from intestinal tissue(11). The focus during this phase is to maintain adequate gas exchange and metabolic homeostasis to prevent lung oedema. This mainly depends on structural and functional deficiencies and lung immaturity(11).

In summary, adequate ventilation immediately after birth is the most effective mechanism to clear the lung. If not, lung oedema might cause respiratory distress and the need for respiratory support during fetal to neonatal transition(22).

1.1.2 Changes in hemodynamics

1.1.2.1 Fetal circulation

Fetal circulation starts with the fetus first heart beat at 22 days of gestational age(23,24). To survive in the hypoxemic intrauterine environment there are many differences between the fetal and neonatal circulation as well as the characteristics of biochemical processes (e.g., presence of fetal hemoglobin)(23–25). Characteristics of fetal circulation are the placenta to

provide gas exchange and the fetal shunts to bypass less working organs in utero. These shunts are the i) ductus venosus, ii) foramen ovale, and iii) ductus arteriosus(24).

In utero, gas exchange is provided by the placenta because the lungs are liquid filled and not aerated. Oxygen is driven from the maternal side to the fetus across the placental intervillous spaces by a positive partial pressure delta gradient of oxygen between mother and fetus(26). The umbilical vein contains oxygenated blood and splits at the level of the fetal liver with 40-50% of the blood perfusing the hepatic circulation, and the remainder directly entering into the ductus venosus(24). Blood is shunted through the ductus venosus to the inferior vena cava into the right atrium(23,27). In the right atrium it mixes with blood from the superior vena cava. While the most blood is shunted through the foramen ovale into the left heart and the aorta, a small portion of the right ventricle output goes to the lungs via the pulmonary arteries for lung perfusion(23,27). However, up to 90% of the right ventricular output is shunted through the ductus arteriosus into the descending aorta bypassing the unaerated fetal lungs(28). The ductus arteriosus connects to the aorta below the carotid and coronary arteries. Hence, the higher oxygenated blood (SpO_2 about 65%) perfuse the brain and heart, whereas the lower oxygenated blood (SpO_2 about 60%) perfuse the abdominal organs and lower body before returning to the placenta(23).

1.1.2.2 Circulation after birth

The placenta is a low resistance system providing a low systemic vascular resistance in utero, while the pulmonary vascular resistance is high due to unaerated lungs(24). The high pulmonary- and low systemic vascular resistance result in a right-to-left shunt blood flow, where the blood shunts from i) the right atrium through the foramen ovale into the left atrium and the aorta ascendens, and ii) from the right ventricle through the ductus arteriosus into the aorta descendens(24). The right ventricle is responsible for around 60% of the cardiac output and is the dominant ventricle in utero(29).

During birth, circulating catecholamines cause an increase in inotropy, HR, and cardiac output, but also anatomical and structural changes of the newborn infants' body are obligatory for successful postnatal transition(28–30). With the first breaths, when the lung gets aerated, the pulmonary vascular resistance decreases while pulmonary blood flow increases. By clamping the umbilical cord and separating the low resistance placenta, the systemic vascular resistance increase leading to a rise in left ventricular afterload, higher pressures in the left

heart and an increase of left ventricular cardiac output (29). The right-to-left shunt reverses and becomes a left-to-right shunt within the first 10 minutes after birth(31,32).

After birth the shunts to enable fetal circulation in utero closes. The rise in pulmonary venous return and increase in left atrial pressure result in the functional closure of the foramen ovale(33). The ductus venosus remains patent for several days without any circulatory consequences(33). Ductus arteriosus closure is a complex mechanism. Closure is induced by i) increase in arterial oxygen content, ii) induction of vasodilatations, and iii) decrease in prostaglandin levels(33–35). The initial functional closure occurs due to smooth muscle contraction followed by anatomical closure caused by muscle cell thinning and remodelling(35). In healthy term infants the ductus arteriosus closes spontaneously in 56% of infants within the first 12-18 hours and in 96% at 30-40 hours after birth(36). In preterm infants the ductus arteriosus closure occurs after several days after birth, and in some cases remain patent might resulting in increased mortality and short-term complications(35,37). Persistent failed lung aeration leads to bradycardia and further on to the need of CPR and chest compressions in the delivery room. Immediately after birth, fetal shunts are not closed yet, implicating that a large part of the blood gets pumped through the patent ductus arteriosus bypassing the lung when providing CC. This results in left-to-right shunt with persistent pulmonary hypertension.

1.1.2.3 Bradycardia after birth

Fetal HR normally ranges between 110-160 beats per minute (bpm) and umbilical venous blood has an oxygen saturation of 70%-80%, might decreasing to 30% during labour before increasing to 95% within the first 10 minutes after birth(23,26,38,39). The transient hypoxia might lead to initial bradycardia until the lung gets aerated. A HR above 100 bpm is presumed to be normal in healthy newborn infants during neonatal transition increasing around 140–170 bpm in the first 10 minutes following delivery and then stabilizing in the range of 100–160 bpm(24,40,41).

Dawson *et al* investigated the changes in HR of healthy term and preterm infants within the first ten minutes after birth who received early cord clamping(41). Under normal conditions one minute after birth 61% of the newborn infants had a HR <100 bpm and thereof 17% had a HR <60 bpm(41). More recently, Padilla-Sanchez *et al* reported that newborn infants who received delayed cord clamping had significantly higher values and earlier stabilization of HR in the first 2 minutes after birth compared to those from Dawson *et al*(21). This is important

since current neonatal resuscitation guidelines recommend to initiate positive pressure ventilation with a HR below 100 bpm and initiate neonatal CPR including chest compressions when HR remains below 60 bpm despite adequate ventilation(4,5).

1.2 Birth asphyxia

Asphyxia is a condition of failed gas exchange and impaired organ perfusion(42). This causes progressive hypoxia, hypercarbia, and metabolic acidosis resulting in shock and in some cases in death(42). Indeed, about 800,000 newborn infants die annually worldwide due to birth asphyxia with a higher incidence in low-resource environments(42).

Birth asphyxia may occur before, during, or after delivery and can be caused by different reasons(42,43). An interrupted placental blood flow is the most common and results from maternal diseases, placental factors, and/or umbilical cord compression (Table 1) (42,43). Also newborn infants' inappropriate respiratory drive to initiate breathing (e.g., infection, circulatory compromise after blood lost, and maternal medications), airway anomalies, neurological disorders, and cardiopulmonary diseases might lead to impaired gas exchange and asphyxia (Table 1) (35). The outcome of asphyxiated newborn infants depends on the extent and duration of impaired gas exchange and the quality of provided resuscitation measures(42,43).

Table 1 Factors associated with birth asphyxia (43–49)

Perinatal	Arterial ischemic stroke Fetal exsanguinations due to bleeding
Uterine	Rupture Chorioamniotitis Uterine overdistention
Placental	Bleeding (Placenta previa/accreta, placental abruption, trauma)
Maternal	Age above 35 years Lifestyle (obesity, smoking, substance abuse) Preeclampsia Circulatory diseases (arterial hyper-/hypotension, severe anemia) Infection Shock Diabetes mellitus
Neonatal	Prematurity Post-dates Multiple Gestation Twin-to-twin transfusion Infection Septic shock Cardiopulmonary diseases Congenital malformations Airway anomalies Neurologic disorders
Umbilical cord	Cord prolapse Nuchal cord Cord Knot Velamentous cord insertion Vasa Praevia
Labour	Labour prolongation or precipitous delivery Shoulder dystocia Abdominal wall dystocia Narcotics during labour Meconium aspiration
Health care	Inadequate antenatal care (low socioeconomic parental status) Poor intra-/postpartum care (unskilled staff in obstetrics and/or neonatal resuscitation, insufficient medical equipment)

The newborn infants' body uses compensatory mechanism to maintain adequate organ perfusion during birth asphyxia. During hypoxia the first effect is to increase HR and redistribute cardiac output which is part of the Frank-Starling mechanism(43). Chemo-receptors, located in the carotid artery, respond to hypoxemia in sympathetic activation and vasoconstriction, consequently leading to centralization(50). Hence, coronary and cerebral blood flow increases to protect heart and brain while renal, pulmonary, intestinal, and muscle blood flow decreases(43). With ongoing hypoxia glycolysis takes over using high-energy phosphates such as adenosine triphosphate. Once all adenosine triphosphate is used up bradycardia occurs, further leading to cardiac arrest and asystole. After successful resuscitation pulmonary hypertension and initial arterial hypertension occurs for about 20 minutes after return of spontaneous circulation(25).

Occurrence of anaerobic glycolysis has an impact on the cell metabolism and leads to cell death via necrosis or apoptosis, resulting in organ failure(43). Renal dysfunction and hypoxic–ischemic brain injury are the most common(43). After restoration of perfusion and oxygenation a second hit 24 to 48 hours later might result in a secondary energy failure(51). The newborn infants' body responds to the injured tissue with inflammation by generating oxygen-free radicals, production of nitric oxide, and lipid peroxidation(51). The supplemented oxygen provided during resuscitation effects the newborn infants' outcome. Oxidant injury can result in intracranial hemorrhage (IVH), bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity and even epigenetic changes in the newborn infants' DNA(52–54). However, a systematic review and meta-analysis, including 1302 term born moderately asphyxiated infants, reported that time to first breath, 5-min Apgar, and survival were better for those resuscitated with 21% rather than 100% oxygen(55). They further reported that one death would be prevented for every 20 asphyxiated newborn infants resuscitated with 21% rather than 100% oxygen(55).

The incidence of birth asphyxia is the highest in resource-limited environments caused by maternal diseases and untrained health care providers to provide adequate basic neonatal resuscitation at birth(56). Neonatal resuscitation measures of asphyxiated term infants in resource-limited differ from those in resource-replete environments(42,57). To globally improve the outcome of asphyxiated newborn infants effective and easy resuscitation techniques are needed.

1.3 Neonatal resuscitation

The outcome of newborn infants receiving extensive resuscitation is poor, including a high risk of death or severe neurological injuries(7,8,58). The survival rate until hospital discharge of newborn infants, who received CC in the delivery room, ranges from 52%- 83% with a lower rate in preterm infants(59). Cardiac arrest in newborn infants is usually secondary to asphyxia rather than to a primary cardiac event, hence resuscitation measures must focus on reoxygenation to achieve return of spontaneous circulation as quickly as possible(60). International neonatal resuscitation guidelines are available and updated every five years. These should be frequently trained and used when performing neonatal resuscitation in the delivery room(3).

1.3.1 Vital parameter monitoring

Current neonatal resuscitation guidelines recommend umbilical cord palpation and/or heart auscultation for initial HR assessment(3–5). However, there is a large inter- and intraobserver variability in clinical assessment of the newborn infants' condition and inaccuracy of HR auscultation or palpation of the umbilical cord(61–63). Hence, in newborn infants with a slow HR (below 100 bpm) or failure to establish spontaneous and effective breathing continuous pulse oximetry monitoring is recommended and additional electrocardiogram (ECG) monitoring can be used(3–5).

Pulse oximetry monitoring is mostly used to monitor SpO_2 in newborn infants with inadequate breathing effort. Centile charts for SpO_2 values are available for the first ten minutes after birth and should be used to titrate supplemental oxygen(17). However, pulse oximetry monitoring might also be used to assess the quality of CC although this is not established in clinical practice and there are no data for neonatal CPR published until now(64,65).

ECG is faster and more accurate to assess the newborn infants' HR compared to pulse oximetry(66). However, ECG monitoring does not replace pulse oximetry(67,68). When using ECG monitoring health care providers should be aware of the occurrence of pulseless electrical activity, defined as the presence of electrical activity without any associated mechanical activity or detectable pulse(69). Since ECG monitoring is recommended to be used in the delivery room, several reports about the presence of pulseless electrical activity in newborn infants were published(69,70). In addition, animal studies reported a pulseless

electrical activity on the ECG in about 40% of asphyxiated neonatal piglets(71,72). During pulseless electrical activity there is no correlating waveform on pulse oximetry and auscultation identifies cardiac arrest accurately (69,72,73). Hence, combining auscultation, palpation, pulse oximetry, and ECG in asphyxiated newborn infants seems to be reasonable(72). If there is a HR above 60 bpm displayed on the ECG but the infant is unresponsive, pulseless electrical activity should be suspected and CC should be started(70).

1.3.2 Respiratory support

Since hypoxia is the predominant cause of cardiovascular collapse in newborn infants, their airways must be cleared of liquid to establish effective pulmonary gas exchange(60). Current neonatal resuscitation guidelines recommend that positive pressure ventilation (PPV) should be provided in bradycardic (HR <100 bpm) and/or apneoic newborn infants with a rate of 40-60/min, a peak inflation pressures of up to 30 cmH_2 in term newborns and 20-25 cmH_2 in preterm newborns, and a positive end-expiratory pressure of 5 cmH_2(3–5). Several studies demonstrated that in response to adequate ventilation, the lungs get aerated and HR increases immediately during delivery room resuscitation(74–76). Hence, a prompt increase of HR is the primary measure of adequate PPV(3,4). The textbook of neonatal resuscitation states that if PPV was started because of bradycardia, the newborn infants' HR should begin to increase within the first 15 sec of PPV(77). However, Espinoza *et al* reported that after 30 sec of PPV only half of the asphyxiated piglets had an increase in HR with a rapid rise in only 20% and a gradual increase in 33%(78).

Inadequate PPV occurs either by too low peak inspiratory pressure, obstruction, or mask leak caused by i) face mask technique, ii) head position, iii) airway obstruction (e.g., meconium-stained amniotic fluid) or iii) glottis closure. MR.SOPA describes a series of actions to improve mask ventilation performance. It is an acronym for M (mask adjustment), R (reposition airway), S (suction mouth and nose), O (open mouth), P (pressure increase), and A (alternate airway) as a laryngeal mask airway (LMA) or endotracheal tube(42).

Studies reported that mask leak occurs in half of newborn infants, and obstruction occurs in up to 75% of newborn infants, independent of the providers experience, and in most cases at the start of PPV and (79,80). However, teaching an improved technique significantly improves face mask ventilation(81).

Besides other causes such as too high ventilation pressures and wrong head position, airway obstruction can also be caused by glottis closure, which is common especially in

preterm infants. Since hypoxia suppresses fetal breathing movements in utero it is suspected that hypoxia in newborn infants results in apnoea and glottic adduction after birth too(82). PPV is likely to be ineffective in apnoeic newborn infants until they become so hypoxic and bradycardic that the glottis relaxes(83). However, health care providers must be aware as prolonged unrecognized airway obstruction could easily lead to further, more aggressive, and hazardous procedures, such as increased pressures and/or chest compressions if not rapidly recognized and relieved(80).

1.3.3 Chest compression

The need for CC in the delivery room is rare; only 0.1% of term infants receive advanced CPR including CC and epinephrine at birth(6). Current neonatal resuscitation guidelines state that if the HR is less than 60 bpm, despite adequate ventilation, CCs are indicated(3–5). CCs should be delivered i) on the lower third of the sternum, ii) to a depth of approximately one third of the anterior-posterior diameter of the chest iii) using the encircling two-thumb technique, iv) allowing the chest re-expand fully during relaxation, and v) using a 3:1 C:V ratio(3–5). However, these recommendations are based on extrapolations from mathematic modeling, animal data, paediatric- and adult studies, and expert opinion rather than on scientific evidence.

The main cause for cardiac arrest in newborn infants is asphyxia, while in adults cardiac collapse is mainly caused by ventricular fibrillation and/or arrhythmia(84). Hence, the focus of neonatal CPR is to restore organ perfusion and improve tissue oxygenation. Restoring myocardium perfusion is the main goal so that the heart regains function to provide adequate vital organ oxygenation. CCs restore myocardium function by increasing coronary perfusion pressure and coronary blood flow(85).

External CCs were first described in 1960 by Kouwenhoven *et al* as an intervention to restore forward blood flow in patients of acute cardiac arrest due to direct mechanical compression (cardiac pump theory)(86). Since then, CC mechanics were investigated extensively and in the 1980s, studies questioned the cardiac pump theory and suggested that blood flow is rather generated due to an increase of the intrathoracic pressure and negative pressure gradient (thoracic pump theory)(87,88). While the i) cardiac pump theory and the ii) thoracic pump theory are still the main theories of CC mechanics, newer hypothesis such as the iii) lung pump theory, the iv) left atrial pump theory, and the v) respiratory pump theory were generated over the last years(89,90).

1.3.3.1 Chest compression mechanics

The i) cardiac pump theory describes, that squeezing the heart (due to external cardiac compression), between the sternum and the paraspinal structures, produces a forward blood flow resulting in blood ejection into circulation(90). The atrioventricular valves are closed during compression(90,91). During recoil (heart relaxation) a minimal retrograde flow occurs and shunts blood into the coronary system(90,91).

The ii) thoracic pump theory describes that CCs effect an increase of intrathoracic, intrapulmonary and intracadiac pressure during compression. These increased pressures establish an arteriovenous pressure gradient across the heart, forcing blood to move down the gradient from the thoracic to the systemic circulation(91). The atrioventricular valves are open during compression(89,91). During decompression intrathoracic, intrapulmonary and intracadiac pressure decrease and fall below venous pressure. This results in blood flow from the extrathoracic space into the chest and cardiac system(89,91).

Georgiou *et al* investigated mechanisms of systemic, coronary, and cerebral blood flow during CPR in a systematic review and reported that the evidence indicate that both cardiac pump and thoracic pump affect chest compression-related blood flow during adult CPR. However, the authors suggest that blood flow during CPR cannot only be explained by these two theories(91).

One of the newer hypothesis is the iii) lung pump theory which describes the components of an inlet valve (the pulmonary valve), a compression chamber (the lung vasculature, left atrium and ventricle), and an outlet valve (the aortic valve)(92). Shaw *et al* proposed that the heart is neither the entire pump nor a passive conduit as described by the cardiac or thoracic pump hypotheses but is an essential part of the lung pump(92).

Another theory is the iv) left atrial pump theory where the left atrium, rather than the left ventricle, is the main target of compressions(93). Ma *et al* used transesophageal two-dimensional and pulsed Doppler echocardiography to investigate mitral valve position and flow and pulmonary venous flow during adult CPR(93). They reported that depending on the timing from cardiac arrest different mechanisms were observed. The cardiac pump mechanism was observed in short existing cardiac arrest while longer times were associated with the thoracic or left atrial pump mechanism(93). They suggested that different patterns of blood flow

appearing in different stages of CPR in the same patient might be caused by the change of lung and heart compliance during CRP(93).

Most recently, the v) respiratory pump theory was described in a review by Convertino *et al* as a variant of the thoracic pump theory(94). By using an impedance threshold device (a small disposable plastic valve that can be attached to a face mask or tracheal tube) in patients who received CPR, the negative intrathoracic vacuum during recoil augmented blood flow to the heart and the brain(89,94).

Although the interaction between the various CC theories is not fully understand yet, it must be considered that CPR is also influenced by other factors including CC depth, rate, ratio, recoil and technique.

1.3.3.2 Chest compression depth

The recommendations on CC depth in newborn infants are based on mathematical models and extrapolation from computer tomography scans(95,96). Meyer *et al* calculated the expected ejection fraction for different anterior-posterior CC depths by analysing computer tomography scans of 54 neonates(95). The normal values for ejection fraction were achieved by using the 1/3 anterior-posterior CC depth compared to 1/4 and 1/2 anterior-posterior CC depth. Furthermore, no subject receiving the 1/3 anterior-posterior CC depth were under-compressed (i.e., had a predicted ejection fraction <50%), whereas 54% were predicted to be under-compressed at the 1/4 anterior-posterior CC depth(95). The 1/3 anterior-posterior compression depth was much less likely to meet criteria for predicted over-compression than the 1/2 compression depth(95). However, this was a mathematical model with its own limitations(95).

Indeed, animal studies reported that CC depth affect hemodynamic parameters including cardiac output and blood pressure(97–99). In small (6–12 kg) dogs cardiac output increased as a linear function of compression depth beyond the compression threshold, whereas there was no cardiac output detectable at compression depths below 2cm(98). This suggests that cardiac output is quite sensitive to small changes in CC depth and that there might be no cardiac output below a critical threshold value of CC depth(100). In addition, Bruckner *et al* observed that 40% anterior-posterior depth resulted in higher cardiac output and arterial blood pressure compared to 33% and 25% anterior-posterior CC depth in asphyxiated newborn piglets(99). So far, there are no studies published investigating the effect

of CC depth on hemodynamics in newborn infants. However, Maher *et al* reported in a retrospective review of six infants (age range from 2 weeks- 7.3 months) who received cardiac surgery, that providing a 1/2 anterior-posterior CC depth increased systolic blood pressure by 62% compared to 1/3 anterior-posterior CC depth. Whether deeper CC depth results in faster time to return of spontaneous circulation or higher survival rates in newborn infants remains unknown. Very recently, Bruckner *et al* reported a randomized animal study, using an automated CC machine with predefined CC depth, that in newborn asphyxiated piglet no return of spontaneous circulation was achieved with an anterior-posterior CC depth of 12.5%. Time to return of spontaneous circulation and survival were similar in 25%, 33%, and 40% anterior-posterior CC depth groups(97).

The main difficulty for a resuscitator remains the inability to distinguish between different CC depths during resuscitation, especially in preterm infants. Using a too shallow anterior-posterior diameter might result in inadequate cardiac output while too deep could cause over-compression resulting in rib fractures, cardiac contusion, and thoracic injuries. It was reported that 30mm in term and 25mm in preterm infants correspond to one-third anterior-posterior CC depth(96). Hence, especially in newborn infants a deviation of few millimetres might have a great impact on the outcome.

1.3.3.3 Chest compression rate

Current neonatal resuscitation guidelines recommend to provide 90 CC/min with a C:V ratio of 3:1(3–5). However, the optimal CC rate during neonatal CPR remains unclear. A mathematical model suggests CC rate depends upon body size and weight and higher CC rates optimize systemic perfusion(101). This would result in a CC rate of 180/min for term and even higher for preterm infants, which is not feasible due to methodological limitations and rescuers' increasing fatigue with increasing CC rate(102,103). In addition, increasing CC rates lead to a decrease in time for pump-filling which might results in a partially filled ventricle and further to a decrease in stroke volume and cardiac output(98,101).

Until now, there are no clinical studies investigating various CC rates during neonatal CPR. Current knowledge about different CC rates comes from animal (piglet) and manikin studies reporting on biomechanical aspects of different CC rates(104).

Li *et al* reported no differences in achieving return of spontaneous circulation, survival rate, and hemodynamic and respiratory parameter comparing a CC rate of 90/min with

120/min in an asphyxiated newborn piglet model(105). However, time to return of spontaneous circulation was shorter with median (IQR) 34 (28-156) sec in the CC rate 90/min group compared to 99 (31-255) sec in the CC rate 120/min group, although not statistically significant (p=0.29)(105). Similar, another randomized controlled asphyxiated newborn piglet study demonstrated no differences in time to return of spontaneous circulation and survival rate when comparing a CC rate of 90/min with 100/min and 120/min(106). Noteworthy, the hemodynamic recovery, cerebral inflammatory, and brain injury markers were superior in the 120/min group compared with the 90/min and 100/min CC rate groups(106). Both studies used continuous CC, one in combination with sustained inflations(105) the other with asynchronized ventilation(106).

Very recently, much higher CC rates were investigated in newborn asphyxiated piglets by using a custom-designed automated CC machine(107). Hemodynamic parameters of CC rates of 60/min, 90/min, 120/min, 150/min, and 180/min were compared and an increase in hemodynamic parameters including stroke volume and end-diastolic volume until a CC rate of 150/min were observed(107). A CC rate of 150-180/min resulted in highest cardiac output and arterial blood pressure compared to lower CC rates(107). This was also observed in a randomized controlled animal trial by Bruckner *et al*, who reported on improved hemodynamic and respiratory parameter and a trend to faster time to return of spontaneous (103 (79-170) sec vs. 189 (96-600) sec, p=0.08) when applying a CC rate of 180/min compared to 90/min(108).

However, such high CC rates cannot be applied in good quality by manual CPR due to fatigue after a short time. In a randomized crossover manikin study was demonstrated that providing continuous CC with a rate of 120/min resulted in participants higher HR and mean arterial pressure as well as more self-assessed fatigue compared to a 3:1 C:V ratio(109). As a consequence CPR quality including the proportion of CCs with adequate depth and leaning, deteriorated(109). This observation was confirmed by another simulation study where a CC depth decrease by 50% within the first 3 min during continuous CC with 120/min, 30% during continuous CC with 90/min and 20% during 3:1 C:V was reported(103). The authors concluded that rescuers should switch after every second cycle of HR assessment during neonatal CPR(103).

1.3.3.4 Chest compression ratio

Since newborn infants physiological heart- and respiratory rate are higher than in infants and adults, current neonatal resuscitation guidelines recommend a C:V ratio of 3:1 resulting in 90 compressions and 30 ventilations per minute(3–5). The main goal of neonatal CPR is to restore vital organs perfusion and oxygenation. However, this might be better achieved when providing uninterrupted CC leading to a more stable increase of coronary perfusion pressure, the main determinant of coronary blood flow(84). Hence, experts of the field investigated whether i) other C:V ratios (e.g., 4:1 or 9:3), ii) continuous CC with asynchronized ventilation (CCaV), or iii) continuous CC during sustained inflations (CC+SI) might be more effective during neonatal CPR than the current recommended approach.

Very recently, twenty-two studies investigating different C:V ratios, CCaV, and CC+SI were identified in a review. The authors reported that there is only one clinical randomized controlled trial published in contrast to six manikin and 14 animal studies(110).

1.3.3.4.1 Compression to ventilation ratio

Several studies compared the recommended 3:1 C:V ratio with other ratios including 2:1, 4:1, 9:3, and 15:2 in asphyxiated newborn piglets(111–115). Those studies reported no differences in time to return of spontaneous circulation, survival rate, hemodynamic parameters or recovery, tissue oxygenation, blood gases, or lung and brain inflammation markers(111–115). In summary, so far there is no indication that different C:V ratios (ranging from 2:1 to 15:2) might have any impact on the outcome of neonatal CPR.

While animal studies focused on hemodynamics, outcome and recovery, manikin studies investigated rescuers fatigue and preference when providing different C:V ratios. Srikatan *et al* compared in a randomized simulation study 3:1 vs. 5:1 vs. 10:2 vs. 15:2 C:V ratios and reported that there were no differences in rescuers fatigue between the C:V ratio groups(116). The 3:1 C:V ratio was rated as more difficult from the participants compared to other ratios(116). However, the study investigated the one rescuer-method and also included infant and adult manikins(116). Contrary, participants in another simulation study preferred 3:1 over 5:1 and 15:2 C:V ratio(117). In addition they reported, that CC depth was greater and more consistent with the 3:1 C:V ratio(117).

1.3.3.4.2 Continuous Chest Compression with asynchronized ventilation (CCaV)

It is recommended to provide CCaV with a CC rate of 100-120/min and a ventilation rate of 20-30/min in advanced pediatric CPR(118) while the recommendation for neonatal CPR is 3:1 C:V ratio resulting in “only” 90 CC/min (although physiological HR of newborn infants is between 120-160/min). The avoidance of interrupting coronary perfusion and improved minute ventilation during CCaV might be advantageous also during neonatal CPR; hence, CCaV during neonatal CPR has been investigated over the last years. Until now there are five animal studies published comparing different C:V ratios/ CC rates with CCaV (106,119–122). The majority of studies observed no differences in return of spontaneous circulation or survival when comparing a 3:1 C:V ratio with CCaV(119–121). However, very recently Aggelina *et al* reported that using CCaV with a CC rate of 90/min improved coronary perfusion pressure, end-tidal CO_2, time to return of spontaneous circulation, return of spontaneous circulation at 30sec and survival rate compared to 3:1 C:V ratio in a newborn asphyxiated piglet model. In addition, CCaV seems to improve respiratory parameter including minute ventilation and oxygenation, and ventilation rate during neonatal CPR(119,120,123,124). However, CCaV also resulted in decreased CC depth and greater rescuers physical fatigue over time compared to 3:1 C:V ratio(102,103,124).

1.3.3.4.3 Continuous chest compressions during sustained inflations (CC+SI)

The CC+SI approach describes simultaneous continuous CCs and sustained inflations during CPR(125). CC+SI forces air out of the chest during CCs, and delivers an adequate tidal volume during the passive chest recoil(125). This leads to an increase of intrathoracic pressure and consequently might result in passive ventilation during CCs(125).

This approach was first described in 2013 by Schmölzer *et al*, who demonstrated that CC+SI significantly improved minute ventilation (i.e., alveolar oxygenation), systemical and regional hemodynamics (i.e., coronary artery pressure), time to return of spontaneous circulation, and survival compared with a 3:1 C:V ratio in newborn asphyxiated piglets(125). These observations were confirmed by further studies using the asphyxiated piglet model, whereby different CC rates (90/min vs. 120/min) and sustained inflations durations (20 sec vs. 30 sec vs. 60 sec) were investigated(125–127). However, CC+SI was superior to a 3:1 C:V ratio independent of pressure and duration of sustained inflations(125–127). Another study compared CC+SI with a 3:1 C:V ratio in a translational lamb model and reported similar time to return of spontaneous circulation and survival(128).

In a clinical pilot study, including preterm infants <32 weeks gestation, time to return of spontaneous circulation was significantly shorter in the CC+SI group than in the 3:1 C:V group, with mean (SD) 31 (9)sec vs. 138 (72)sec, respectively (p=0.011)(129). Whether CC+SI during neonatal CPR will improve short- and long-term outcomes in preterm and term newborns will show the currently ongoing randomized controlled multicentre multinational study “SURV1VE” (ClinicalTrials.Gov Trial NCT02858583)(130).

1.3.3.5 Chest Compression technique

Current neonatal resuscitation guidelines stated that “it may be reasonable to choose the two-thumb–encircling hands technique over the two-finger technique, as the two-thumb–encircling hands technique is associated with improved blood pressure and less provider fatigue”(4). However, there are an increasing number of studies investigating different hand positions and assistive compression devices to improve CC technique during neonatal CPR. The majority of studies investigating various CC techniques are manikin studies. A recent review identified 29 studies investigating various CC techniques in randomized crossover manikin studies (n=27) and clinical trials (n=2)(110). However, until now there are no studies investigating different CC techniques in animal experiments published.

1.3.3.5.1 Encircling two-thumb-technique (TTT) vs. two-finger-technique (TFT)

The most known CC techniques are the TTT and the TFT. For the TTT the torso gets encircled with both hands supporting the back, placing the two adjacent thumbs V-shaped on the infant’s chest and compressing the chest with the two thumbs (Figure 6A). When using the TFT, index and middle finger are placed on the infant’s chest, and the chest gets compressed with the tips of these two adjacent fingers (Figure 6B).

The majority of manikin studies reported on greater CC depth and CC force using the TTT compared to the TFT(131–133). A greater CC depth leads to improved hemodynamics might resulting in a better outcome(99,132). Dorfsmann *et al* demonstrated in a randomized crossover experiment using a modified manikin that the TTT produced higher blood- and pulse pressures when compared with TFT during prolonged CPR(132). Further on, manikin studies reported on higher finger strength and less fatigue using the TTT compared to the TFT(134,135). Although the majority of studies described the TTT to be superior to the TFT,

there are a few experiments published showing no differences between those two techniques(136,137).

Further on, manikin studies as well as a randomized clinical trial demonstrated the higher proportion of correct placements when using the TTT compared to the TFT(138,139). Saini *et al* reported that the proportion of correct placements with TFT and TTT were 6.7 and 77% in all neonates, 10.6 and 89.5% in full term and 1.2 and 59% in preterm neonates, respectively ($p<0.001$)(138).

1.3.3.5.2 Knocking finger technique (KFT)

For the KFT the CC provider stretches the metacarpophalangeal joint 180° from the dorsum of the hand, bending the proximal and distal interphalangeal joints 90°, and placing the tip of the thumb against the palmar side of the middle phalanx of the index finger. The CCs are performed with the dorsal side of the middle phalanx(140)(Figure 6C). Current studies reported similar CC quality when comparing the knocking-finger-technique (KFT) with the TTT and the TFT.

In a recent randomized manikin study was demonstrated that the ratio of correct CC depth was the highest with the TTT technique 100 (99–100)%, followed by the KFT 99 (93–100)% and TFT techniques 92 (53–98)% ($p<0.001$)(140). Using the KFT resulted in shorter total hands-off time than the TTT and the TFT as well as in less fatigue and finger pain compared to the TFT(140). These advantages might qualify the KFT as preferred technique when performing neonatal CPR as a single rescuer. Another advantage of this technique might be the small area of CC compared to the TTT and the TFT which might decrease the chance of ribs or organs contusion(140).

Another manikin study reported on similar CC quality comparing the TTT with the KFT(141). However, the participants rated the KFT as more difficult than the TTT(141).

1.3.3.5.3 Over-the-head two-thumb encircling technique (OTTT)

The OTTT is a modification of the TTT, where the CC provider uses the finger position of the TTT but stands behind the newborn infants head. Simulation studies compared the OTTT with the TFT and reported that the OTTT resulted in greater CC depth and proportion of effective CC as well as in a faster CC rate(142,143). Further on, OTTT resulted in smaller

proportion of complete recoil and fatigue than the TFT, while the hands-off time was not significantly different between the two groups(142,143). However, in these studies CPR was performed by a single rescuer using a CC rate of 100/min with a 30:2 C:V ratio(142,143).

An advantage of the OTTT might be rescuers standing position. Standing on the infants head during ventilation is the most familiar position when performing neonatal resuscitation. This might be one reason for the reduction of fatigue when using the OTTT, as the rescuer is not required to rotate arms and waist to place the mask correctly while performing CPR(143). Indeed, the volume of each ventilation was significantly higher in the OTTT group compared to the TFT with mean (SD) 49.4 (11.5) vs. 44.9 (11.4) mL, p=0.038. However, the study participants provided a bag-valve mask ventilation in the OTTT group, whereas for TFT they provided pocket-mask ventilation(143).

The OTTT might be superior to the TFT, especially when CPR is provided by a single rescuer; however, there are no studies published comparing the OTTT to the TTT until now.

1.3.3.5.4 Alternative techniques and assistive compression devices

Other CC techniques are mostly modifications of the TTT and TFT. However, there is very limited and heterogeneous data about alternative TFT (e.g., using i) flexed fingers(144), ii) the ring finger instead of the index finger(145), iii) the thumb, the index- and middle finger(146), or iv) the right or left hand when providing CC with the TFT(145)).

A modification of the TTT was described by Smereka *et al* who published a series of studies investigating a “novel-two-thumb-technique” (also called “two-thumbs-fist-technique”). For this technique both thumbs are directed at the angle of 90 degrees at the lower third of the sternum, while the fingers of both hands are closed in a fist(147–149). They investigated the quality of CC provided by paramedics, nurses, novice providers or single rescuers when using the novel-two-thumb-technique, the TTT or the TFT. Overall, using the novel-two-thumb-technique is comparable to the current standards concerning CC depth, CC rate, recoil, hands-off time and ventilation quality(141,150–152). Further on, the novel-two-thumb-technique achieved higher blood pressures compared to the TTT and TFT in an infant manikin model(147).

Very recently, the use of certain assistive compression devices was reported. All of these devices consist of a small plate (in different shapes), where the fingers or palm position are predefined(146,153,154). In those studies better correct hand position during manikin CRP

was described(146,153,154). Further on, greater and more accurate CC depth, less fatigue and higher participant satisfaction was reported when comparing CC with and without the device(146,154).

1.3.4 Vascular Access

Current neonatal resuscitation guidelines state that umbilical venous catheterization is the primary method for vascular access in the delivery room(3,4). Alternative methods are the intraosseous route(3–5) and the peripheral access(5). However, data about vascular access implementation in the delivery room is scarce and there are no clinical randomized controlled trials comparing different approaches(155).

While the umbilical vein catheter is the most common used vascular access, the number of cases describing intraosseous routes in newborn infants increased recently. Scrivens *et al* reviewed data from case series including a total of 46 intraosseous punctures in 41 neonates(156). Mileder *et al* reported on 12 additional cases of intraosseous needle insertions using a battery-driven drill in newborn infants(157). They described a complication rate of 10-30% including mostly malpositioned/ displaced needles, paravasation and local infection(156,157). Rare complications were osteomyelitis, fracture, compartment syndrome, limb ischemia, and fat or air emboli(156,157). Although the complication rate of intraosseous accesses might be higher than in umbilical vein catheters, a faster insertion, even for experienced providers of umbilical vein catheterization, was reported(156,158).

Besides the intraosseous access, the peripheral vein puncture seems to be a fast and safe alternative to implement vascular access during neonatal resuscitation. Baik-Schneditz *et al* demonstrated that implementing peripheral intravenous accesses in preterm neonates (mean (SD) 31.5 (2.2) weeks of gestation) takes median (IQR) 5 (4-9) min and is successful at the first attempt in 63%(159). However, in cardiocirculatory depressed infants establishment of peripheral vascular accesses might take longer due to centralization and therefore might delay medication application(159).

Another alternative might be the direct puncture of the umbilical vein through Wharton's jelly(160). A case series of ten cases described that the whole procedure from puncture to drug administration took 15-20 sec(160). In neonatal CPR, this method could be time saving; however, more evidence is needed before recommending this technique.

Implementing a vascular access in asphyxiated newborn infants during neonatal CPR is challenging. While an umbilical vein catheter enables a direct access to the systemic circulation, this method might be too time consuming. Also the establishment of a peripheral intravenous access takes several minutes and might not be successful due to centralization. A rapid and effective way to implement a vascular access is the intraosseous route, which should be considered as an alternative especially in asphyxiated term infants(3–5).

1.3.5 Medications during neonatal resuscitation

Current neonatal resuscitation guidelines suggest the administration of intravascular epinephrine using a dosage of 0.01 to 0.03 mg/kg every 3 to 5 min during neonatal CPR(3,4). Epinephrine restores cardiac function by increasing cardiac contractility, chronotropy, and vasodilatating the coronaries(161). In addition, it causes peripheral vasoconstriction consequently increasing venous return(161).

Epinephrine might be administrated via different routes. Especially initial administration via endotracheal tube and nostrils gained on interest, as implementation of a vascular access often takes several minutes. In a retrospective study, investigating the efficacy of intravenous and endotracheal epinephrine administration in newborn infants during CPR was observed, that 75% of newborn infants who received the first dose of epinephrine intravenously, achieved return of spontaneous circulation, while only 20% of the infants received initial endotracheal epinephrine, responded to a single endotracheal dose alone(162). Recently, Songstad *et al* compared the effects of intravenously, endotracheal, and nasally administrated epinephrine during resuscitation of near-term asphyxiated lambs and demonstrated that intravenously administered epinephrine is the most effective(164). They reported that time to return of spontaneous circulation was shorter and rates of increase in blood pressure, HR, carotid- and pulmonary blood flow were significantly greater in the intravenously administered epinephrine group than in the endotracheal and nasal group(164). However, as nasal administration is easy and had a similar effect as endotracheal administration it is suggested that nasal high-dose adrenaline administration for neonatal resuscitation should be further investigated(164).

The most effective epinephrine dosage during neonatal CPR remains unknown. However, there are no clinical studies comparing different intravenous epinephrine dosages in newborn infants. Halling *et al* reported on no improvement in response rate to the greater doses of endotracheal epinephrine (0.03 vs. 0.05 mg/kg) in a retrospective study. In the pediatric population higher dosages of epinephrine show no benefit in improved rates of return of

spontaneous circulation or survival(165–168) and in adult patients higher cumulative epinephrine dosages were even associated with higher rates of severe adverse events and mortality(169–171).

Besides route of administration and epinephrine dosage, also the time intervals between consecutive epinephrine applications might have an impact on the newborn infants' outcome. In pediatric patients (mean(SD) 4.1(5.6) years of age, n=1639) was demonstrated that longer intervals between epinephrine dosages (>5-<8 min and 8-<10min) during CPR than currently recommended (3-5 min) were associated with improved survival to hospital discharge(172). This might also be the case in newborn infants; however, studies investigating the optimal time interval between epinephrine administrations are lacking.

While epinephrine is internationally recommended to administer during neonatal CPR, there are insufficient data supporting the routine use of other medications including fluids or sodium bicarbonate. Fluids (normal saline (0.9% sodium chloride) or preferably uncrossmatched type O, Rh-negative blood) might be considered for volume replacement when blood loss is suspected in newborn infants, who show a poor respond to resuscitation(4,5). The application of sodium bicarbonate may be considered during prolonged cardiac arrest after adequate ventilation is established and there is no response to other therapies(3).

1.3.6 Outcome after neonatal cardiopulmonary resuscitation

The risk for mortality and poor neurological outcome of newborn infants who received CPR immediately after birth is influenced by various factors including gestational age, birth weight, demographic characteristics, cause of cardiac arrest, medical setting (low- vs. high resource settings), CPR duration, and Apgar score(8,58,173,174). However, survival rates vary widely between the studies due to the heterogeneity of data and high risk of bias(175). Very recently, the International Liaison Committee on Resuscitation Neonatal Life Support Task Force reviewed the outcome of newborn infants after receiving CPR in the delivery room and identified a total of 16 studies(175). The included studies reported on survival rates ranging from 2%-100%(175). However, pooled data showed that 41% of the 579 included newborn infants survived to the last follow-up (hospital discharge through 12 years)(175).

An important factor for survival is the duration of CPR; the longer the duration of CPR the lower the survival rate until discharge(176). Indeed, Ahmad *et al* reported that each added minute of CC decreased the odds of return to spontaneous circulation by 11% in newborn

infants(177). In addition, several retrospective studies identified gestational age as an important factor for neonatal outcome after CPR in the delivery room(58,59,175). The lower the gestational age the higher is the risk for death before discharge. Foglia *et al* analyzed the outcome of 1022 newborn infants who received delivery room CPR and reported survival rates of 83% (≥36 weeks), 66% (33-35 weeks), 60% (29-32 weeks), 52% (25-28 weeks), and 25% (22-24 weeks)(59). Hence, term newborn infants have the highest chance to survive after delivery room CPR.

Since birth asphyxia in term newborn infants is one of the major causes for neonatal death worldwide, especially those infants might benefit from sufficient CPR. However, most of these infants (98%) are born in resource limited environments and neonatal mortality is about 50-55 times higher in low- and middle-income countries compared to high-income countries(56,178,179). Recently, Tylleskär *et al* reported that in a low-resource country (Uganda) 98% of newborn infants (≥ 34 weeks gestation) with an Apgar score of 0–1 at 10 min of resuscitation died within two days after birth(173).

Optimizing CC in newborn infants is an important step to improve the outcome of infants who received CPR after birth. Improved CC techniques are easy to implement during delivery room CPR independent of available resources.

2 Aim and Objectives

Aim of the study was to investigate the effect of different CC techniques in a neonatal asphyxiated piglet model.

2.1 Primary objective of the study

To investigate the hemodynamic effects of four CC techniques (encircling two-thumb-technique (TTT) vs. two-finger-technique (TFT) vs. knocking-fingers technique (KFT) vs. over-the-head two-thumb encircling technique (OTTT)) in a neonatal piglet model of asphyxia.

P In newborn asphyxiated piglets

I does the encircling-two-thumb-technique compared to

C the two-finger-technique, knocking-fingers technique, and over-the-head two-thumb encircling technique

O improve carotid blood flow during CPR.

2.2 Secondary objectives of the study

Do CC techniques during neonatal CPR effect

i) hemodynamic parameters
ii) respiratory parameter
iii) cerebral tissue oxygen saturation
iv) CC force
v) CC depth

2.3 Outcome parameters

2.3.1 Primary outcome parameters

- Carotid blood flow (mL/min/kg)

2.3.2 Secondary outcome parameters

i) Hemodynamic parameters
- Arterial blood pressure (mmHg)
- Stroke volume (mL)
- End diastolic volume (mL)
- Maximal rate of rise of left ventricular pressure
- Minimum rate of change of ventricular pressure

ii) Respiratory parameters:
- Tidal volume (mL/kg)
- Minute Ventilation (mL/kg/min)
- Peak Inspiratory Flow (L/min)
- Peak Expiration Flow (L/min)
- Peak Inflation Pressure (cmH_2O)
- Positive End Expiratory Pressure (cmH_2O)
- End-tidal CO_2 (mmHg)
- Respiratory Rate (/min)

iii) Cerebral tissue oxygenation saturation (%)

iv) CC force (N)

v) CC depth (cm)

3 Animal models

Animal experiments make a big contribution to improve the understanding of physiological and pathophysiological processes in humans(180,181). Due to the similarities in anatomy, physiology, and pathophysiology between newborn infants and newborn piglets, the newborn piglet model is an adequate model to investigate perinatal asphyxia. Newborn piglets are often used for neonatal CPR studies due to their chest shape. Lambs and rabbit pups are frequently used to study lung physiology and ventilation due to the similarity in lung physiology, however, other organ systems including gastrointestinal tract are not comparable and therefore other models are used(180).

To receive precise data implemented animal models including similarity in genetics and standardized study protocols are used. Possible bias, including gestational age, maternal factors (e.g, age, pre-existing conditions, or pregnancy related diseases including preeclampsia, acute bleeding, and gestation diabetes), or growth patterns such as small- or large for gestational age or intrauterine growth restriction, can be minimized in animal experiments. However, results from animal experiments cannot fully be translated in newborn infants due to their individuality (e.g., gestational age or weight) and different circumstances (e.g. birth mode, birth complications). In addition, there are always factors in clinical studies which cannot be controlled in advance, for example the severity of birth asphyxia(180).

Animal experiments are very suitable for examining rare events such as neonatal CPR. Performing clinical studies to investigate CC in newborn infants is challenging, not only because it is an uncommon situation which makes it difficult to generate an adequate sample size, but also that the need for CC is a sudden event and a stressful situation for healthcare providers. In addition, there are legitimate ethical concerns performing resuscitation studies in such a vulnerable group without previous knowledge from animal experiments.

A good example for translating animal experiments to clinical studies is the work by Schmölzer *et al*(97,99,182–184). This group uses a well established newborn asphyxiated piglet model, inducing normocapnic hypoxia, followed by asphyxia and cardiac arrest to investigate different resuscitation techniques(97,99,182–184). In 2013, this study group demonstrated, that providing consecutive continuous high pressure inflations for 30 sec during cardiopulmonary resuscitation (approach named CC+SI) in newborn asphyxiated piglets compared to the 3:1 compression to ventilation ratio significantly improved respiratory and hemodynamic parameter as well as time to return of spontaneous circulation(126). These

results were translated in a clinical pilot study, demonstrating that CC+SI resulted in a significant shorter time to return of circulation in newborn infants(129). This was followed by a multicenter, multinational randomized controlled trial comparing short- and long-term outcome using the CC+SI approach compared to the currently internationally recommended 3:1 compression to ventilation ratio approach(3,5) in preterm infants >28 weeks gestation during delivery room resuscitation (SURV1VE trial, ClinicalTrials.Gov Trial NCT02858583).

3.1 Animal models for neonatal asphyxia

There are different approaches described in literature to achieve asphyxia in the newborn animal model including i) clamping the cord in utero(185), or reduce the fraction of inspired oxygen, which can be achieved by ii) putting the piglet in an ambient oxygen reduced chamber, iii) increase the nitrogen or carbon dioxide concentration during mechanical ventilation and/or iv) clamp the endotracheal tube(2,186). The experimental protocol we used for this study is in a large part based on the protocol by Cheung *et al*(2).

3.1.1 Rodents and rabbits

Whereas mice and rats are not a suitable model to investigate mechanical interventions during neonatal resuscitation due to their small size, this model is adequate when investigating interventions for long exposure which trigger biochemical processes (e.g., applying oxygen to an immature lung and eyes)(180,187–189).

Preterm rabbit pups are very suitable to investigate respiratory physiology during immediate transition(180). The lung maturity is similar to humans and the small size is an advantage in performing phase-contrast X-ray imaging (to investigate lung liquid clearance and lung aeration) and lung volume measurements with plethysmography (to investigate the effect of ventilation)(180,190–192).

3.1.2 Piglets

The neonatal piglet model was used over decades to investigate the pathophysiology of perinatal asphyxia and perinatal hypoxic-ischemic brain injury (193–195). Saugstad investigated biochemical effects during hypoxemia and after oxygen and surfactant application

in a newborn piglet model over decades providing basic knowledge about the newborn infants physiology(196–199). However, it is the most used model to investigate neonatal CC(181). Newborn piglets show remarkable similarities to newborn infants including similar development, body size, hemodynamics, anatomy and physiology of the heart, (cerebral) metabolism, vascular pharmacology, and drug responses(2,193,194,200). Further on, the piglets' resting HR and blood pressure is comparable with the newborn infants' parameters(200). Indeed, the neonatal piglet model suits to investigate acute hypoxia and asphyxia since the piglets first physiological response to hypoxia is bradycardia like in newborn infants(200). Additionally, both newborn piglets and newborn infant have glycogen reserves available to maintain cardiac contraction for minutes under anaerobic conditions(200). Those characteristics enable the asphyxiated newborn piglet model to be used in experiments, especially when investigating interventions during neonatal resuscitation(97,99,182–184).

3.1.3 Lambs

A perinatal asphyxiated lamb model is used to investigate fetal- to neonatal transition and neonatal resuscitation(201). The lambs experience intrapartum asphyxia by clamping the cord in utero implicating that the lambs undergo postnatal transition (including lung aeration after birth) during the experiment(201). In the lamb model the ewes are mostly multiparous littering twins(180). The uterus constitution as well as the relatively quiescent uterus are advantageous for performing fetal surgery with a low risk to trigger birth(180). This model allows a detailed understanding of physiological changes during immediate transition including fetal growth, lung liquid clearance, gas exchange and cardiovascular physiology(11,31,202).

3.1.4 Piglet vs. lamb model

There are advantages and disadvantages for both models. While the lamb model is a transition model providing information about (physiological) changes during fetal-to-neonatal transition, the asphyxiated piglet model is a post-transition model and suits better to investigate mechanical delivery room interventions during neonatal resuscitation (e.g., CC, vascular access or medication application). Vali *et al* used newborn piglets during neonatal transition to investigate birth asphyxia(203). They observed that clamping the cord in utero to induce asphyxia in piglets resulted in a too mild mixed-respiratory metabolic acidosis and that the repeatability was not satisfying enough to implement this model in an experimental setup(203).

However, the concurrent development of newborn piglets are reflecting term newborn infants whereas lambs are often used as a preterm model reflecting preterm infants 26-28 weeks of gestation(2). Also the litter size varies between piglets and sheep. Sows litter up to ten piglets and sheep mostly only two lambs, which is an advantage especially when using a transition model(180)(2). The asphyxiated neonatal piglet model is the best and most often used to investigate CC during neonatal cardiopulmonary resuscitation because of the chest size and shape(181). Performing cardiac compressions on a piglet feels very similar to cardiopulmonary resuscitation in newborn infants(180). In addition, the newborn piglets' chest most likely resembles the newborns chest compared to lambs, which chests show a more triangular shape(181).

4 Materials and Methods

The study was conducted as part of my PhD at the Centre for the Studies for Asphyxia and Resuscitation at the University of Alberta, Edmonton, Canada in 2020. For the experiments mixed breed newborn piglets were used. These piglets were 0-3 days of age and transferred from the Swine Research Technology Center, University of Alberta to the laboratory on the day of experimentation. The Swine Research Technology Center is located in Edmonton and the transport of the piglets to the laboratory took about half an hour. Usually, the piglets arrived in the morning before nine o`clock in an appropriate animal transport box. We investigated a maximum of one piglet per day.

To make a contribution to the animal experiments it is mandatory to successfully complete the University of Alberta Animal User Training Program prior to animal experiments. This includes following courses: “Concepts in Biosafety”, “Laboratory and Chemical Safety”, “Animal Research Ethics and Use at the University of Alberta”, “Basic Principles of Animal Ethics and Welfare of Animal Use”, “Care and Use of Swine in Research”, “Introduction to basic surgical techniques in research”, and “Aseptic techniques in surgery”. The experiment was approved by the Animal Care and Use Committee (Health Sciences) (AUP00002651), University of Alberta, registered at preclincialtrials.eu. (PTCE0000249), and performed in concordance with the Animal Research Reporting In Vivo Experiments guidelines(204).

4.1 Animal Preparation

Animal preparation included i) continuous vital parameter monitoring implementation, ii) anesthesia conduction, iii) performance of surgical procedures to implement vascular access, invasive monitoring and airway management as well as iv) animal recovery before starting the interventions. Animal preparation took about half an hour for operation and one hour recovery afterwards.

4.1.1 Non-invasive monitoring and anesthesia

Immediately after the piglets were hauled out of the transportation box they were placed on the resuscitation table and further on anesthetized with Isofloran 1-5% in 100% oxygen. Isofloran was administrated by using a conventional face mask which fitted the newborn

piglets' snout. The resuscitation table and the experimental setup are displayed in Figure 1. Since newborn piglets are sensitive to cold temperatures, especially when they are anesthetized, a heating pad and an overhead warmer was used to maintain a rectal body temperature between 38.5°C to 39.5°C. To monitor their vital parameters a pulse oximetry sensor was fixed on the piglets' hind leg and ECG electrodes were placed on the thorax. Peripheral SpO_2 and HR were monitored continuously. After induction of anesthesia and correct placement and implementation of basis monitoring, the operation was started.

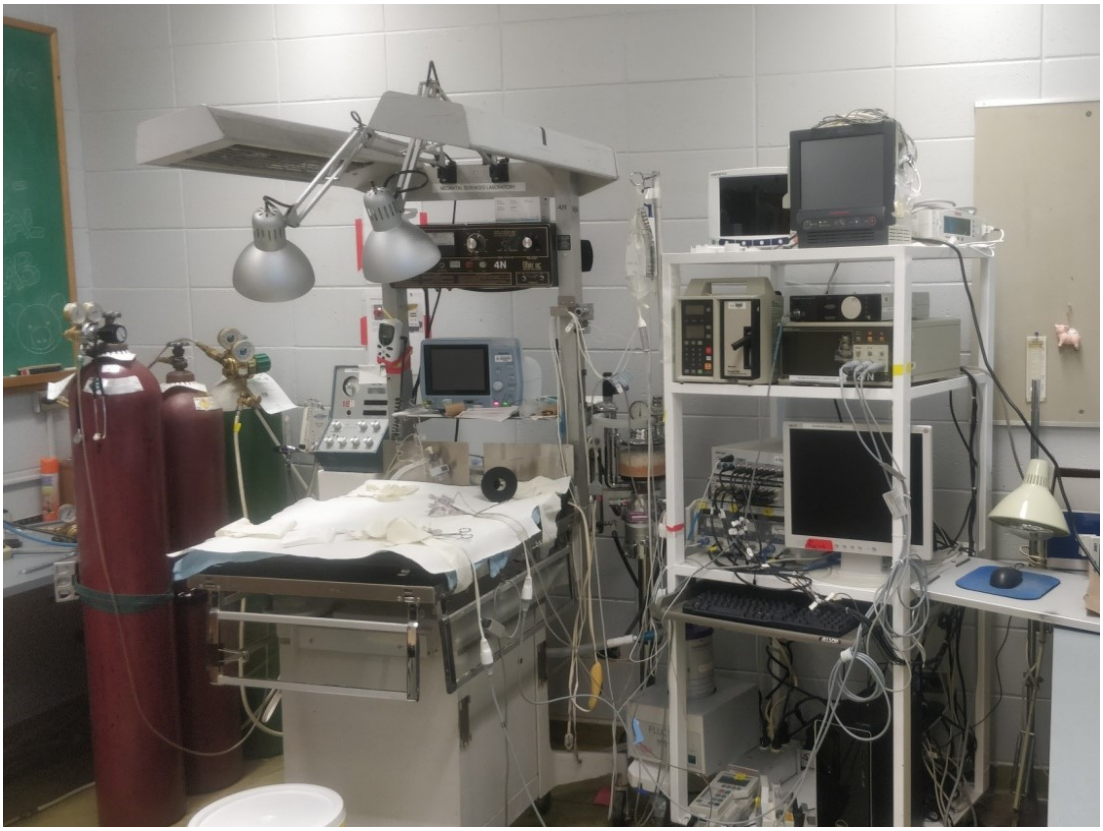

Figure 1 Experimental setup with resuscitation table and monitoring devices

4.1.2 Vascular access implementation

A 2-3 cm long incision was made in the piglet's right groin and the femoral vein and artery were dissected. After putting strings around the vessels, the femoral vein was incised and a double-lumen catheter was inserted to 15 cm. Afterwards the strings were tighten to secure the placed catheter (Figure 2). This technique is called "the cut-off technique". A femoral vein catheter was used to administer medications and fluids during the experiment. This enabled to change from narcotic gas to intravenous anesthetics, which was mandatory to continue with airway management. Therefore we started Morphine (2-4ml/hr; 100-200 µg/kg/h) and Propofol (2-6ml/hr; 10-30mg/kg/h) application through the femoral vein catheter immediately after implementation. To maintain the piglets' glucose level and hydration during the experiment we additionally infused 5% dextrose at 10 mL/kg/h intravenously. After femoral vein catheter implementation and start with intravenous anesthetic a single-lumen catheter was inserted into the femoral artery to 5cm, again by using the cut-off technique. This catheter was used to continuously monitor the invasive arterial blood pressure and to draw blood for blood gas analysis during recovery time (Figure 2).

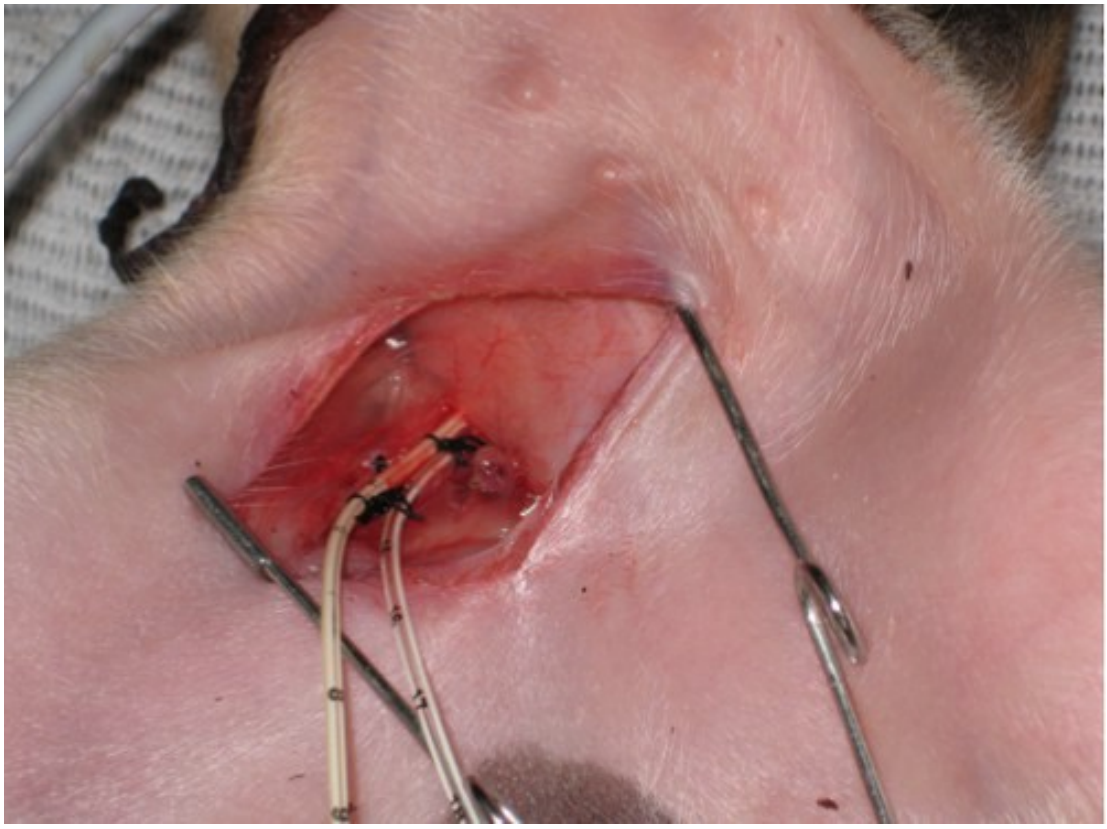

Figure 2 "Groin incision with the placement of femoral arterial and venous catheters"**.** Reproduced from (2) with permission of publisher (Nam Nguyen)

4.1.3 Airway securement

During femoral vein/ artery catheterization the piglets were ventilated using a face mask. However, after vascular access was implemented the next step was to continue with airway management. To secure the airway and establish mechanical ventilation a 2-3cm long horizontal incision was made in the piglet's neck and 1cm of the trachea was dissected and exposed in a first step. Again two strings were put around the trachea and incised the trachea and inserted an endotracheal tube at 1 cm in a second step (Figure 3). During the endotracheal tube was fixed by tighten the strings the ventilator was connected to the tube and pressure-controlled ventilation was started. For mechanical ventilation a 25/min rate, a peak inspiratory pressure (PIP) of 25 cmH_2O and a positive end-expiratory pressure (PEEP) of 5 cmH_2O was used.

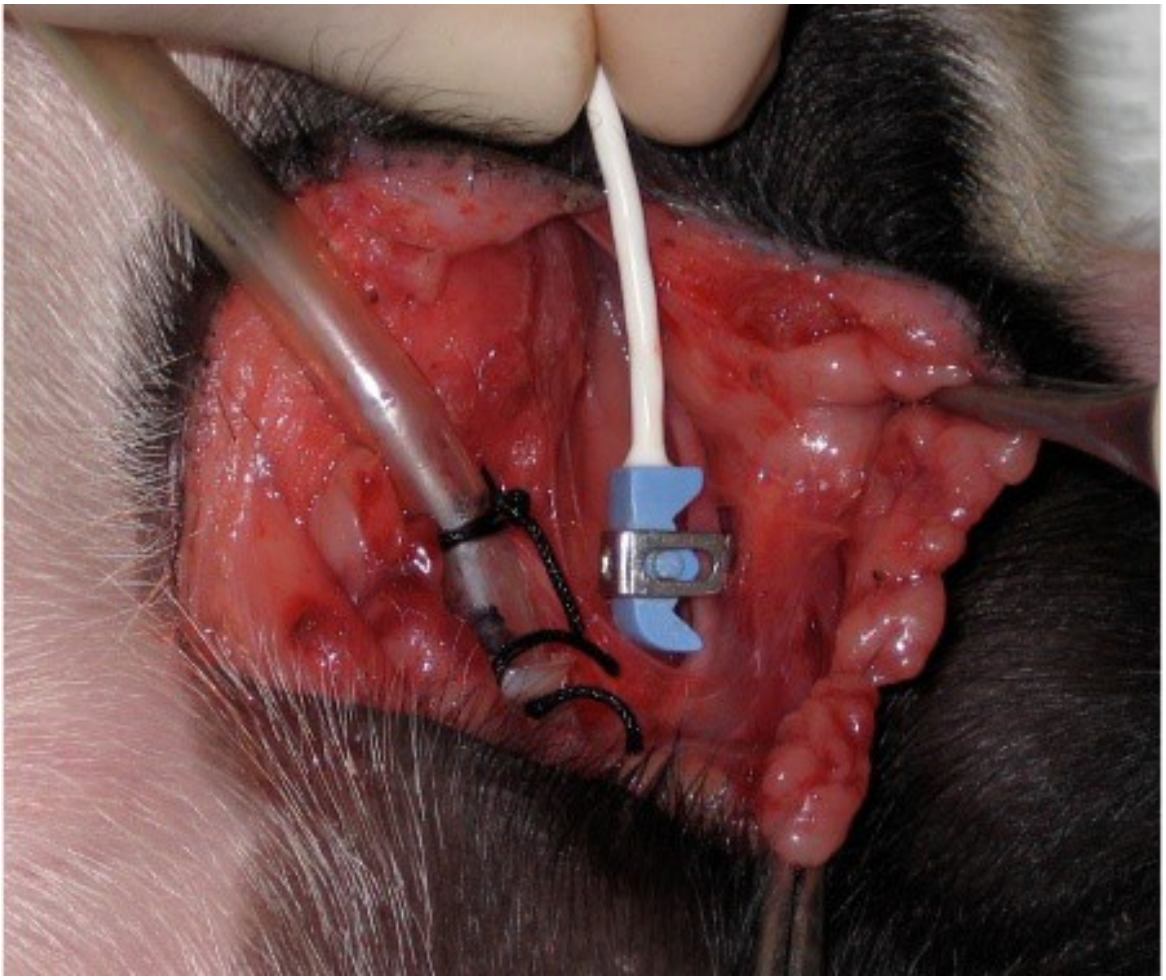

Figure 3 “Neck incision with the placement of an endotracheal tube and a flow probe around the common carotid artery”

Reproduced from (2) with permission of publisher (Nam Nguyen)

4.1.4 Invasive monitoring implementation

After completed airway securement, the next step was to dissect and expose the common carotid artery and encircle it with a transit time ultrasound flow probe to continuously measure the carotid blood flow (CBF), again by using the cut-off technique (Figure 3). Further on, a Millar catheter was inserted into the left ventricle through the common carotid artery. The Millar catheter was used to measure left ventricular pressure, including composite and segmental volumes, which served as a surrogate for cardiac output(205). Because of the size difference between the Millar catheter and left ventricular longitudinal axis, which poses a limitation for the accuracy of in vivo volume measurement, an alpha factor = 0.46, based on comparison between Millar's recording and direct echocardiographic measurements in three piglets was used to correct the conductance volume(205).

After operation completion the piglets were placed in a supine position and allowed to recover from operation for at least one hour before starting the intervention. Mechanical ventilation was adapted when needed, to make sure that the piglets SpO_2 was kept within 90% and 100% and the partial pressure of carbon dioxide (pCO_2) was kept within 35 and 45mmHg, regularly measured with arterial blood gas analysis during recovery.

4.2 Monitoring

Continuous vital parameter monitoring during the experiment was mandatory to guarantee the newborn piglets welfare (e.g., painlessness, hydration, and normothermia), and evaluate anesthetic state and mechanical ventilation. Further on, it was necessary to collect predefined outcome parameters.

4.2.1 Measurement of Hemodynamic Parameters

We continuously assessed HR starting immediately after the newborn piglet was placed on the resuscitation table and until the piglet was euthanized. HR was measured using a conventional ECG with ECG-electrodes placed on the newborn piglet's chest. In addition, the following hemodynamic parameter were measured invasively: i) arterial blood pressure via the femoral artery catheter, ii) CBF via the transit time ultrasound flow probe, and iii) stroke volume, end-diastolic volumes, and maximal and minimal rate of change of ventricular pressure via the Millar catheter placed in the left ventricle through the common carotid artery.

4.2.2 Measurement of Respiratory Parameters

SpO_2 was assessed continuously starting immediately after the newborn piglet was placed on the resuscitation table and until the piglet was euthanized. SpO_2 was measured using a conventional pulse oximetry with a sensor placed on the piglets' hind leg. During mechanical ventilation tidal volume (V_T), minute ventilation, airway pressures including peak inspiratory flow (PIF), peak expiratory flow (PEF), PIP, and PEEP, as well as gas flow, end-tidal CO_2, and ventilation rate were continuously measured using a respiratory function monitor. The respiratory function monitor sensor was placed between the endotracheal tube and the ventilator just as in human newborn studies. V_T was calculated by integrating the flow signal(206) and end-tidal CO_2 was measured using non-dispersive infrared absorption technique(207). The accuracy for gas flow is ±0.125L/min, end-tidal CO_2 ±2mmHg(207).

4.2.3 Measurement of Cerebral Oxygenation

Cerebral tissue oxygenation was measured with near-infrared spectroscopy. The sensor was placed on the piglets head and secured with tape, which also serves as a light

shield to reduce light artefacts (Figure 4). The oxygenated and deoxygenated hemoglobin is measured by near-infrared spectroscopy and calculates tissue oxygen saturation in the area of interest e.g., the brain. Cerebral tissue oxygen saturation ($CrSO_2$) reflects the balance between oxygen delivery and oxygen consumption within a tissue compartment and is a mixed saturation value consisting of arterial/capillary and venous perfusion(208). $CrSO_2$ values were stored every second with a sample rate of 0.13 Hz.

Figure 4 Cerebral tissue oxygen saturation measurement using near-infrared spectroscopy

4.2.4 Measurement of Force and Depth

FlexiForce sensors were placed on the piglets' chest and on the finger, which was used to perform CC, to measure the applied force on the chest during CC. In addition, the CC depth was measured with an infrared transmitter and receiver by placing the transmitter on the piglets' chest and the receiver stationary on the resuscitation table in the region of the newborn piglets' spine. The applied CC force and depth was recorded with a sample rate von 200Hz(97,99).

This set-up allowed us to simultaneously and continuously monitor HR, blood pressure, CBF, stroke volume, end-diastolic volumes, maximal and minimal rate of change of ventricular pressure, SpO_2, V_T, PIF, PEF, PIP, PEEP, gas flow, end-tidal CO_2, $CrSO_2$, and CC force and depth during the experiments.

4.3 Materials

- Endotracheal tube size 3.0 (Mallinckrodt™, Covidien, Dublin, Ireland))
- Femoral vein catheter (5-French Argyle® double-lumen catheter [Klein-Baker Medical Inc. San Antonio, TX])
- Femoral artery catheter (5-French Argyle® single-lumen catheter [Klein-Baker Medical Inc. San Antonio, TX])
- Millar catheter (MPVS Ultra, ADInstruments, Houston, TX)
- Carotid blood flow was measured with a carotid artery ultrasound flow probe (2mm, Transonic Systems Inc., Ithica, NY).
- Transonic flow probe, heart rate and pressure transducer outputs were digitized and recorded with LabChart programming software (AD Instruments, Houston, TX).
- V_T, airway pressures, gas flow and end-tidal CO_2 were measured with a respiratory function monitor (NM3, Respironics, Philips, Andover, MA)
- Positive pressure ventilation was provided by using a Neopuff T-Piece (Fisher & Paykel, Auckland, New Zealand).
- Mechanical ventilation was provided by using Sechrist infant ventilator model IV-100 (Sechrist Industries, Anaheim, CA)
- Arterial blood pressure, HR, and SpO_2, was measured with a Hewlett Packard 78833B monitor (Hewlett Packard Co, Palo Alto, CA).

- Applied force on the chest was measured with FlexiForce A201 sensors (TekScan, Boston, MA) and depth with an infrared transmitter and receiver (Gikfun, Guangdong, China)
- CC force and depth were recorded with Arduino Software (Somerville, MA).
- $CrSO_2$ was measured using the Invos Cerebral/Somatic Oximeter Monitor (Invos 5100, Somanetics, Troy, MI) with the neonatal sensor.

4.4 Study protocol

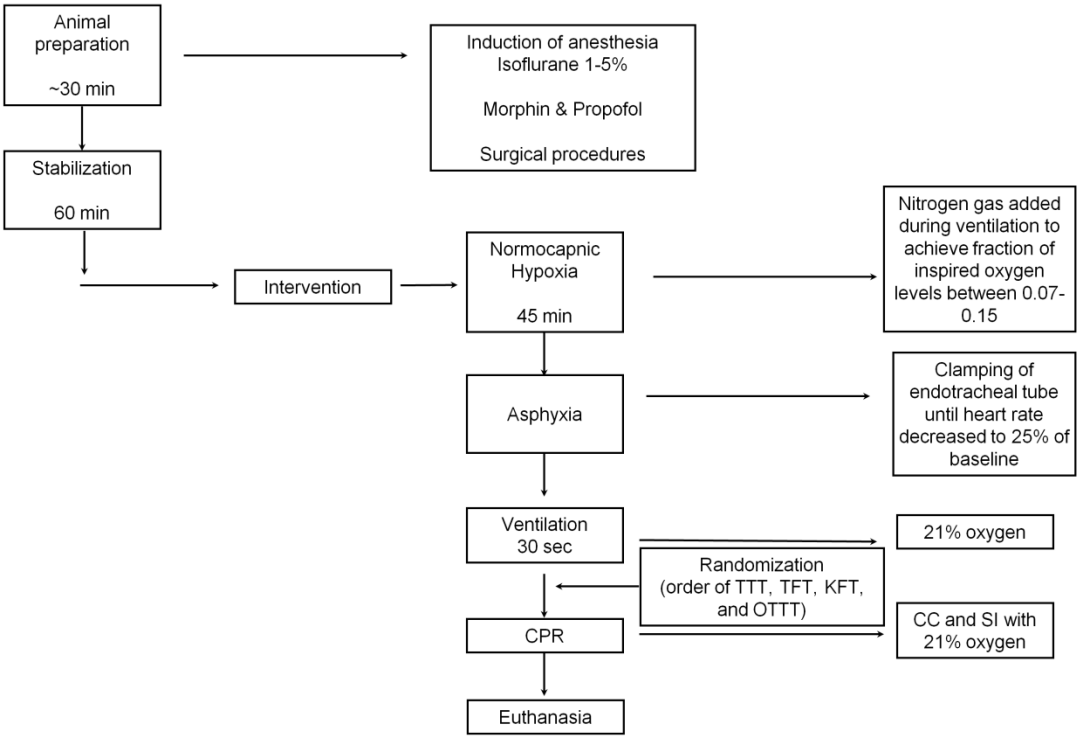

Figure 5 Study flow diagram. Encircling two-thumb-technique (TTT), two-finger-technique (TFT), knocking-fingers technique (KFT), over-the-head two-thumb encircling technique (OTTT), cardiopulmonary resuscitation (CPR), chest compression (CC), sustained inflation

4.4.1 Chest compression techniques

Current neonatal resuscitation guidelines recommend to use the encircling two-thumb-technique when providing CC in neonates(3). Using this technique the CC provider stands either on the left or right site of the infant or above the infant's head. The hands encircling the chest and CC are provided by depressing the sternum with the two thumbs building a "V-shape"(4). This recommendation is based on i) manikin studies investigating the CC providers performance during neonatal cardiopulmonary resuscitation (3,209) and ii) a case report from 1988 describing two cases where the newborn infants received CC initially with the two-finger-technique, which was switched to the encircling two-thumb-technique(210). It was observed that using the encircling two-thumb-technique generated higher blood pressures compared with the two-finger-technique(210).

The International Liaison Committee on Resuscitation reviewed this topic in 2020, identifying 19 manikin studies published since the last search in 2015(3). While there were no changes from the neonatal resuscitation guidelines 2015, other CC techniques including the knocking-finger-technique have been reported in manikin studies(140,141,144). However, there are no studies investigating the impact on hemodynamics or respiratory parameter using different CC techniques neither in newborn animals nor in infants since this case report.

For this study we compared the following CC techniques: i) the encircling two-thumb-technique (TTT), where the CC provider stood on the piglet's left side encircling the torso with both hands supporting the back, placing the two adjacent thumbs on the piglet's chest, and compressed the chest with the two thumbs (Figure 6A), ii) the two-finger-technique (TFT), where the CC provider stood on the piglet's left side, placing the index and middle finger on the piglet's chest, and compressed the chest with the tips of these two adjacent fingers (Figure 6B), iii) the knocking-fingers technique (KFT), where the CC provider stood on the piglet's left side stretching the metacarpophalangeal joint 180° from the dorsum of the hand, bending the proximal and distal interphalangeal joints 90°, and placing the tip of the thumb against the palmar side of the middle phalanx of the index finger. The CC was performed with the dorsal side of the middle phalanx(140) (Figure 6C). And iv) the over-the-head two-thumb encircling technique (OTTT), where the CC provider stood behind the piglets' head and compress the chest using the TTT(143) (Figure 6D).

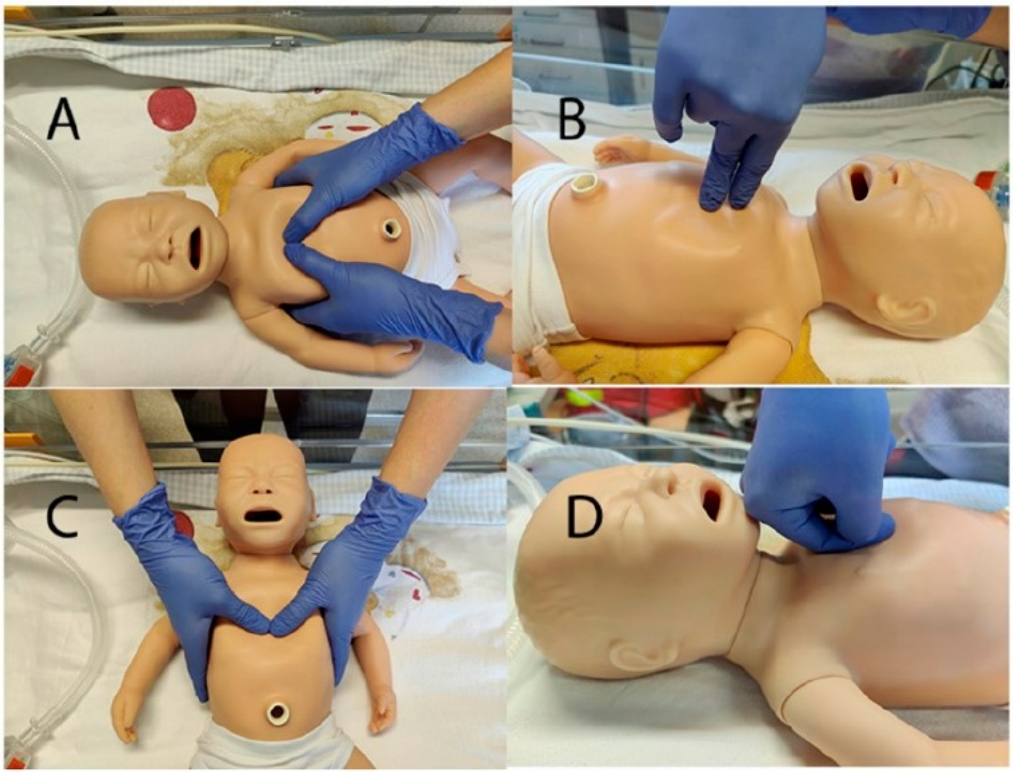

Figure 6 Chest compression techniques: A) encircling two-thumb-technique (TTT), B) two-finger-technique (TFT), C) over-the-head two-thumb encircling technique (OTTT), D) knocking-fingers technique (KFT). Reproduced from (1) with permission of publisher (Donna Ding)

4.4.2 Randomization and blinding

Each of the four CC techniques (TTT, TFT, KFT, and OTTT) was sequently performed in each piglet in random order. The order was randomized using a computer-generated randomization program (http://www.randomizer.org). Sequentially numbered, sealed, brown envelopes containing the order of CC techniques were opened during the experiment (Figure 5).

Blinding was not feasible for the CC provider. The piglet's chest was covered with a sterile drape during cardiopulmonary resuscitation to blind all other team members (except when OTTT was performed as the CC providers standing position changed). We also blinded the statistical analysis to group allocation and unblinded it after completion.

4.4.3 Inclusion and exclusion criteria

We included newborn mixed-breed piglets, between zero and three days of age obtained on the day of experimentation from the University Swine Research Technology Center, University of Alberta. There were no exclusion criteria.

4.4.4 Sample Size and Power Estimates

This is the first study investigating various CC techniques in an asphyxiated newborn piglet model. Since there are no reference data a sample size calculation including power estimates was not feasible. Based on previous publications investigate cardiopulmonary resuscitation by using the newborn asphyxiated piglet model a convenient sample of seven was used.

4.4.5 Experimental protocol

After the newborn piglets recovered from operation for at least one hour the intervention started. The newborn piglets were exposed to 45 minutes normocapnic hypoxia. This was achieved by reducing the inspired oxygen concentration to 7-15% by introducing nitrogen gas. During hypoxia SpO_2 was maintained between 30-40%, partial pressure of oxygen between 20-40 mmHg and pH <7.10. Hypoxia was then followed by asphyxia until the HR decreased to 25% of baseline, which was achieved by disconnecting the ventilator and clamping the

endotracheal tube(126). Ten seconds later, positive pressure ventilation was commenced for 30sec with 21% oxygen, PIP of 30 cmH_2O, PEEP of 5 cmH_2O, and gas flow of 8 L/min. Then the sequentially numbered, sealed, brown envelopes containing the order of CC techniques were opened. After 30sec of positive pressure ventilation, CC was initiated, using 21% oxygen(211). All four CC techniques were performed by a single provider. Each CC technique was performed for one minute in every piglet. The piglets received sustained inflations with a PIP of 30 cmH_2O for the duration of 30sec. During the sustained inflations, CCs with a rate of 90/min were provided. Sustained inflations were interrupted after 30sec for 1sec before a further 30sec of sustained inflation was provided(127,212). The combination of CCs and sustained inflations results in passive ventilation during CCs(129,183).

In this study setting Epinephrine was not administered during cardiopulmonary resuscitation. Piglets were euthanized immediately after all four CC techniques were performed with an intravenous overdose of sodium pentobarbital (120mg/kg).

4.4.6 Data collection and statistical analysis

We recorded age, weight and sex of the study piglets. The LabChart® programming software was used to continuously record transonic flow probe and pressure transducers output as well as HR (Figure 7). One file for each piglet was generated and the LabChart® programming software was used to perform the peak analysis during CPR. This data were then extracted and collected in a Microsoft Excel database (Microsoft, Redmond, WA).

Airway pressures, gas flow, V_T, and end-tidal CO_2 were measured and analyzed using Flow Tool Physiologic Waveform Viewer (Philips Healthcare, Wallingford, CT) (Figure 8). To analyze the respiratory data we calculated the median values for each cardiopulmonary resuscitation sequence in a first step and then calculated the mean of the median for comparison.

Data are presented as mean (standard deviation [SD]) for normally distributed continuous variables and median (interquartile range [IQR]) when the distribution was skewed. The data were tested for normality by using the Shapiro-Wilk and Kolmogorov-Smirnov test and we used the two-way repeated measures ANOVA with Bonferroni post-test for data comparison. P-values are 2-sided and a p-value <0.05 was considered statistically significant. Statistical analyses were performed with SigmaPlot (Systat Software Inc, San Jose, USA) and IBM SPSS 25 (IBM Corporation, Armonk, NY).

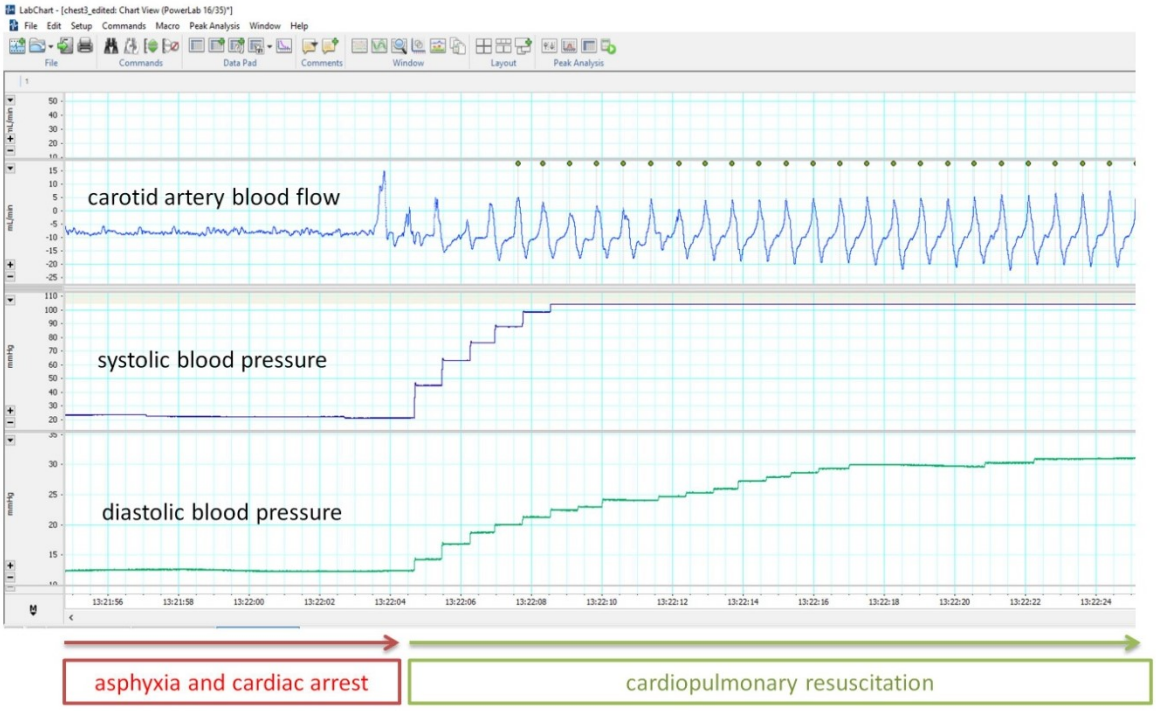

Figure 7 Example of hemodynamic data peak analysis in LabChart® programming software

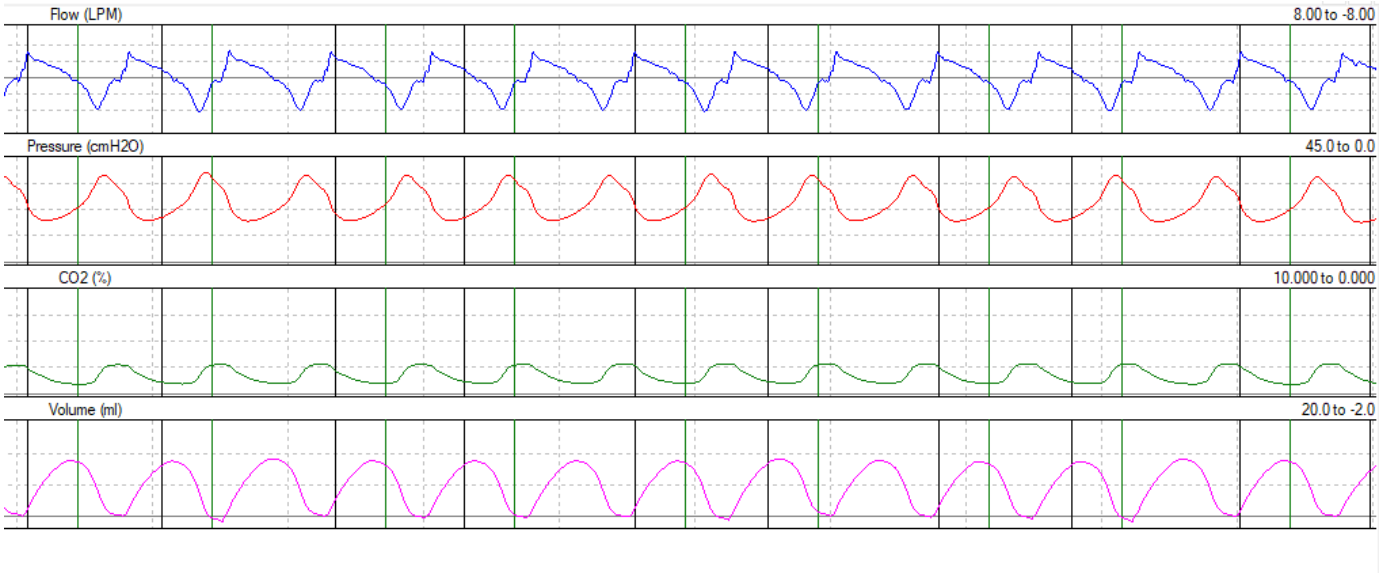

Figure 8 Example of respiratory data analysis using the Flow Tool Physiologic Waveform Viewer

5 Results

5.1.1 Demographic data and baseline characteristics

A total of seven piglets were included with a median (range) age of 3 (1-4) days old and weight 2.0 (1.8-2.1) kg. Three piglets (43%) were female.

The baseline characteristics were mean (SD) i) heart rate 187 (52) beats per minute, ii) mean arterial blood pressure 55 (14) mmHg, and iii) carotid blood flow 38 (13) mL/min/kg, iv) stroke volume 1.3 (0.3) mL/min/kg, v) end diastolic volume 3.2 (1.8) mL/min/kg, vi) maximal rate of rise of left ventricular pressure 2925 (601) mmHg and vii) minimum rate of change of ventricular pressure -3334 (1077) mmHg.

5.1.2 Carotid blood flow

Mean (SD) carotid blood flow was 10 (6) ml/min/kg with the TTT, 5 (3) mL/min/kg with the TFT, 4 (3) mL/min/kg with the KFT, and 6 (5) mL/min/kg with the OTTT ($p=0.13$) during CPR (Table 2). The slope rise of carotid blood flow was significantly higher with the TTT and the OTTT (118 (45) and 121 (46) mL/min/s) compared to the TFT and the KFT (75 (48) and 71 (67) mL/min/s) ($p<0.001$), while there were no differences between the TTT and the OTTT, as well as between the TFT and KFT ($p=1.000$) (Figure 9).

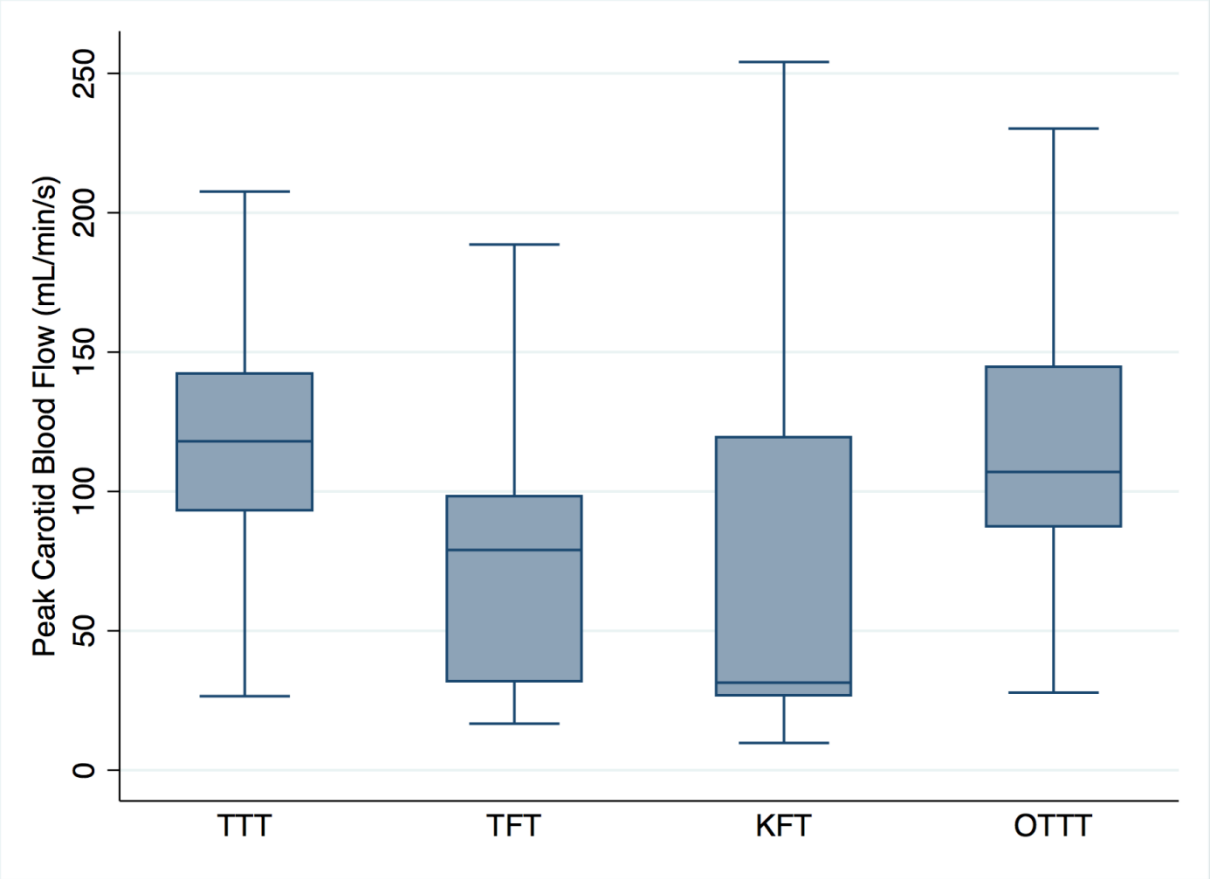

Figure 9 Peak analysis of carotid blood flow with the encircling two-thumb-technique (TTT), two-finger-technique (TFT), knocking-fingers technique (KFT), and over-the-head two-thumb encircling technique (OTTT).

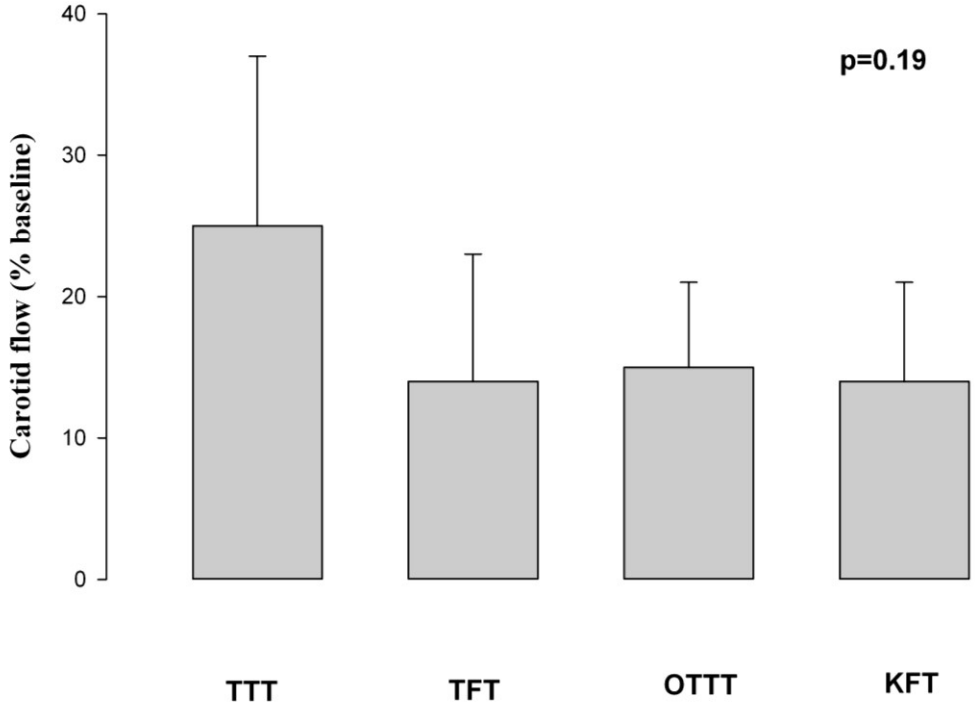

Figure 10 Percentage changes of mean carotid blood flow to baseline with the encircling two-thumb-technique (TTT), two-finger-technique (TFT), knocking-fingers technique (KFT), and over-the-head two-thumb encircling technique (OTTT).

5.1.3 Secondary outcome parameters

Table 2 Hemodynamic parameters from start until the end of CPR. Encircling two-thumb-technique (TTT), two-finger-technique (TFT), knocking-fingers technique (KFT), over-the-head two-thumb encircling technique (OTTT), maximal rate of rise of left ventricular pressure (dp/dt max), minimum rate of change of ventricular pressure

	TTT (n=7)	**TFT (n=7)**	**KFT (n=7)**	**OTTT (n=7)**	**p value**
Heart rate (bpm)	107 (17)	109 (19)	115 (25)	109 (16)	0.87
Mean arterial blood pressure (mmHg)	19 (9)	10 (5)	12 (7)	12 (5)	0.12
Diastolic blood pressure (mmHg)	9 (4)	8(2)	8(2)	8 (2)	0.67
Carotid blood flow (ml/min/kg)	10 (6)	5 (3)	4 (3)	6 (5)	0.13
Stroke volume (mL /kg)	0.8 (0.3)	0.5 (0.2)	0.6 (0.3)	0.8 (0.3)	0.12
End diastolic volume (mL /kg)	2.6 (1.4)	2.3 (1.3)	2.1 (1.2)	2.4 (1.5)	0.94
dp/dt max (mmHg/s)	1128 (405)	790 (398)	796 (357)	877 (478)	0.40
dp/dt min (mmHg/s)	-1052 (369)	-568 (229)*	-578 (180)*	-711 (310)	0.012

Data are presented as mean (SD), * Significantly different from TTT group (Tukey)

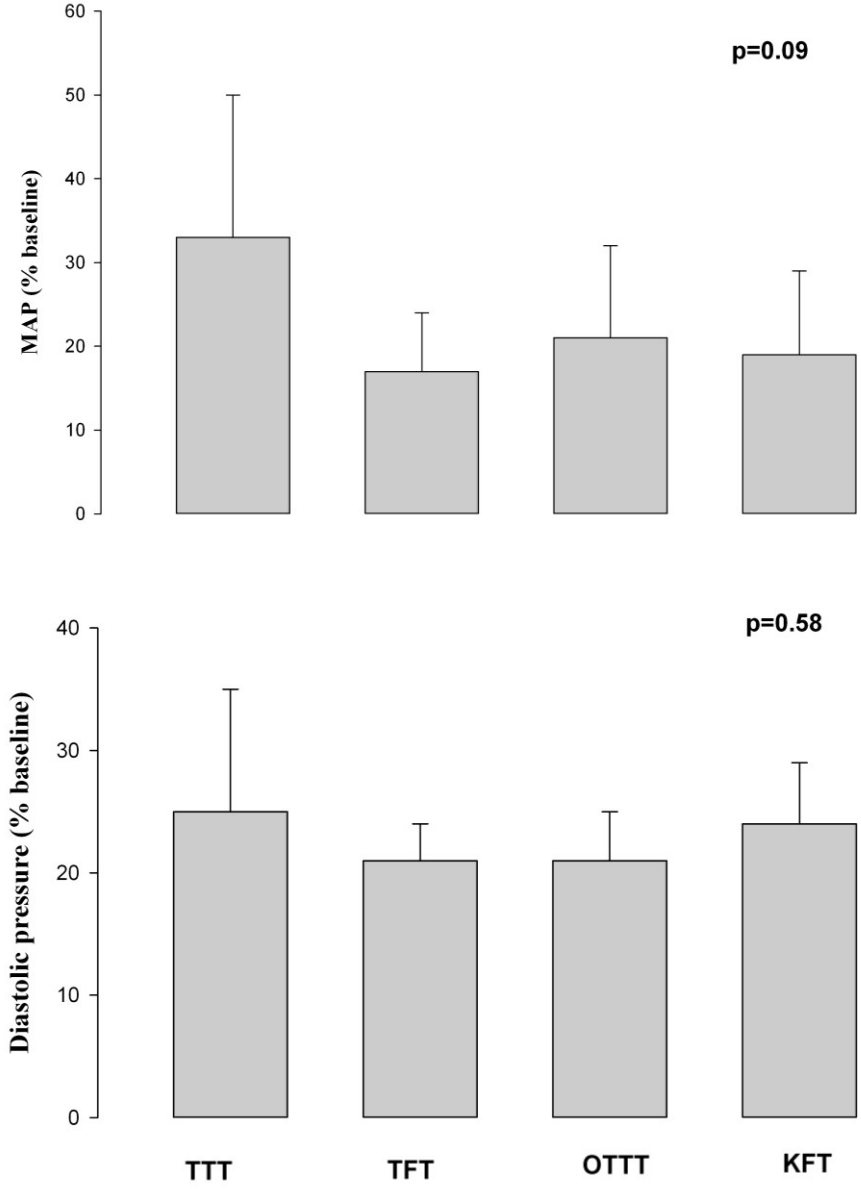

Figure 11 Percentage changes of mean arterial pressure (MAP) and diastolic blood pressure to baseline with the encircling two-thumb-technique (TTT), two-finger-technique (TFT), knocking-fingers technique (KFT), and over-the-head two-thumb encircling technique (OTTT)

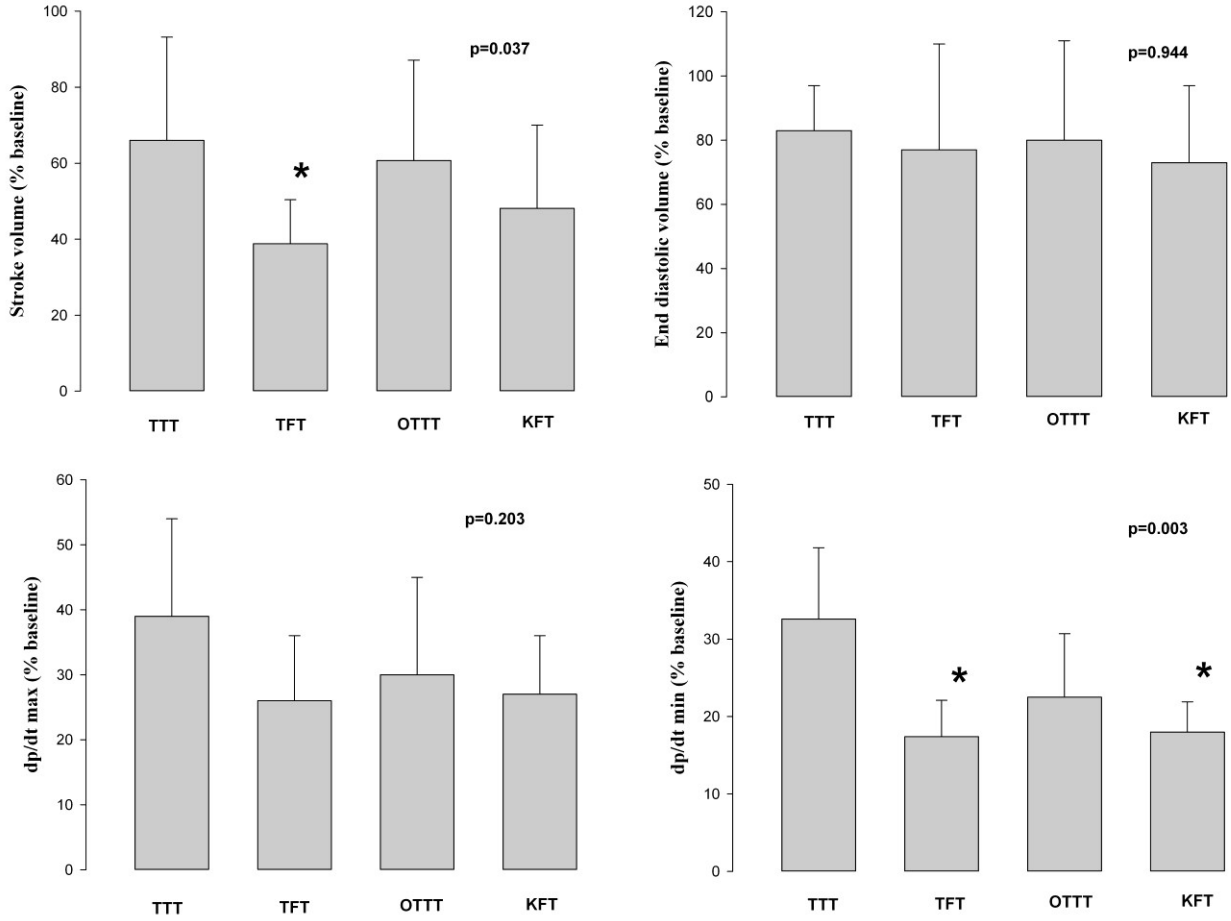

Figure 12 Percentage changes of stroke volume, end diastolic volume, maximal rate of rise of left ventricular pressure (dp/dt max), and minimum rate of change of ventricular pressure (dp/dt min) to baseline. Encircling two-thumb-technique (TTT), two-finger-technique (TFT), knocking-fingers technique (KFT), over-the-head two-thumb encircling technique (OTTT). * Significantly different from TTT ($p<0.05$, Tukey). Reproduced from (1) with permission of publisher (Donna Ding)

5.1.4 Respiratory parameters

Table 3 Respiratory parameters from start until the end of CPR. Encircling two-thumb-technique (TTT), two-finger-technique (TFT), knocking-fingers technique (KFT), over-the-head two-thumb encircling technique (OTTT)

	TTT (n=7)	TFT (n=7)	KFT (n=7)	OTTT (n=7)	p-value
Tidal volume (mL/kg)	9.5 (3.6)	8.5 (3.5)	7.8 (2.4)	7.6 (1.9)	0.611
Minute Ventilation (mL/kg/min)	855 (320)	763 (313)	702 (2019)	680 (172)	0.432
Peak Inspiratory Flow (L/min)	5.7 (1.6)	5.5 (0.8)	5.0 (0.9)	4.7 (0.3)	0.291
Peak Expiration Flow (L/min)	-9.1 (1.5)	-8.7 (3.0)	-9.3 (1.8)	-7.4 (1.7)	0.337
Peak Inflation Pressure (cm H_2O)	29 (10)	30 (13)	30 (11)	28 (12)	0.996
Positive End Expiratory Pressure (cm H_2O)	29 (10)	30 (13)	30 (11)	28 (12)	0.996
End-tidal CO_2 (mmHg)	2.6 (2.8)	1.6 (1.2)	1.6 (1.0)	1.9 (1.7)	0.676
Rate (/min)	90 (1)	90 (1)	90 (1)	90 (1)	1.000

Data are presented as mean (SD), Rate=Ventilation and number of chest compression, which corresponds with number of ventilations per min

5.1.5 Cerebral tissue oxygenation

The cerebral tissue oxygen saturation at baseline was 40 (39-43) %. During hypoxia and asphyxia the value dropped to 15%. There was no rise in cerebral tissue oxygen saturation above 15% during CPR regardless of the CC technique used. The lowest possible displayed value is 15% which is a limitation of the device.

5.1.6 Chest compression force and depth

The applied force with TTT was 1.30 (0.54) kg, with TFT was 1.23 (0.62) kg, with the KFT was 1.29 (0.66) kg, and with the OTTT was 1.04 (0.51) kg during CC (p=0.594).

The applied CC depth with TTT was 3.3 (1.0) cm, with TFT was 2.3 (1.0) cm, with the KFT was 2.4 (1.1) cm, and with the OTTT was 3.3 (1.6) cm during CC (p=0.325).

The anterior-posterior CC depth fraction was 38 (0) % with TTT, 25 (0) % with TFT, 26 (0) % with the KFT, and 38 (0) % with the OTTT during CC.

5.1.7 Summary

5.1.7.1 Primary outcome

There were no differences in carotid blood flow (ml/min/kg) or percentage changes of mean carotid blood flow to baseline between the groups. The rise of carotid blood flow per CC was significantly faster with the TTT and OTTT compared to the TFT and the KFT.

5.1.7.2 Hemodynamic parameter

To summarize, i) there were no differences in blood pressure, end diastolic volume, and maximal rate of rise of left ventricular pressure between the CC techniques, ii) using the TFT resulted in significantly lower stroke volume compared to the TTT, iii) there were no differences in stroke volume between the TTT, the KFT, and the OTTT encircling technique, iv) using the

TFT and the KFT resulted in significantly lower minimum rate of change of ventricular pressure compared to the TTT.

5.1.7.3 Respiratory parameter

There were no differences in respiratory parameter including, tidal volume, minute ventilation, peak inspiratory flow, peak expiration flow, peak inflation pressure, positive end expiratory pressure, end-tidal CO2, and respiratory rate between the different CC techniques during CPR.

5.1.7.4 Cerebral tissue oxygenation

None of the used CC techniques resulted in a rise of cerebral tissue oxygen saturation above 15%.

5.1.7.5 Chest compression force and depth

There were no differences in CC force and depth between the different CC techniques during CPR.

6 Discussion

To improve outcomes of newborn infants who receive CPR in the delivery room is from worldwide interest. Providing an improved CC technique during neonatal CPR would be easy to implement and is feasible in high- and low resource environments. However, there is lack of data about different CC techniques during neonatal CPR. Current neonatal resuscitation guidelines state to rather use the TTT than the TFT because of improved blood pressure and less provider fatigue with the TTT(4). However, this recommendation is based on manikin studies and expert opinion rather than on human data.

There are several manikin studies that investigated different CC techniques in regard to rescuers fatigue, CC technique feasibility, correct finger position ,applied CC depth and CC force(131–137). However, there are no animal or clinical studies reporting on the effect of different CC techniques on circulation or newborn infants' outcome.

To our knowledge no study has compared different CC techniques during neonatal CPR and their effect on hemodynamic and respiratory parameter, applied CC depth and CC force in an animal experiment. The results of this study can be summarized as follows: i) The rise of carotid blood flow per CC was significantly faster with the TTT and OTTT compared to the other techniques, ii) the TTT resulted in significantly higher changes of stroke volume compared to the TFT, iii) the TFT and the KFT resulted in significantly lower minimum rate of change of ventricular pressure compared to the TTT, iv) there were no differences in other examined hemodynamic or respiratory parameter as well as in cerebral tissue oxygen saturation, and v) there were no significant differences in applied CC depth and CC force between the different CC techniques.

6.1 Changes in carotid blood flow

Carotid blood flow, as a surrogate for cardiac output, increases with manoeuvres that increase intrathoracic pressure including greater CC depth, faster CC rate, and ventilation strategies with higher pressures(97,99,107,183). In this study, no differences in carotid blood flow or percentage changes of mean carotid blood flow to baseline between the groups were observed. However, the rise of carotid blood flow (mL/min/s) during a single CC was significantly higher with the TTT and OTTT compared to the TFT and the KFT. This implicates that blood possibly gets ejected faster from the left heart when using the TTT or the OTTT compared to the other two techniques; however, this did not influence further blood flow.

The absent increase of carotid blood flow despite faster rise of carotid blood flow during CC might be explained by the applied CC rate. The physiological HR of newborn infants and piglets is higher than the recommended 90/min. A higher CC rate results in a decreased time interval between the compressions which might have kept the starting advantage of the fast left ventricular ejection when using the TTT/OTTT. This could have resulted in a more constant and increased flow.

The faster rise of carotid blood flow might be explained by a difference in duty cycle (i.e., compression duration divided by total cycle time) between the CC techniques. A lower duty cycle (faster compression and slower decompression) leads to increased hemodynamic parameter (e.g., coronary perfusion pressure and arterial blood pressure)(213). Dean *et al* demonstrated in 2-week old piglets that a duty cycle of 30% compared to 60% (delivered with a pneumatic chest compression machine) resulted in higher left ventricular blood flow, aortic pressure and improved cerebral perfusion(214). Noteworthy, a manikin study reported on differences in duty cycle comparing neonatal CPR with the TTT and the TFT(215). They defined a duty cycle of 30–50% as most effective and reported that duty cycle compliance during manikin infant CPR was 0% of all TTT compressions and 23% of all TFT compressions(215). The mean (SD) duty cycle was 61 (8)% and 53 (8)% with the TTT and the TFT ($p<0.001$)(215). However, we did not measure the duty cycle during the experiment, hence, we cannot rule out an impact of different duty cycles when providing the TTT/OTTT compared to the TFT/KFT.

Animal studies reported that the position of the left ventricle and therefore the CC position influences hemodynamic parameter during CPR(216,217). Anderson *et al* demonstrated in an adult piglet model that closed CC directed over the left ventricle resulted in improved hemodynamics and a higher rate of return of spontaneous circulation(217). Further on, they reported that left ventricular position changes during cardiac arrest compared to the pre-arrest baseline(216). Manikin studies as well as a randomized clinical trial in which the TTT was compared with the TFT showed that using the TTT resulted in a higher proportion of correct placements(138,139). Especially in preterm infants there were great differences in the proportion of correct placements between the TFT and the TTT. However, the newborn piglets used for this study had a median (range) weight of 2.0 (1.8-2.1) kg. As we did not mark the correct finger position on the piglets chest we can only speculate whether the finger position changed during the experiment and may have influenced the cardiac output, although CC were always performed by the same provider. Hwang *et al* demonstrated that hands position and the area of maximal compression during adult CPR affect the outflow of the left ventricle(218). This is caused by varying degrees of narrowing the left ventricular outflow tract which was directly observed with transesophageal echocardiography during resuscitation(218). We

performed all four CC techniques in a random order in each piglet; hence, left ventricular position changes during CPR as reported may occurred due to the duration of CPR.

The KFT was compared to the TFT and the TTT in few manikin studies until now(140,141). Interestingly, using the KFT seems to be similar in CC quality as the TTT and the TFT, however, it was rated as most difficult from the participants(140,141). While the slope rise of carotid blood flow was similar between TTT and OTTT, using the KFT resulted in similar means as the TFT. However, the KFT resulted in a wide range of carotid blood flow slope rise and it reached a slope rise above those of TTT and OTTT. Such fast slope rises were not generated using the TFT (Figure 1). Although there were significant differences in slope rise of carotid blood flow between the KFT and the TTT/OTTT in this study, the KFT might have the potential to be as effective as the TTT if the CC provider complete simulation trainings and gets familiar to this new technique.

6.2 Changes in hemodynamic parameter

The minimum rate of change of left ventricular pressure (LV dp/dt min) indicates end-ejection and is widely used as a marker for the start of left ventricular relaxation(219). Ventricular relaxation is an active and dynamic process that starts at mid-ejection, includes the entire isovolumic relaxation phase, and ends with the diastolic filling phase(219). LV dp/dt min occurs shortly after aortic valve closure(219). Maximum rate of change of left ventricular pressure (LV dp/dt max) is a surrogate for contractility and occurs before aortic valve closure(220,221). LV dp/dt is a surrogate for cardiac function, dependents on load and HR and is related to changes in left ventricular systolic volume, contractility, and coronary flow(222).

In this study LV dp/dt min was similar with the TTT and the OTTT. However, the TFT and the KFT resulted in significantly lower LV dp/dt min compared to the TTT indicating worse ventricular relaxation. Since the HR did not differ between the groups during CPR we speculate that using the TFT/KFT did not generate adequate compression to provide as much load as the TTT to the heart. This agrees with the findings that changes of stroke volume and slope rise of carotid blood flow differed significantly between the TFT/KFT and the TTT/OTTT.

Although there are hints that left ventricular ejection might have been superior using the TTT/OTTT compared to the TFT/KFT, this did not result in significant differences of other hemodynamic parameters including absolute stroke volume, carotid blood flow, and blood pressure. Although absolute values of stroke volume were lower with the TFT/KFT compared to the TTT/OTT this did not reach statistical significance. One explanation for the absent differences in stroke volume, carotid blood flow, and blood pressure might be that the

differences in slope rise and LV dp/dt min were very small between the groups. Another explanation might be the used ventilation strategy. It was shown that inspiratory pressures have a slight effect on systolic function and a more pronounced effect on diastolic function(223). We used sustained inflations with a peak inspiratory pressure of 30 cmH_2O, which might have compensated for the different CC techniques.

In a randomized crossover manikin study was reported that the TTT produced higher blood- and pulse pressures when compared with TFT during prolonged CPR(132). However, the authors used an experimental circuit consisted of a modified manikin with a fixed-volume arterial system attached to a neonatal monitor via an arterial pressure transducer and provided a 5:1 C:V ratio with a CC rate of 100/min. The used experimental model, which is not as close as to a newborn infant as a newborn piglet is, and the difference in used compression/ventilation strategies might explain the different results compared to the present study.

6.3 Changes in respiratory parameter

There are very limited data about the effect of CC techniques on respiratory parameter. Udassi *et al* reported in a randomized manikin study, that using the TTT compared to the TFT the CC provider required 0.6 sec longer time to deliver two breaths when using the TTT(134). They used a 30:2 C:V ratio, performed single rescuer CPR and provided mouth-to-mouth breaths; however, there were no differences in number of ventilations and percentage of effective breaths(134). Similar, another manikin study showed no differences in total number of ventilations comparing the OTTT (+ bag-valve mask ventilation) with the TFT (+pocket-mask ventilation)(143). The authors reported that the volume of each ventilation was significantly higher in the OTTT group compared to the TFT; however, one must consider that different ventilation devices were used which might have influenced the results(143). In contrast to the abovementioned studies, Jung *et al* reported that the total number of ventilations was higher with the KFT and TFT compared with the TTT, while the ratio of correct ventilations was similar(140).

To the best of our knowledge there are no animal experiments investigating the effect of different CC techniques on respiratory parameters. Recently, Lopez *et al* compared the effectiveness of manual and mechanical CC with a thumper device in a pediatric cardiac arrest animal model and reported on no significant differences in end-tidal CO_2(224). However, neither the manikin studies nor the animal study reported on respiratory parameter including minute ventilation, tidal volume, gas flow, or ventilation pressures.

As expected, in this study there were no differences in respiratory parameter observed between the four CC techniques. Using distending pressure with a constant high pressure (30 cmH_2O) for 30 sec before 1 sec pause during continuous CCs lead to an increase of intrathoracic pressure and consequently result in passive ventilation(125). Previous studies demonstrated that the CC+SI approach might be an optimized ventilation strategy during neonatal CPR. It was reported that CC+SI compared to other ventilation strategies resulted in improved respiratory and hemodynamic parameter, time to return of spontaneous circulation, and survival(125–127,129). We suggest that using CC+SI during this experiment could have been so effective, that the impact of various CC techniques on respiratory parameter was negligible. We can only speculate whether using other ventilation strategies in combination with different CC techniques would influence respiratory parameter. Using a 3:1 C:V ratio might have resulted in more significant differences between the TTT/OTTT and the KFT/TFT. However, we chose the CC+SI approach to provide continuous CC over a predefined time to minimize interruption of coronary perfusion and ejection.

6.4 Chest Compression force and depth

There were no significant differences in applied CC depth and CC force between the different CC techniques. However, due to the small chest size of newborn infants and piglets even very small deviations of CC depth and CC force might have an effect on CC quality. It was reported that 3cm in term and 2.5 cm in preterm infants correspond to 33% anterior-posterior CC depth(96).

A previous animal experiment investigated CC depth with an automated CC machine in newborn piglets and demonstrated that an anterior-posterior chest diameter of 25% resulted in a CC depth of 2.0–2.3 cm while 40% resulted in 3.2-3.6 cm CC depth(97). In another newborn piglet study a CC depth ranging from 2.0-4.1 cm represented an anterior-posterior CC depth between 25-40%(99). It was reported that a 40% anterior-posterior CC depth resulted in the highest tidal volume, minute ventilation, cardiac output and arterial blood pressure(97)(99). In the present study the anterior-posterior CC depth was mean 3.3 cm with TTT and the OTTT while it was about 1 cm shallower with the TFT and the KFT. As previous studies showed that even 1 cm difference in CC depth during newborn piglet CPR affect hemodynamic parameter, the difference in CC depth between TTT/OTTT and TFT/KFT should not be underestimated (although not statistically significant different).

In addition, current neonatal resuscitation guidelines recommend a CC depth of 33% anterior-posterior chest diameter during neonatal CPR. Noteworthy, the anterior-posterior CC depth with the TTT/OTTT (38%) was closer to the recommended CC depth compared to the

TFT/KFT (25-26%). This is in concordance with a randomized manikin study by Jung *et al* who demonstrated that the ratio of correct CC depth was the highest with the TTT with 100 (99–100)% followed by the KFT with 99 (93–100)%, and the TFT with 92 (53–98)% (p<0.001)(140). Similar, Yang *et al* compared a novel flexed two finger technique, where the distal interphalangeal joint and proximal interphalangeal joint of the dominant hand flexed and CC performed with the dorsum of the phalanges (similar to the KFT) with the TTT and the TFT(144). They reported that the ratio of the adequate compression depth was highest with the TTT, followed by the novel flexed two finger technique and TFT(144). In another manikin study was reported that the KFT was the one with the lowest percentage of correct CC depth although, in all three techniques (TTT, TFT, and KFT) median depth compressions were reached according to the recommended standards(141). However, there is only one study investigating CC depth with the OTTT(143). They demonstrated that the performance of OTTT resulted in greater CC depth (mean (SD) 4.3 (0.1) cm versus 4.1 (0.1) cm, p<0.001) and higher proportion of effective CC compared to the TFT (mean (SD) 99 (6)% versus 93 (15)%, p=0.019)(143). The present study is the first comparing the TTT with the OTTT. There are no differences in applied CC depth between the TTT and the OTTT so we suggest that the OTTT is comparable to the TTT concerning CC depth. In addition, the KFT seems to be comparable to the TFT which is in concordance with results from manikin studies.

While the absolute values of applied CC depth widely differed between the CC techniques, the range of applied CC force was very small between the groups. In this study a greater CC depth was achieved with the same force using the TTT/OTTT than with the KFT/TFT. This is in contrast to manikin studies where higher pressures and finger strength were applied with the TTT compared to the TFT resulting in greater CC depths(134,135). However, the chest of a manikin is stiffer than those of piglets or newborn infants and therefore more force and finger strength is needed to provide CCs. In previous animal studies (using a plunger with an automated CC machine) higher forces than in this study with all four investigated CC techniques were needed to achieve the recommended CC depth(99,107). This could be explained by the smaller finger-chest contact surface than with the V-shaped CC machine plunger. Jung *et al* demonstrated that the area of CC was the widest with the TTT, followed by the TFT and KFT(140). However, we speculate that the contact surface size difference between the CC techniques is so small that they do not affect CC force during manual CPR in newborn infants.

6.5 Cerebral tissue oxygenation

There was no rise in cerebral tissue oxygen saturation above 15% during CPR, regardless of the CC technique used. However, the lowest possible displayed value is 15% which is a limitation of the device. A case series reported that cerebral tissue oxygen saturation (measured with the same device that was used in this study) in infants with cardiac arrest was 15% in many cases at the beginning of pediatric CPR(225). However, an abrupt increase was observed in those who achieved return of spontaneous circulation(225). The patients who did not achieve return of spontaneous circulation had lower minimum cerebral tissue oxygen saturation values and the percentage of median time with values under 30% were significantly higher(225). However, the cause for cardiac arrest in those infants was not birth asphyxia. This study was designed to investigate different CC techniques not expecting the piglets to achieved return of spontaneous circulation. Hence, cerebral tissue oxygen saturation behaved as expected during the experiment. Besides providing baseline data of used animals, cerebral tissue oxygen saturation is rather used to monitor cerebral oxygen kinetics after return of spontaneous circulation then during cardiac arrest and CPR.

6.6 Manikin versus animal studies

Both, manikin studies and animal experiments are valuable methods to investigate different interventions during neonatal CPR. However, the method must fit the aim of the study, hence, advantages and disadvantages of the used model must be considered. While manikin studies are often designed to include many participants to receive results for a population of CC providers, in animal studies CC should preferably be provided by the same person in every experiment to generate rigor results and avoid bias. Hence, the aim and investigated parameters differ between methods used to investigate different CC techniques.

The following parameters were recently investigated in manikin studies when comparing different CC techniques to each other: CC depth, CC force, fatigue, proportion of right hand position and correct compressions, recoil, and participant's preference(131–137). Those parameters are particularly interesting if one wants to study the feasibility of different CC techniques. However, it provides only uncertain and indirect information of the effect on a living mechanism and patient's outcome. Manikin studies are more about investigating the mechanics, performance, and ease of use of the CC technique. In contrast, the focus of animal studies should be on examining the influence of the CC techniques on a living object and intact circulation. However, animal experiments are not only advantageous about investigating interventions on a living circulating organism, but also of examining the CC technique on real

tissue, which closely mimics those of a newborn infant. Therefore, it is reasonable to examine not only hemodynamic parameters such as carotid blood flow and blood pressure, but also CC depth and CC force. However, animal studies are more complex to perform, need more resources and are way more expensive compared to manikin studies. Further on, expertise in performing animal experiments and ethical approval is necessary.

6.7 Strengths and limitations

A great strength of this study is that we used an established animal model of severe asphyxia which closely simulates delivery room events(2). The asphyxiated newborn piglet model is the best to investigate CC due to the similarity in anatomy and circulation to newborn infants. For the first time, different CC techniques were applied to real tissue instead of a manikins' stiff plastic chest reporting on CC depth and CC force. Another strength is the used setting including continuous monitoring which provides detailed information about blood flow, circulation and cardiac function. In addition, in this study a total of four different CC techniques were compared to each other, whereas in manikin studies mostly two various CC techniques were investigated. This is also the first time that the TTT was compared to the OTTT. To the best of our knowledge, this is the first animal study investigating different CC techniques and it was shown that it is feasible to use different CC techniques in the newborn asphyxiated piglet model.

There are certain limitations to this study. The piglets already underwent neonatal transition and therefore needed to be anaesthetized and intubated. Although the used model closely mimics a newborn infant the results cannot be fully translated to the human body. Another limitation is that we performed each CC technique in each piglet; however, we used a randomized order to minimize bias. In this study the piglets did not achieve return of spontaneous circulation, hence we can only speculate about the effect on the outcome when using different CC techniques. Further on, the CC+SI approach was used which might have influenced the results. Using a 3:1 C:V ratio might have yield different results.

6.8 Research gaps

Current recommendations on CC technique during neonatal CPR are based on manikin studies and expert opinion. Manikin studies are an adequate method to investigate CC providers' performance and CC technique mechanics, however, only very limited information can be gained about the effect on the organism and the outcome. This study was an important

first step to investigating different CC techniques in animal models. It was shown that investigating CC techniques in an asphyxiated newborn piglet model is feasible and provide adequate results.

Future animal studies should focus on investigating different CC techniques in combination with different CC rates and/or ventilation strategies. In this study a faster rise in carotid blood flow and indirect signs for a better ejection were observed with the TTT/OTTT, hence, the effect on higher CC rates with the different CC techniques might provide more significant results. In a next step the effect of different CC techniques on short term outcomes including time to return of spontaneous circulation and survival rate should be investigated before conducting clinical studies in newborn infants.

7 Conclusion

This study demonstrated that investigating different CC techniques in an asphyxiated newborn piglet model is feasible. The effect on hemodynamic parameter was comparable between the TTT and the OTTT, and between the TFT and KFT. There were differences in some hemodynamic parameters such as faster rise of carotid blood flow, higher changes of stroke volume, and higher minimum rate of change of ventricular pressure suggesting a slightly better left ventricular ejection with the TTT/OTTT compared to the TFT/KFT. However, those differences did not result in improved carotid blood flow, absolute stroke volume, or blood pressure within all four CC techniques.

Although there were no significant differences in applied CC force and CC depth between the different CC techniques, the TTT/OTTT resulted in 1 cm deeper compressions than the TFT/KFT did. The anterior-posterior CC depth was closer to the currently recommended CC depth with the TTT/OTTT compared with the TFT/KFT.

Further animal studies are warranted to investigate the outcome of CC techniques with different CC rates, compression to ventilation ratios, and ventilation strategies before conducting clinical studies in newborn infants.

8 References

1. Bruckner M, Neset M, O'Reilly M, Lee T, Cheung P, Schmölzer GM. Four Different Finger Positions and Their Effects on Hemodynamic Changes during Chest Compression in Asphyxiated Neonatal Piglets. Children. 2023 Feb 1;10(2):283.
2. Cheung P-Y, Gill RS, Bigam DL. A Swine Model of Neonatal Asphyxia. J Vis Exp. 2011 Oct 11;(56):1–8.
3. Wyckoff MH, Wyllie J, Aziz K, de Almeida MF, Fabres JW, Fawke J, et al. Neonatal Life Support 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Resuscitation. 2020 Nov;156(16 SUPPL. 2):A156–87.
4. Aziz K, Lee HC, Escobedo MB, Hoover A V., Kamath-Rayne BD, Kapadia VS, et al. Part 5: Neonatal Resuscitation: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020 Oct 20;142(16_suppl_2):S524–50.
5. Madar J, Roehr CC, Ainsworth S, Ersdal H, Morley C, Rüdiger M, et al. European Resuscitation Council Guidelines 2021: Newborn resuscitation and support of transition of infants at birth. Resuscitation. 2021 Apr;161:291–326.
6. Barber CA, Wyckoff MH. Use and Efficacy of Endotracheal Versus Intravenous Epinephrine During Neonatal Cardiopulmonary Resuscitation in the Delivery Room. Pediatrics. 2006 Sep 1;118(3):1028–34.
7. Shah PS, Shah P, Tai KFY. Chest compression and/or epinephrine at birth for preterm infants <32 weeks gestational age: matched cohort study of neonatal outcomes. J Perinatol. 2009 Oct 25;29(10):693–7.
8. 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. Am J Obstet Gynecol. 2007 May;196(5):463.e1-463.e5.
9. Hooper SB, Harding R. Fetal lung liquid: a major determinant of the growth and functional development of the fetal lung. Clin Exp Pharmacol Physiol. 1995;22(4):235–41.
10. Bruckner M, Schmölzer GM. Physiologic Changes during Neonatal Transition and the Influence of Respiratory Support. Clin Perinatol. 2021 Dec;48(4):697–709.
11. Hooper SB, Te Pas AB, Kitchen MJ. Respiratory transition in the newborn: A three-phase process. Arch Dis Child Fetal Neonatal Ed. 2016;101(3):F266–71.

12. Olver RE, Walters D V, M. Wilson S. Developmental Regulation of Lung Liquid Transport. Annu Rev Physiol. 2004;66(1):77–101.

13. Hooper SB, Kitchen MJ, Wallace MJ, Yagi N, Uesugi K, Morgan MJ, et al. Imaging lung aeration and lung liquid clearance at birth. FASEB J. 2007;21(12):3329–37.

14. Siew ML, Wallace MJ, Kitchen MJ, Lewis RA, Fouras A, Te Pas AB, et al. Inspiration regulates the rate and temporal pattern of lung liquid clearance and lung aeration at birth. J Appl Physiol. 2009;106(6):1888–95.

15. Schmölzer GM, Hooper SB, Wong C, Kamlin COF, Davis PG. Exhaled carbon dioxide in healthy term infants immediately after birth. J Pediatr. 2015;166(4):844-849.e3.

16. Blank DA, Gaertner VD, Kamlin COF, Nyland K, Eckard NO, Dawson JA, et al. Respiratory changes in term infants immediately after birth. Resuscitation. 2018 Sep;130:105–10.

17. Dawson JA, Kamlin COF, Vento M, Wong C, Cole TJ, Donath SM, et al. Defining the Reference Range for Oxygen Saturation for Infants After Birth. Pediatrics. 2010 Jun 1;125(6):e1340–7.

18. te Pas AB, Wong C, Kamlin COF, Dawson JA, Morley CJ, Davis PG. Breathing Patterns in Preterm and Term Infants Immediately After Birth. Pediatr Res. 2009 Mar;65(3):352–6.

19. Taguchi Y, Hosono S, Kayama K, Kato R, Hine K, Nagano N, et al. Target value of oxygen saturation during the first 10 min after birth. Pediatr Int. 2017;59(10):1064–8.

20. Vento M, Saugstad OD. Targeting Oxygen in Term and Preterm Infants Starting at Birth. Clin Perinatol. 2019;46(3):459–73.

21. Padilla-Sánchez C, Baixauli-Alacreu S, Cañada-Martínez AJ, Solaz-García Á, Alemany-Anchel MJ, Vento M. Delayed vs Immediate Cord Clamping Changes Oxygen Saturation and Heart Rate Patterns in the First Minutes after Birth. J Pediatr. 2020 Dec;227:149-156.e1.

22. Swanson JR, Sinkin RA. Transition from Fetus to Newborn. Pediatr Clin North Am. 2015;62(2):329–43.

23. Morton SU, Brodsky D. Fetal Physiology and the Transition to Extrauterine Life. Clin Perinatol. 2016 Sep;43(3):395–407.

24. Tan CMJ, Lewandowski AJ. The Transitional Heart: From Early Embryonic and Fetal Development to Neonatal Life. Fetal Diagn Ther. 2020;47(5):373–86.

25. Rainaldi MA, Perlman JM. Pathophysiology of Birth Asphyxia. Clin Perinatol [Internet]. 2016;43(3):409–22. Available from: http://dx.doi.org/10.1016/j.clp.2016.04.002

26. Lara-Cantón I, Solaz A, Parra-Llorca A, García-Robles A, Millán I, Torres-Cuevas I, et al. Oxygen Supplementation During Preterm Stabilization and the Relevance of the First 5 min After Birth. Front Pediatr. 2020;8(January):1–7.

27. Friedman AH, Fahey JT. The transition from fetal to neonatal circulation: normal responses and implications for infants with heart disease. Semin Perinatol. 1993 Apr;17(2):106–21.

28. Wu TW, Azhibekov T, Seri I. Transitional hemodynamics in preterm neonates: Clinical relevance. Pediatr Neonatol. 2016;57(1):7–18.

29. Gill AW. Postnatal cardiovascular adaptation. Arch Dis Child Fetal Neonatal Ed. 2018;

30. Anderson PAW. The heart and development. Semin Perinatol. 1996;20(6):482–509.

31. Crossley KJ, Allison BJ, Polglase GR, Morley CJ, Davis PG, Hooper SB. Dynamic changes in the direction of blood flow through the ductus arteriosus at birth. J Physiol. 2009 Oct 1;587(19):4695–704.

32. Van Vonderen JJ, Te Pas AB, Kolster-Bijdevaate C, Van Lith JM, Blom NA, Hooper SB, et al. Non-invasive measurements of ductus arteriosus flow directly after birth. Arch Dis Child Fetal Neonatal Ed. 2014;99(5):408–12.

33. Vrancken SL, van Heijst AF, de Boode WP. Neonatal Hemodynamics: From Developmental Physiology to Comprehensive Monitoring. Front Pediatr. 2018 Apr 5;6(April):1–15.

34. Clyman RI. Mechanisms Regulating the Ductus Arteriosus. Neonatology. 2006;89(4):330–5.

35. Deshpande P, Baczynski M, McNamara PJ, Jain A. Patent ductus arteriosus: The physiology of transition. Semin Fetal Neonatal Med. 2018;23(4):225–31.

36. Jain A, Mohamed A, El-Khuffash A, Connelly KA, Dallaire F, Jankov RP, et al. A Comprehensive Echocardiographic Protocol for Assessing Neonatal Right Ventricular Dimensions and Function in the Transitional Period: Normative Data and Z Scores. J Am Soc Echocardiogr. 2014 Dec;27(12):1293–304.

37. Semberova J, Sirc J, Miletin J, Kucera J, Berka I, Sebkova S, et al. Spontaneous Closure of Patent Ductus Arteriosus in Infants ≤1500 g. Pediatrics. 2017 Aug;140(2):e20164258.

38. Schneider H. Oxygenation of the placental–fetal unit in humans. Respir Physiol Neurobiol. 2011 Aug;178(1):51–8.

39. Michel A, Lowe NK. The Successful Immediate Neonatal Transition to Extrauterine Life. Biol Res Nurs. 2017;19(3):287–94.

40. Apgar V. A proposal for a new method of evaluation of the newborn infant. Curr Res Anesth Analg. 32(4):260–7.

41. Dawson JA, Kamlin COF, Wong C, Te Pas AB, Vento M, Cole TJ, et al. Changes in heart rate in the first minutes after birth. Arch Dis Child Fetal Neonatal Ed. 2010;95(3).

42. Bruckner M, Lista G, Saugstad OD, Schmölzer GM. Delivery room management of asphyxiated term and near-term infants. Neonatology. 2021;118(4):487–99.

43. Rainaldi MA, Perlman JM. Pathophysiology of Birth Asphyxia. Clin Perinatol. 2016 Sep;43(3):409–22.

44. Martin RJ, Fanaroff AA, Walsh MC. Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. 10th ed. Elsevier Health Sciences; 2014.

45. Mir IN, Johnson-Welch SF, Nelson DB, Brown LS, Rosenfeld CR, Chalak LF. Placental pathology is associated with severity of neonatal encephalopathy and adverse developmental outcomes following hypothermia. Am J Obstet Gynecol. 2015 Dec;213(6):849.e1-849.e7.

46. Herrera CA, Silver RM. Perinatal Asphyxia from the Obstetric Standpoint: Diagnosis and Interventions. Clin Perinatol. 2016;43(3):423–38.

47. Rani S, Chawla D, Huria A, Jain S. Risk factors for perinatal mortality due to asphyxia among emergency obstetric referrals in a tertiary hospital. Indian Pediatr. 2012;49(3):191–4.

48. Himmelmann K, Ahlin K, Jacobsson B, Cans C, Thorsen P. Risk factors for cerebral palsy in children born at term. Acta Obstet Gynecol Scand. 2011;90(10):1070–81.

49. Marshall S, Lang AM, Perez M, Saugstad OD. Delivery room handling of the newborn. J Perinat Med. 2019 Dec 18;48(1):1–10.

50. Kara T, Narkiewicz K, Somers VK. Chemoreflexes - physiology and clinical implications. Acta Physiol Scand. 2003 Mar;177(3):377–84.

51. Calvert JW, Zhang JH. Pathophysiology of an hypoxic–ischemic insult during the perinatal period. Neurol Res. 2005 Apr 19;27(3):246–60.

52. Saugstad OD, Aune D. Optimal Oxygenation of Extremely Low Birth Weight Infants: A Meta-Analysis and Systematic Review of the Oxygen Saturation Target Studies. Neonatology. 2014;105(1):55–63.

53. Lorente-Pozo S, Parra-Llorca A, Núñez-Ramiro A, Cernada M, Hervás D, Boronat N, et al. The Oxygen Load Supplied during Delivery Room Stabilization of Preterm Infants Modifies the DNA Methylation Profile. J Pediatr. 2018 Nov;202:70-76.e2.

54. Kapadia V, Rabi Y, Oei JL. The Goldilocks principle. Oxygen in the delivery room: When is it too little, too much, and just right? Semin Fetal Neonatal Med. 2018 Oct;23(5):347–54.

55. Davis PG, Tan A, O'Donnell CP, Schulze A. Resuscitation of newborn infants with 100% oxygen or air: a systematic review and meta-analysis. Lancet. 2004 Oct;364(9442):1329–33.

56. Wall SN, Lee AC, Niermeyer S, English M, Keenan WJ, Carlo W, et al. Neonatal resuscitation in low-resource settings: What, who, and how to overcome challenges to scale up? Int J Gynecol Obstet. 2009 Oct;107(Supplement):S47–64.

57. Versantvoort JMD, Kleinhout MY, Ockhuijsen HDL, Bloemenkamp K, De Vries WB, Van Den Hoogen A. Helping Babies Breathe and its effects on intrapartum-related stillbirths and neonaatal mortality in low-resource settings: A systematic review. Arch Dis Child. 2020;105(2):127–33.

58. 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 Feb;85(2):238–43.

59. Foglia EE, Jensen EA, Wyckoff MH, Sawyer T, Topjian A, Ratcliffe SJ. Survival after delivery room cardiopulmonary resuscitation: A national registry study. Resuscitation. 2020 Jul;152:177–83.

60. Perlman JM, Wyllie J, 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. Vol. 132, Circulation. 2015. 204–241 p.

61. O'Donnell CPF, Kamlin COF, Davis PG, Carlin JB, Morley CJ. Interobserver variability of the 5-minute Apgar score. J Pediatr. 2006 Oct;149(4):486–9.

62. Kamlin COF, O'Donnell CPF, Everest NJ, Davis PG, Morley CJ. Accuracy of clinical assessment of infant heart rate in the delivery room. Resuscitation. 2006 Dec;71(3):319–21.

63. Hawkes G, Hawkes C, Kenosi M, Demeulemeester J, Livingstone V, Ryan C, et al. Auscultate, palpate and tap: time to re-evaluate. Acta Paediatr. 2016 Feb;105(2):178–82.

64. Xu J, Li C, Zheng L, Han F, Li Y, Walline J, et al. Pulse Oximetry: A Non-Invasive, Novel Marker for the Quality of Chest Compressions in Porcine Models of Cardiac Arrest. Lazzeri C, editor. PLoS One. 2015 Oct 20;10(10):e0139707.

65. Fu Y, Yin L, Seery S, Dai J, Zhu H, Jin K, et al. Pulse rate as an alternative, real-time feedback indicator for chest compression rate: a porcine model of cardiac arrest. J Clin Monit Comput. 2021 Oct 11;35(5):1159–67.

66. Phillipos E, Solevåg AL, Pichler G, Aziz K, Van Os S, O'Reilly M, et al. Heart rate assessment immediately after birth. Neonatology. 2016;109(2):130–8.

67. Baik N, Urlesberger B, Schwaberger B, Freidl T, Schmölzer GM, Pichler G. Cardiocirculatory monitoring during immediate fetal-to-neonatal transition: A systematic qualitative review of the literature. Neonatology. 2015;107(2):100–7.

68. Katheria A, Rich W, Finer N. Electrocardiogram Provides a Continuous Heart Rate Faster Than Oximetry During Neonatal Resuscitation. Pediatrics. 2012 Nov 1;130(5):e1177–81.

69. Sillers L, Handley SC, James JR, Foglia EE. Pulseless Electrical Activity Complicating Neonatal Resuscitation. Neonatology. 2019;115(2):95–8.

70. Luong D, Cheung PY, Barrington KJ, Davis PG, Unrau J, Dakshinamurti S, et al. Cardiac arrest with pulseless electrical activity rhythm in newborn infants: A case series. Arch Dis Child Fetal Neonatal Ed. 2019;104(6):F572–4.

71. Solevåg AL, Luong D, Lee T-F, O'Reilly M, Cheung P-Y, Schmölzer GM. Non-perfusing cardiac rhythms in asphyxiated newborn piglets. PLoS One. 2019;14(4):e0214506.

72. Patel S, Cheung PY, Solevåg AL, Barrington KJ, Kamlin COF, Davis PG, et al. Pulseless electrical activity: A misdiagnosed entity during asphyxia in newborn infants? Arch Dis Child Fetal Neonatal Ed. 2019;104(2):F215–7.

73. Luong DH, Cheung P-Y, O'Reilly M, Lee T-F, Schmolzer GM. Electrocardiography vs. Auscultation to Assess Heart Rate During Cardiac Arrest With Pulseless Electrical Activity in Newborn Infants. Front Pediatr. 2018 Nov 27;6:1–4.

74. Yam CH, Dawson JA, Schmolzer GM, Morley CJ, Davis PG. Heart rate changes during resuscitation of newly born infants <30 weeks gestation: an observational study. Arch Dis Child - Fetal Neonatal Ed. 2011 Mar 1;96(2):F102–7.

75. Hooper SB, Fouras A, Siew ML, Wallace MJ, Kitchen MJ, Pas AB te., et al. Expired CO2 Levels Indicate Degree of Lung Aeration at Birth. Szyld E, editor. PLoS One. 2013 Aug 12;8(8):e70895.

76. Blank D, Rich W, Leone T, Garey D, Finer N. Pedi-cap color change precedes a significant increase in heart rate during neonatal resuscitation. Resuscitation. 2014 Nov;85(11):1568–72.

77. American Academy of Pediatrics and American Heart Association. Textbook of neonatal resuscitation. 7 edn. 2016.

78. Espinoza ML, Cheung P-Y, Lee T-F, O'Reilly M, Schmölzer GM. Heart rate changes during positive pressure ventilation after asphyxia-induced bradycardia in a porcine model of neonatal resuscitation. Arch Dis Child - Fetal Neonatal Ed. 2019 Jan;104(1):F98–101.

79. Schmölzer GM, Dawson JA, Kamlin COF, O'Donnell CPF, Morley CJ, Davis PG. Airway obstruction and gas leak during mask ventilation of preterm infants in the delivery room. Arch Dis Child Fetal Neonatal Ed. 2011;96(4):254–7.

80. Finer NN, Rich W, Wang C, Leone T. Airway Obstruction During Mask Ventilation of Very Low Birth Weight Infants During Neonatal Resuscitation. Pediatrics. 2009 Mar 1;123(3):865–9.

81. Wood FE, Morley CJ, Dawson JA, Kamlin COF, Owen LS, Donath S, et al. Improved techniques reduce face mask leak during simulated neonatal resuscitation: Study 2. Arch Dis Child Fetal Neonatal Ed. 2008;93(3).

82. Crawshaw JR, Kitchen MJ, Binder-Heschl C, Thio M, Wallace MJ, Kerr LT, et al. Laryngeal closure impedes non-invasive ventilation at birth. Arch Dis Child Fetal Neonatal Ed. 2018;103(2):F112–9.

83. Hooper SB, Kitchen MJ, Polglase GR, Roehr CC, Te Pas AB. The physiology of neonatal resuscitation. Curr Opin Pediatr. 2018;30(2):187–91.

84. Solevåg AL, Cheung P-Y, O'Reilly M, Schmölzer GM. A review of approaches to optimise chest compressions in the resuscitation of asphyxiated newborns. Arch Dis Child - Fetal Neonatal Ed. 2016 May;101(3):F272–6.

85. Mildenhall LFJ, Huynh TK. Factors modulating effective chest compressions in the neonatal period. Semin Fetal Neonatal Med. 2013 Dec;18(6):352–6.

86. Kouwenhoven W, Jude J, Knickerbocker G. CLOSED-CHEST CARDIAC MASSAGE. JAMA [Internet]. 1960 Jul 9;173(10):1064. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.1960.03020280004002

87. Rudikoff MT, Maughan WL, Effron M, Freund P, Weisfeldt ML. Mechanisms of blood flow during cardiopulmonary resuscitation. Circulation. 1980 Feb;61(2):345–52.

88. Werner JA, Greene HL, Janko CL, Cobb LA. Visualization of cardiac valve motion in man during external chest compression using two-dimensional echocardiography. Implications regarding the mechanism of blood flow. Circulation. 1981 Jun;63(6):1417–21.

89. Cipani S, Bartolozzi C, Ballo P, Sarti A. Blood flow maintenance by cardiac massage during cardiopulmonary resuscitation: Classical theories, newer hypotheses, and clinical utility of mechanical devices. J Intensive Care Soc. 2019 Feb 18;20(1):2–10.

90. Higano ST, Oh JK, Ewy GA, Seward JB. The Mechanism of Blood Flow During Closed Chest Cardiac Massage in Humans: Transesophageal Echocardiography Observations. Mayo Clin Proc. 1990 Nov;65(11):1432–40.

91. Georgiou M, Papathanassoglou E, Xanthos T. Systematic review of the mechanisms driving effective blood flow during adult CPR. Resuscitation. 2014;85(11):1586–93.

92. Shaw DP, Rutherford JS, Williams MJA. The mechanism of blood flow in cardiopulmonary resuscitation - Introducing the lung pump. Resuscitation. 1997;35(3):255–8.

93. Ma MH-M, Hwang J-J, Lai L-P, Wang S-M, Huang G-T, Shyu K-G, et al. Transesophageal Echocardiographic Assessment of Mitral Valve Position and Pulmonary Venous Flow During Cardiopulmonary Resuscitation in Humans. Circulation. 1995 Aug 15;92(4):854–61.

94. Convertino VA, Ryan KL, Rickards CA, Glorsky SL, Idris AH, Yannopoulos D, et al. Optimizing the respiratory pump: harnessing inspiratory resistance to treat systemic hypotension. Respir Care. 2011 Jun;56(6):846–57.

95. Meyer A, Nadkarni V, Pollock A, Babbs C, Nishisaki A, Braga M, et al. Evaluation of the Neonatal Resuscitation Program's recommended chest compression depth using computerized tomography imaging. Resuscitation. 2010;81(5):544–8.

96. Lee J, Lee DK, Oh J, Park SM, Kang H, Lim TH, et al. Evaluation of the proper chest compression depth for neonatal resuscitation using computed tomography: A retrospective study. Medicine (Baltimore). 2021;100(26):e26122.

97. Bruckner M, Kim SY, Shim GH, Neset M, Garcia-Hidalgo C, Lee T-F, et al. Assessment of optimal chest compression depth during neonatal cardiopulmonary resuscitation: a randomised controlled animal trial. Arch Dis Child - Fetal Neonatal Ed. 2022 May 30;107(3):262–8.

98. Fitzgerald KR, Babbs CF, Frissora HA, Davis RW, Silver DI. Cardiac output during cardiopulmonary resuscitation at various compression rates and durations. Am J Physiol Circ Physiol. 1981 Sep 1;241(3):H442–8.

99. Bruckner M, O'Reilly M, Lee T-F, Neset M, Cheung P-Y, Schmölzer GM. Effects of varying chest compression depths on carotid blood flow and blood pressure in asphyxiated piglets. Arch Dis Child - Fetal Neonatal Ed. 2021 Feb 4;fetalneonatal-2020-319473.

100. Babbs CF. Chest Compression Technique: A Neglected Key to Success. In:

Cardiopulmonary Resuscitation. 2005. p. 155–77.

101. Babbs CF, Meyer A, Nadkarni V. Neonatal CPR: Room at the top—A mathematical study of optimal chest compression frequency versus body size. Resuscitation. 2009 Nov;80(11):1280–4.

102. Boldingh AM, Jensen TH, Bjørbekk AT, Solevåg AL, Nakstad B. Rescuers' physical fatigue with different chest compression to ventilation methods during simulated infant cardiopulmonary resuscitation. J Matern Neonatal Med. 2016 Oct 15;29(19):3202–7.

103. Li ES, Cheung P-Y, O'Reilly M, Aziz K, Schmölzer GM. Rescuer fatigue during simulated neonatal cardiopulmonary resuscitation. J Perinatol. 2015 Feb 11;35(2):142–5.

104. Solevåg AL, Schmölzer GM. Optimal Chest Compression Rate and Compression to Ventilation Ratio in Delivery Room Resuscitation: Evidence from Newborn Piglets and Neonatal Manikins. Front Pediatr. 2017 Jan 23;5(January):1–7.

105. Li ES, Cheung P-Y, Lee TF, 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. Ahrens I, editor. PLoS One. 2016 Jun 15;11(6):e0157249.

106. Patel S, Cheung P-Y, Lee T-F, Pasquin MP, Lu M, O'Reilly M, et al. Asynchronous ventilation at 120 compared with 90 or 100 compressions per minute improves haemodynamic recovery in asphyxiated newborn piglets. Arch Dis Child - Fetal Neonatal Ed. 2020 Jul;105(4):357–63.

107. Bruckner M, Neset M, O'Reilly M, Lee T-F, Cheung P-Y, Schmölzer GM. Haemodynamic changes with varying chest compression rates in asphyxiated piglets. Arch Dis Child - Fetal Neonatal Ed. 2022 Feb 8;fetalneonatal-2021-323271.

108. Bruckner M, Neset M, Garcia-Hidalgo C, Lee T, O'Reilly M, Cheung P, et al. Chest Compression Rates of 90/min versus 180/min during Neonatal Cardiopulmonary Resuscitation: A Randomized Controlled Animal Trial. Children [Internet]. 2022 Nov 28;9(12):1838. Available from: https://www.mdpi.com/2227-9067/9/12/1838

109. Boldingh AM, Jensen TH, Bjørbekk AT, Solevåg AL, Nakstad B. Rescuers' physical fatigue with different chest compression to ventilation methods during simulated infant cardiopulmonary resuscitation. J Matern Neonatal Med. 2016 Oct 15;29(19):3202–7.

110. Ramachandran S, Bruckner M, Wyckoff MH, Schmölzer GM. Chest compressions in newborn infants : a scoping review. Arch Dis Child Fetal Neonatal Ed. 2022;Epub ahead(1):1–9.

111. Solevåg AL, Dannevig I, Wyckoff M, Saugstad OD, Nakstad B. Extended series of cardiac compressions during CPR in a swine model of perinatal asphyxia. Resuscitation. 2010 Nov;81(11):1571–6.

112. Solevag AL, Dannevig I, Wyckoff M, Saugstad OD, Nakstad B. Return of spontaneous circulation with a compression:ventilation ratio of 15:2 versus 3:1 in newborn pigs with cardiac arrest due to asphyxia. Arch Dis Child - Fetal Neonatal Ed. 2011 Nov 1;96(6):F417–21.

113. Dannevig I, Solevåg AL, Sonerud T, Saugstad OD, Nakstad B. Brain inflammation induced by severe asphyxia in newborn pigs and the impact of alternative resuscitation strategies on the newborn central nervous system. Pediatr Res. 2013;73(2):163–70.

114. Pasquin MP, Cheung P-Y, Patel S, Lu M, Lee T-F, Wagner M, et al. Comparison of Different Compression to Ventilation Ratios (2: 1, 3: 1, and 4: 1) during Cardiopulmonary Resuscitation in a Porcine Model of Neonatal Asphyxia. Neonatology. 2018;114(1):37–45.

115. Dannevig I, Solevåg AL, Saugstad OD, Nakstad B. Lung Injury in Asphyxiated Newborn Pigs Resuscitated from Cardiac Arrest - The Impact of Supplementary Oxygen, Longer Ventilation Intervals and Chest Compressions at Different Compression-to- Ventilation Ratios. Open Respir Med J. 2012 Sep 20;6(1):89–96.

116. Srikantan SK, Berg RA, Cox T, Tice L, Nadkarni VM. Effect of one-rescuer compression/ventilation ratios on cardiopulmonary resuscitation in infant, pediatric, and adult manikins. Pediatr Crit Care Med. 2005 May;6(3):293–7.

117. Hemway RJ, Christman C, Perlman J. 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 - Fetal Neonatal Ed. 2013 Jan;98(1):F42–5.

118. Topjian AA, Raymond TT, Atkins D, Chan M, Duff JP, Joyner BL, et al. Part 4: Pediatric Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020 Oct 20;142(16_suppl_2).

119. Schmölzer GM, O'Reilly M, LaBossiere J, Lee TF, 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(2):270–5.

120. Mendler MR, Maurer M, Hassan MA, Huang L, Waitz M, Mayer B, et al. Different Techniques of Respiratory Support Do Not Significantly Affect Gas Exchange during

Cardiopulmonary Resuscitation in a Newborn Piglet Model. Neonatology. 2015;108(1):73–80.

121. Mendler MR, Weber C, Hassan MA, Huang L, Waitz M, Mayer B, et al. Effect of Different Respiratory Modes on Return of Spontaneous Circulation in a Newborn Piglet Model of Hypoxic Cardiac Arrest. Neonatology. 2016;109(1):22–30.

122. Aggelina A, Pantazopoulos I, Giokas G, Chalkias A, Mavrovounis G, Papalois A, et al. Continuous chest compressions with asynchronous ventilation improve survival in a neonatal swine model of asphyxial cardiac arrest. Am J Emerg Med. 2021 Oct;48:60–6.

123. 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(1):73.

124. Boldingh AM, Solevåg AL, Aasen E, Nakstad B. Resuscitators who compared four simulated infant cardiopulmonary resuscitation methods favoured the three-to-one compression-to-ventilation ratio. Acta Paediatr. 2016 Aug;105(8):910–6.

125. Schmölzer GM, O'Reilly M, LaBossiere J, Lee T-F, Cowan S, Qin S, et al. Cardiopulmonary Resuscitation With Chest Compressions During Sustained Inflations. Circulation. 2013 Dec;128(23):2495–503.

126. Li ES, Görens I, Cheung P-Y, Lee T-F, Lu M, O'Reilly M, et al. Chest Compressions during Sustained Inflations Improve Recovery When Compared to a 3:1 Compression:Ventilation Ratio during Cardiopulmonary Resuscitation in a Neonatal Porcine Model of Asphyxia. Neonatology. 2017;112(4):337–46.

127. Mustofa J, Cheung P-Y, Patel S, Lee TF, Lu M, Pasquin MP, et al. Effects of different durations of sustained inflation during cardiopulmonary resuscitation on return of spontaneous circulation and hemodynamic recovery in severely asphyxiated piglets. Resuscitation. 2018 Aug;129(June):82–9.

128. Vali P, Chandrasekharan P, Rawat M, Gugino S, Koenigsknecht C, Helman J, et al. Continuous Chest Compressions During Sustained Inflations in a Perinatal Asphyxial Cardiac Arrest Lamb Model. Pediatr Crit Care Med [Internet]. 2017 Aug;18(8):e370–7. Available from: http://journals.lww.com/00130478-201708000-00032

129. Schmölzer GM, O Reilly M, Fray C, van Os S, Cheung P-Y. Chest compression during sustained inflation versus 3:1 chest compression:ventilation ratio during neonatal cardiopulmonary resuscitation: a randomised feasibility trial. Arch Dis Child - Fetal

Neonatal Ed. 2018 Sep;103(5):F455–60.

130. Schmölzer GM, Pichler G, Solevåg AL, Fray C, van Os S, Cheung P-Y. The SURV1VE trial—sustained inflation and chest compression versus 3:1 chest compression-to-ventilation ratio during cardiopulmonary resuscitation of asphyxiated newborns: study protocol for a cluster randomized controlled trial. Trials. 2019 Dec 19;20(1):139.

131. Christman C, Hemway RJ, Wyckoff MH, Perlman JM. The two-thumb is superior to the two-finger method for administering chest compressions in a manikin model of neonatal resuscitation. Arch Dis Child - Fetal Neonatal Ed. 2011 Mar 1;96(2):F99–101.

132. Dorfsman ML, Menegazzi JJ, Wadas RJ, Auble TE. Two-thumb vs Two-finger Chest Compression in an Infant Model of Prolonged Cardiopulmonary Resuscitation. Acad Emerg Med. 2000 Oct;7(10):1077–82.

133. Pellegrino JL, Bogumil D, Epstein JL, Burke R V. Two-thumb-encircling advantageous for lay responder infant CPR: a randomised manikin study. Arch Dis Child. 2019 Jun;104(6):530–4.

134. Udassi S, Udassi JP, Lamb MA, Theriaque DW, Shuster JJ, Zaritsky AL, et al. Two-thumb technique is superior to two-finger technique during lone rescuer infant manikin CPR. Resuscitation. 2010 Jun;81(6):712–7.

135. Lee SY, Hong JY, Oh JH, Son S-H. The superiority of the two-thumb over the two-finger technique for single-rescuer infant cardiopulmonary resuscitation. Eur J Emerg Med. 2018 Oct;25(5):372–6.

136. Whitelaw CC, Slywka B, Goldsmith LJ. Comparison of a two-finger versus two-thumb method for chest compressions by healthcare providers in an infant mechanical model. Resuscitation. 2000 Feb;43(3):213–6.

137. Reynolds C, Cox J, Livingstone V, Dempsey EM. Rescuer Exertion and Fatigue Using Two-Thumb vs. Two-Finger Method During Simulated Neonatal Cardiopulmonary Resuscitation. Front Pediatr. 2020 Apr 2;8(April):1–6.

138. Saini SS, Gupta N, Kumar P, Bhalla AK, Kaur H. A comparison of two-fingers technique and two-thumbs encircling hands technique of chest compression in neonates. J Perinatol. 2012;32(9):690–4.

139. Jiang J, Zou Y, Shi W, Zhu Y, Tao R, Jiang Y, et al. Two-thumb–encircling hands technique is more advisable than 2-finger technique when lone rescuer performs cardiopulmonary resuscitation on infant manikin. Am J Emerg Med. 2015 Apr;33(4):531–4.

140. Jung WJ, Hwang SO, Kim H Il, Cha YS, Kim OH, Kim H, et al. ‘Knocking-fingers’ chest

compression technique in infant cardiac arrest. Eur J Emerg Med. 2019 Aug;26(4):261–5.

141. Rodriguez-Ruiz E, Martínez-Puga A, Carballo-Fazanes A, Abelairas-Gómez C, Rodríguez-Nuñez A. Two new chest compression methods might challenge the standard in a simulated infant model. Eur J Pediatr. 2019;178(10):1529–35.

142. Jo CH, Jung HS, Cho GC, Oh YJ. Over-The-head two-Thumb encircling technique as an alternative to the two-finger technique in the in-hospital infant cardiac arrest setting: A randomised crossover simulation study. Emerg Med J. 2015;32(9):703–7.

143. Jo CH, Cho GC, Lee CH. Two-thumb encircling technique over the head of patients in the setting of lone rescuer infant CPR occurred during ambulance transfer: A crossover simulation study. Pediatr Emerg Care. 2017;33(7):462–6.

144. Yang D, Kim KH, Oh JH, Son S, Cho J, Seo KM. Development and Evaluation of a New Chest Compression Technique for Cardiopulmonary Resuscitation in Infants. Pediatr Cardiol. 2019 Aug 15;40(6):1217–23.

145. Kim YS, Oh JH, Kim CW, Kim SE, Lee DH, Hong JY. Which fingers should we perform two-finger chest compression technique with when performing cardiopulmonary resuscitation on an infant in cardiac arrest? J Korean Med Sci. 2016;31(6):997–1002.

146. Paek SH, Kim DK, Lee JH, Kwak YH. Comparison of standard and alternative methods for chest compressions in a single rescuer infant CPR: A prospective simulation study. PLoS One. 2019;14(12):1–10.

147. Ladny JR, Smereka J, Rodríguez-Núñez A, Leung S, Ruetzler K, Szarpak L. Is there any alternative to standard chest compression techniques in infants? A randomized manikin trial of the new “2-thumb-fist” option. Med (United States). 2018;97(5):1–6.

148. Smereka J, Kasinski M, Smereka A, Ladny JR, Szarpak L. The quality of a newly developed infant chest compression method applied by paramedics: A randomised crossover manikin trial. Kardiol Pol. 2017;75(6):589–95.

149. Smereka J, Madziala M, Szarpak Ł. Comparison of two infant chest compression techniques during simulated newborn cardiopulmonary resuscitation performed by a single rescuer: A randomized, crossover multicenter trial. Cardiol J. 2019;26(6):761–8.

150. Smereka J, Szarpak L, Smereka A, Leung S, Ruetzler K. Evaluation of new two-thumb chest compression technique for infant CPR performed by novice physicians. A randomized, crossover, manikin trial. Am J Emerg Med [Internet]. 2017;35(4):604–9. Available from: http://dx.doi.org/10.1016/j.ajem.2016.12.045

151. Smereka J, Bielski K, Ladny JR, Ruetzler K, Szarpak L. Evaluation of a newly developed

infant chest compression technique. Med (United States). 2017;96(14):0–5.

152. Smereka J, Szarpak L, Ladny JR, Rodriguez-Nunez A, Ruetzler K. A novel method of newborn chest compression: A randomized crossover simulation study. Front Pediatr. 2018;6(May):1–6.

153. Lee SU, Kim DK, Chang I, Jung JY, Paek SH, Park JW, et al. Two-Thumb Encircling Technique with a Novel Compression Assist Device Provides Safe and Effective Chest Compressions in Infants. Pediatr Emerg Care. 2020;36(12):E700–3.

154. Park JW, Jung JY, Kim J, Kwak YH, Kim DK, Lee JC, et al. A Novel Infant Chest Compression Assist Device Using a Palm Rather Than Fingers: A Randomized Crossover Trial. Prehospital Emerg Care [Internet]. 2019;23(1):74–82. Available from: https://doi.org/10.1080/10903127.2018.1471559

155. Wagner M, Olischar M, O'Reilly M, Goeral K, Berger A, Cheung PY, et al. Review of routes to administer medication during prolonged neonatal resuscitation. Pediatr Crit Care Med. 2018;19(4):332–8.

156. Scrivens A, Reynolds PR, Emery FE, Roberts CT, Polglase GR, Hooper SB, et al. Use of Intraosseous Needles in Neonates: A Systematic Review. Neonatology. 2019;116(4):305–14.

157. Mileder LP, Urlesberger B, Schwaberger B. Use of Intraosseous Vascular Access During Neonatal Resuscitation at a Tertiary Center. Front Pediatr. 2020;8(September):1–5.

158. Schwindt EM, Hoffmann F, Deindl P, Waldhoer TJ, Schwindt JC. Duration to establish an emergency vascular access and how to accelerate it: A simulation-based study performed in real-life neonatal resuscitation rooms. Pediatr Crit Care Med. 2018;19(5):468–76.

159. Baik-Schneditz N, Pichler G, Schwaberger B, Mileder L, Avian A, Urlesberger B. Peripheral Intravenous Access in Preterm Neonates during Postnatal Stabilization: Feasibility and Safety. Front Pediatr. 2017 Aug 10;5(171).

160. Borrhomée S, Merbouche S, Kern-Duciau N, Boize P. Umbilical vein catheterization through Wharton's jelly: A possibility for a fast and safe way to deliver treatments in the delivery room? Arch Pediatr. 2019;26(6):381–4.

161. Attaran RR, Ewy GA. Epinephrine in resuscitation: curse or cure? Future Cardiol. 2010 Jul;6(4):473–82.

162. Halling C, Sparks JE, Christie L, Wyckoff MH. Efficacy of Intravenous and Endotracheal Epinephrine during Neonatal Cardiopulmonary Resuscitation in the Delivery Room. J

Pediatr. 2017;185:232–6.

163. Halling C, Sparks JE, Christie L, Wyckoff MH. Efficacy of Intravenous and Endotracheal Epinephrine during Neonatal Cardiopulmonary Resuscitation in the Delivery Room. J Pediatr [Internet]. 2017;185:232–6. Available from: http://dx.doi.org/10.1016/j.jpeds.2017.02.024

164. Songstad NT, Klingenberg C, McGillick E V., Polglase GR, Zahra V, Schmölzer GM, et al. Efficacy of Intravenous, Endotracheal, or Nasal Adrenaline Administration During Resuscitation of Near-Term Asphyxiated Lambs. Front Pediatr. 2020;8(June):1–11.

165. Patterson MD, Boenning DA, Klein BL, Fuchs S, Smith KM, Hegenbarth MA, et al. The Use of High-Dose Epinephrine for Patients With Out-of-Hospital Cardiopulmonary Arrest Refractory to Prehospital Interventions. Pediatr Emerg Care. 2005 Apr;21(4):227–37.

166. Perondi MBM, Reis AG, Paiva EF, Nadkarni VM, Berg RA. A Comparison of High-Dose and Standard-Dose Epinephrine in Children with Cardiac Arrest. N Engl J Med. 2004 Apr 22;350(17):1722–30.

167. Carpenter TC, Stenmark KR. High-dose Epinephrine Is Not Superior to Standard-dose Epinephrine in Pediatric In-hospital Cardiopulmonary Arrest. Pediatrics. 1997 Mar 1;99(3):403–8.

168. Dieckmann RA, Vardis R. High-dose epinephrine in pediatric out-of-hospital cardiopulmonary arrest. Pediatrics. 1995 Jun;95(6):901–13.

169. Warren SA, Huszti E, Bradley SM, Chan PS, Bryson CL, Fitzpatrick AL, et al. Adrenaline (epinephrine) dosing period and survival after in-hospital cardiac arrest: A retrospective review of prospectively collected data. Resuscitation. 2014 Mar;85(3):350–8.

170. Fothergill RT, Emmerson AC, Iyer R, Lazarus J, Whitbread M, Nolan JP, et al. Repeated adrenaline doses and survival from an out-of-hospital cardiac arrest. Resuscitation. 2019 May;138:316–21.

171. Rivers EP, Wortsman J, Rady MY, Blake HC, McGeorge FT, Buderer NM. The Effect of the Total Cumulative Epinephrine Dose Administered During Human CPR on Hemodynamic, Oxygen Transport, and Utilization Variables in the Postresuscitation Period. Chest. 1994 Nov;106(5):1499–507.

172. Hoyme DB, Patel SS, Samson RA, Raymond TT, Nadkarni VM, Gaies MG, et al. Epinephrine dosing interval and survival outcomes during pediatric in-hospital cardiac arrest. Resuscitation. 2017 Aug;117:18–23.

173. Tylleskär T, Cavallin F, Höök SM, Pejovic NJ, Lubulwa C, Byamugisha J, et al. Outcome

of infants with 10 min Apgar scores of 0–1 in a low-resource setting. Arch Dis Child - Fetal Neonatal Ed. 2021 Nov 1;fetalneonatal-2021-322545.

174. Halling C, Raymond T, Brown LS, Ades A, Foglia EE, Allen E, et al. Neonatal delivery room CPR: An analysis of the Get with the Guidelines®—Resuscitation Registry. Resuscitation. 2021 Jan;158:236–42.

175. Foglia EE, Weiner G, de Almeida MFB, Wyllie J, Wyckoff MH, Rabi Y, et al. Duration of Resuscitation at Birth, Mortality, and Neurodevelopment: A Systematic Review. Pediatrics. 2020;146(3).

176. Ali N, Lam T, Gray MM, Clausen D, Riley M, Grover TR, et al. Cardiopulmonary resuscitation in quaternary neonatal intensive care units: a multicenter study. Resuscitation. 2021 Feb;159(December 2020):77–84.

177. Ahmad KA, Velasquez SG, Kohlleppel KL, Henderson CL, Stine CN, LeVan JM, et al. The Characteristics and Outcomes of Cardiopulmonary Resuscitation within the Neonatal Intensive Care Unit Based on Gestational Age and Unit Level of Care. Am J Perinatol. 2020 Dec 31;37(14):1455–61.

178. Wang H, Bhutta ZA, Coates MM, Coggeshall M, Dandona L, Diallo K, et al. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016 Oct;388(10053):1725–74.

179. UNICEF, WHO WBG and UN. Levels and trends in child mortality 2020 Estimates developed by the UN Inter-agency group for child mortality estimation [Internet]. Available from: https://www.unicef.org/media/60561/file/UN-IGME-child-mortality-report-2019.pdf

180. Hooper SB, te Pas AB, Polglase GR, Wyckoff M. Animal models in neonatal resuscitation research: What can they teach us? Semin Fetal Neonatal Med. 2018 Oct;23(5):300–5.

181. Solevåg AL, Cheung P-Y, Lie H, O'Reilly M, Aziz K, Nakstad B, et al. Chest compressions in newborn animal models: A review. Resuscitation. 2015 Nov;96:151–5.

182. Pasquin MP, Cheung P-Y, Patel S, Lu M, Lee T-F, Wagner M, et al. Comparison of Different Compression to Ventilation Ratios (2: 1, 3: 1, and 4: 1) during Cardiopulmonary Resuscitation in a Porcine Model of Neonatal Asphyxia. Neonatology. 2018;114(1):37–45.

183. Schmölzer GM, O'Reilly M, Labossiere J, Lee TF, 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(23):2495–503.

184. 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 Feb;85(2):270–5.

185. Ong T, Sobotka KS, Siew ML, Crossley KJ, van Vonderen JJ, Polglase GR, et al. The cardiovascular response to birth asphyxia is altered by the surrounding environment. Arch Dis Child - Fetal Neonatal Ed. 2016 Nov;101(6):F540–5.

186. Thoresen M, Haaland K, Løberg EM, Whitelaw A, Apricena F, Hankø E, et al. A Piglet Survival Model of Posthypoxic Encephalopathy. Pediatr Res. 1996 Nov;40(5):738–48.

187. Revhaug C, Bik-Multanowski M, Zasada M, Rognlien AGW, Günther C-C, Książek T, et al. Immune System Regulation Affected by a Murine Experimental Model of Bronchopulmonary Dysplasia: Genomic and Epigenetic Findings. Neonatology. 2019;116(3):269–77.

188. Bik-Multanowski M, Revhaug C, Grabowska A, Dobosz A, Madetko-Talowska A, Zasada M, et al. Hyperoxia induces epigenetic changes in newborn mice lungs. Free Radic Biol Med. 2018 Jun;121:51–6.

189. Zasada M, Madetko-Talowska A, Revhaug C, Rognlien AGW, Baumbusch LO, Książek T, et al. Short- and long-term impact of hyperoxia on the blood and retinal cells' transcriptome in a mouse model of oxygen-induced retinopathy. Pediatr Res. 2020 Feb 2;87(3):485–93.

190. Hooper SB, Kitchen MJ, Wallace MJ, Yagi N, Uesugi K, Morgan MJ, et al. Imaging lung aeration and lung liquid clearance at birth. FASEB J. 2007;21(12):3329–37.

191. te Pas AB, Siew M, Wallace MJ, Kitchen MJ, Fouras A, Lewis RA, et al. Establishing Functional Residual Capacity at Birth: The Effect of Sustained Inflation and Positive End-Expiratory Pressure in a Preterm Rabbit Model. Pediatr Res. 2009 May;65(5):537–41.

192. Lang JAR, Pearson JT, Binder-Heschl C, Wallace MJ, Siew ML, Kitchen MJ, et al. Increase in pulmonary blood flow at birth: role of oxygen and lung aeration. J Physiol. 2016 Mar 1;594(5):1389–98.

193. Raju TN. Some Animal Models for the Study of Perinatal Asphyxia. Neonatology. 1992;62(4):202–14.

194. Roohey T, Raju TNK, Moustogiannis AN. Animal models for the study of perinatal

hypoxic-ischemic encephalopathy: a critical analysis. Early Hum Dev. 1997 Jan;47(2):115–46.

195. Koehler RC, Yang Z-J, Lee JK, Martin LJ. Perinatal hypoxic-ischemic brain injury in large animal models: Relevance to human neonatal encephalopathy. J Cereb Blood Flow Metab. 2018 Dec 28;38(12):2092–111.

196. Sanderud J, Norstein J, Saugstad OD. Reactive Oxygen Metabolites Produce Pulmonary Vasoconstriction in Young Pigs. Pediatr Res. 1991 Jun;29(6):543–7.

197. Rootwelt T, Løberg EM, Moen A, Øyasæter S, Saugstad OD. Hypoxemia and Reoxygenation with 21% or 100% Oxygen in Newborn Pigs: Changes in Blood Pressure, Base Deficit, and Hypoxanthine and Brain Morphology. Pediatr Res. 1992 Jul;32(1):107–13.

198. Sanderud J, Saugstad OD. Oxygen Radicals Induce Pulmonary Vasoconstriction in Pigs without Activating Plasma Proteolytic Cascade Systems. Eur Surg Res. 1993;25(3):137–45.

199. Rootwelt T, Odden JP, Hall C, Ganes T, Saugstad OD. Cerebral blood flow and evoked potentials during reoxygenation with 21 or 100% O2 in newborn pigs. J Appl Physiol. 1993 Nov 1;75(5):2054–60.

200. Aroni F, Xanthos T, Varsami M, Argyri I, Alexaki A, Stroumpoulis K, et al. An experimental model of neonatal normocapnic hypoxia and resuscitation in Landrace/Large White piglets. J Matern Neonatal Med. 2012 Sep 23;25(9):1750–4.

201. Vali P, Gugino S, Koenigsknecht C, Helman J, Chandrasekharan P, Rawat M, et al. The Perinatal Asphyxiated Lamb Model: A Model for Newborn Resuscitation. J Vis Exp. 2018 Aug 15;2018(138):1–10.

202. Bhatt S, Alison BJ, Wallace EM, Crossley KJ, Gill AW, Kluckow M, et al. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. J Physiol. 2013 Apr;591(8):2113–26.

203. van Dijk AJ, van Loon JPAM, Taverne MAM, Jonker FH. Umbilical cord clamping in term piglets: A useful model to study perinatal asphyxia? Theriogenology. 2008 Sep;70(4):662–74.

204. Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research. PLoS Biol. 2010 Jun 29;8(6):e1000412.

205. Wagner M, Cheung PY, Li ES, Lee TF, Lu M, O'Reilly M, et al. Effects of epinephrine on hemodynamic changes during cardiopulmonary resuscitation in a neonatal piglet

model. Pediatr Res. 2018;83(4):897–903.

206. Schmolzer GM, Kamlin OCOF, Dawson JA, te Pas AB, Morley CJ, Davis PG. Respiratory monitoring of neonatal resuscitation. Arch Dis Child - Fetal Neonatal Ed. 2010 Jul 1;95(4):F295–303.

207. 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 Paediatr. 2014 Aug;103(8):796–806.

208. Bruckner M, Pichler G, Urlesberger B. NIRS in the fetal to neonatal transition and immediate postnatal period. Semin Fetal Neonatal Med. 2020 Apr;25(2):101079.

209. Douvanas A, Koulouglioti C, Kalafati M. A comparison between the two methods of chest compression in infant and neonatal resuscitation. A review according to 2010 CPR guidelines. J Matern Neonatal Med. 2018 Mar 19;31(6):805–16.

210. David R. Closed chest cardiac massage in the newborn infant. Pediatrics. 1988 Apr;81(4):552–4.

211. Hidalgo CG, Solevag AL, Kim SY, Shim GH, Cheung P-Y, Lee T-F, et al. Sustained inflation with 21% versus 100% oxygen during cardiopulmonary resuscitation of asphyxiated newborn piglets - A randomized controlled animal study. Resuscitation. 2020 Oct;155:39–47.

212. Shim G-H, Kim SY, Cheung P-Y, Lee T-F, O'Reilly M, Schmölzer GM. Effects of sustained inflation pressure during neonatal cardiopulmonary resuscitation of asphyxiated piglets. Nair J, editor. PLoS One. 2020 Jun 23;15(6):e0228693.

213. Kim T, Kim KS, Suh GJ, Kwon WY, Jung YS, Ko J-I, et al. Duty cycle of 33% increases cardiac output during cardiopulmonary resuscitation. Lionetti V, editor. PLoS One. 2020 Jan 28;15(1):e0228111.

214. Dean JM, Koehler RC, Schleien CL, Atchison D, Gervais H, Berkowitz I, et al. Improved blood flow during prolonged cardiopulmonary resuscitation with 30% duty cycle in infant pigs. Circulation. 1991 Aug;84(2):896–904.

215. Martin PS, Kemp AM, Theobald PS, Maguire SA, Jones MD. Do chest compressions during simulated infant CPR comply with international recommendations? Arch Dis Child. 2013;98(8):576–81.

216. Jung YH, Jeung KW, Lee DH, Jeong YW, Lee SM, Lee BK, et al. Relationship Between Left Ventricle Position and Haemodynamic Parameters During Cardiopulmonary Resuscitation in a Pig Model. Hear Lung Circ. 2018 Dec;27(12):1489–97.

217. Anderson KL, Castaneda MG, Boudreau SM, Sharon DJ, Bebarta VS. Left Ventricular Compressions Improve Hemodynamics in a Swine Model of Out-of-Hospital Cardiac Arrest. Prehospital Emerg Care. 2017 Mar 4;21(2):272–80.

218. Hwang SO, Zhao PG, Choi HJ, Park KH, Cha KC, Park SM, et al. Compression of the Left Ventricular Outflow Tract During Cardiopulmonary Resuscitation. Acad Emerg Med [Internet]. 2009 Oct;16(10):928–33. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1553-2712.2009.00497.x

219. Constable P, III WM, Sisson D. Clinical Assessment of Left Ventricular Relaxation. J Vet Intern Med. 1999 Jan;13(1):5–13.

220. Schmidt HD, Hoppe H. Influence of the Contractile State of the Heart on the Preload Dependence of the Maximal Rate of Intraventricular Pressure Rise dP/dt max. Cardiology. 1978;63(2):112–25.

221. Kawasaki H, Seki M, Saiki H, Masutani S, Senzaki H. Noninvasive assessment of left ventricular contractility in pediatric patients using the maximum rate of pressure rise in peripheral arteries. Heart Vessels. 2012 Jul 17;27(4):384–90.

222. Udelson JE, Bacharach SL, Cannon RO, Bonow RO. Minimum left ventricular pressure during beta-adrenergic stimulation in human subjects. Evidence for elastic recoil and diastolic “suction” in the normal heart. Circulation [Internet]. 1990 Oct;82(4):1174–82. Available from: https://www.ahajournals.org/doi/10.1161/01.CIR.82.4.1174

223. Ogilvie LM, Edgett BA, Gray S, Al-Mufty S, Huber JS, Brunt KR, et al. A new approach to improve the hemodynamic assessment of cardiac function independent of respiratory influence. Sci Rep [Internet]. 2021;11(1). Available from: https://doi.org/10.1038/s41598-021-96050-y

224. López J, Fernández SN, González R, Solana MJ, Urbano J, Toledo B, et al. Comparison between manual and mechanical chest compressions during resuscitation in a pediatric animal model of asphyxial cardiac arrest. Ito E, editor. PLoS One. 2017 Nov 30;12(11):e0188846.

225. Çağlar A, Er A, Ulusoy E, Akgül F, Çitlenbik H, Yılmaz D, et al. Cerebral oxygen saturation monitoring in pediatric cardiopulmonary resuscitation patients in the emergency settings: a small descriptive study. Turk J Pediatr. 2017;59(6):642.