Resuscitation of term and near-term newborns in low-resourced settings

Studies of positive end-expiratory pressure and expired CO_2 during bag-mask ventilation at birth

by

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"Ultimately, we seek survival without permanent impairment of any function, particularly that of the brain"

Geoffrey Dawes (1968)[1]

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Scientific environment

This research has been conducted as part of the Safer Birth study group. The studies included were performed in close collaboration between researchers employed at Østfold Hospital Trust, Stavanger University Hospital, Laerdal Global Health, the University of Stavanger, the Arctic University of Tromsø, the University of Oslo and the Norwegian Institute of Public Health in Norway, and Aga Khan University and Haydom Lutheran Hospital in Tanzania.

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Abbreviations

BMV	Bag-mask ventilation
BPD	Bronchopulmonary dysplasia
Bpm	Beats per minute
BW	Birth weight
CoSTR	Consensus on Science and Treatment Recommendations
CPAP	Continuous positive airway pressure
ECG	Electrocardiogram
ECO_2	Expired carbon dioxide
FRC	Functional Residual Capacity
GA	Gestational age
HBB	Helping Babies Breathe
HLH	Haydom Lutheran Hospital
HR	Heart rate
iHR	Initial heart rate (median of first 5 recorded heart beats)
ILCOR	International Liaison Committee on Resuscitation
MAP	Mean airway pressure
PEEP	Positive end expiratory pressure
PIP	Peak inspiratory pressure
PPV	Positive pressure ventilation
RDS	Respiratory distress syndrome
RCT	Randomized Controlled Trial
SIB	Self-inflating bag
TPR	T-piece resuscitator
VR	Ventilation rate
V_T	Tidal volume
V_{TE}	Expired tidal volume
WHO	World Health Organization

Definitions

Apgar	Scoring system to evaluate clinical condition of newborns, named after Virginia Apgar (1909-1974).
Asphyxia	Original meaning: "pulseless" (Greek: *a* – without, *sphuxis* – heartbeat). WHO definition: Failure to initiate spontaneous respiration and/or 5-minute Apgar score <7.
Intrapartum-related events	Complications related to birth causing risk of hypoxia for the newborn. Intrapartum related events cause birth asphyxia and meconium aspiration syndrome.
Stillbirth	A baby born with no signs of life at or after 28 weeks of gestation (WHO). Apgar score 0 at 1 and 5 minutes or GA < 28 weeks (practical definition at HLH)
Gestational age	Gestational age based on self-reported last menstrual period and distance from symphysis pubis to fundus (the definition applies to data collected at HLH)
Perinatal mortality	Number of stillbirths and deaths between 28 completed gestational weeks and the first 7 days of life
Early neonatal mortality	Newborn deaths within the first 7 days of life per 1000 live births
Neonatal mortality	Newborn deaths within the first 28 days of life per 1000 live births
Primary apnea	Heart rate considered to be ≥60 bpm with compensated blood pressure
Secondary apnea	Progressive bradycardia <60 bpm and hypotension with final gasping

Abstract

Background: An estimated 0.7 million newborns die due to perinatal asphyxia each year, most are born at or near term. The major burden of preventable newborn deaths occur in low-resourced settings. A self-inflating bag is the most used and available equipment to save newborn lives globally. To aerate the lungs is key to survival. Expired CO_2 (ECO_2) may be an indicator for lung aeration, and positive end-expiratory pressure (PEEP) may facilitate aeration of the lungs. Research aiming to improve ventilation in term and near-term newborns using a self-inflating bag is needed.

Aims: To investigate interpretation of ECO_2 measured during bag-mask ventilation in the immediate newborn period, and assess whether this can be used as a marker for lung aeration, effective ventilation technique and prognosis. To study the effects of PEEP during bag-mask ventilation at or near term.

Methods: Two observational studies and one randomized clinical trial were performed at Haydom Lutheran Hospital in Tanzania. Data were collected using direct observation, side-stream CO_2-monitoring, respiratory function monitoring and dry-electrode ECG. In the randomized trial, newborns in need of ventilation were assigned in blocks based on weeks to receive ventilations by self-inflating bag with or without a PEEP-valve.

Results: ECO_2 during bag-mask ventilation at birth was significantly associated with both ventilation factors and clinical factors. Tidal volumes of 10-14 ml/kg and a low ventilation frequency of around 30 inflations/minute were associated with the fastest rise and highest levels of ECO_2. ECO_2 increased before heart rate, and measured levels of ECO_2 during resuscitation could, similar to heart rate, predict 24-hours survival. Adding a PEEP-valve to the self-inflating bag did not improve heart rate, ECO_2 or outcomes in term and near-term newborns despite delivery of an adequate PEEP.

Conclusions: ECO_2 may be seen as a combined marker for lung aeration, airway patency and pulmonary circulation at birth. Tidal volumes of 10-14 ml/kg and ventilation frequencies of around 30 inflations/minute may be favorable to achieve a fast lung aeration. We found no clinical benefit of adding a PEEP-valve during bag-mask ventilation at birth in term and near-term newborns, and our study does not support routine use.

List of publications

Paper I:
Holte K, Ersdal HL, Eilevstjønn J, Thallinger M, Linde J, Klingenberg C, Holst R, Jatosh S, Kidanto H, Størdal K
Predictors of expired CO2 in neonatal bag-mask ventilation at birth: observational study
BMJ Paediatrics Open 2019 September;3:e000544.doi:10.1136/bmjpo-2019-000544

Paper II:
Holte K, Ersdal HL, Klingenberg C, Eilevstjønn J, Stigum H, Jatosh S, Kidanto H, Størdal K
Expired Carbon Dioxide during Newborn Resuscitation as Predictor of Outcome
Manuscript accepted in Resuscitation, May 2021

Paper III:
Holte K, Ersdal HL, Eilevstjønn J, Gomo Ø, Klingenberg C, Thallinger M, Linde J, Stigum H, Yeconia A, Kidanto H, Størdal K
Positive End-Expiratory Pressure in Newborn Resuscitation Around Term: A Randomized Controlled Trial
PEDIATRICS Volume 146, number 4, October 2020: e20200494

Thesis at a glance

Paper I	*Participants: 434 bag-mask ventilated newborns, initial HR <120bpm*
Aims	To study and compare the impact of ventilation factors and clinical factors on ECO_2 during the first 5 minutes of bag-mask ventilation in newborn resuscitation.
Methods	Descriptive study using side-stream CO_2-monitoring, respiration function monitoring, ECG and observation during newborn resuscitation in Tanzania. Random intercept linear regression and Cox-regression analyses.
Results	Ventilation factors explained 31% of variation in ECO_2 compared to 11% for clinical factors. ECO_2 rose non-linearly with increasing V_{TE} up to >10ml/kg, sufficient V_{TE} was critical for the time to reach ECO_2 >2%. VR around 30/min was associated with the highest ECO_2.
Conclusions	Ventilation factors are important predictors of ECO_2 in newborn resuscitation, clinical factors must be accounted for in the interpretation. Higher V_{TE} than currently recommended and a low ventilation frequency may be favourable to achieve fast lung aeration.
Paper II	*Participants: The same cohort of newborns as in Paper I*
Aims	To explore ECO_2 as a marker of clinical response to resuscitation and compare ECO_2 and HR as indicators of 24-hour outcome.
Methods	Descriptive study using side-stream CO_2-monitoring, ECG and observation during newborn resuscitation in Tanzania. Logistic regression, ROC-curves.
Results	ECO_2 and HR were both significant predictors of 24-hour outcome. In the first minute of ventilation ECO_2 added extra predictive information compared to HR alone. ECO_2 increased before HR in 70% of newborns.
Conclusions	ECO_2 may serve as an early marker for treatment response and prognosis during newborn resuscitation.
Paper III	*Participants: 417 bag-mask ventilated newborns (206 no PEEP, 211 PEEP)*
Aims	To study if adding a PEEP-valve to the bag-mask could improve HR-response during resuscitation of term and near term newborns
Methods	Randomized controlled trial at Haydom Lutheran Hospital. Data collected by ECG, respiration function monitoring and observation. Three level random intercept linear regression analyses, Wilcoxon rank sum tests.
Results	There were no differences in HR-response for newborns ventilated with compared to without PEEP. The PEEP-group received lower V_{TE} (median 4.3 vs 6.3 ml/kg) and had lower ECO_2 (2.9 vs.3.3 %). 24-hour mortality was 9% in both groups.
Conclusions	Adding a PEEP-valve to the bag-mask did not improve HR-response. The findings do not support routine use of PEEP during resuscitation of term and near term newborns.

Table of Contents

1 Introduction

Despite great progress in children's health in the last few decades, to be born is still dangerous. The newborn baby (Fig. 1) goes from a protected, liquid environment in the uterus with intravenous provision of oxygen and nutrients through the placenta, to an atmosphere of gases. Those who do not breathe may die.

This thesis mainly concentrates on methods to optimize bag-mask ventilation and monitor responses in term and near-term newborns who need assisted ventilation at birth. All data collection was done in Tanzania. However, as the studies focus on physiological mechanisms, the results may have implications in both high- and low-resourced settings.

In the following chapters of this introduction, I will describe the global problem of neonatal deaths, explain the mechanisms for neonatal transition and present guidelines and equipment for newborn resuscitation to frame the thesis into a broader perspective.

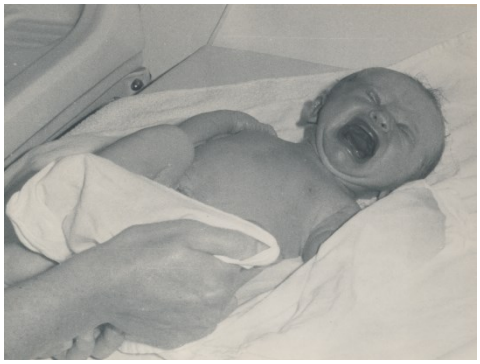


Figure 1 – Surviving birth. The author of this thesis at 5 minutes of age. Photo: Stian Holte

1.1 Neonatal mortality and international efforts to save newborn lives

Around 140 million infants are born globally every year.[2] The majority manage the transition from placental to pulmonary gas exchange without help. An estimated 5-10% will not start breathing without some assistance (Fig. 2).[3] The need for interventions is higher in low-resourced settings, where access to intrapartum obstetric care is poor and the incidence of intrapartum-related events is high.[4-11]

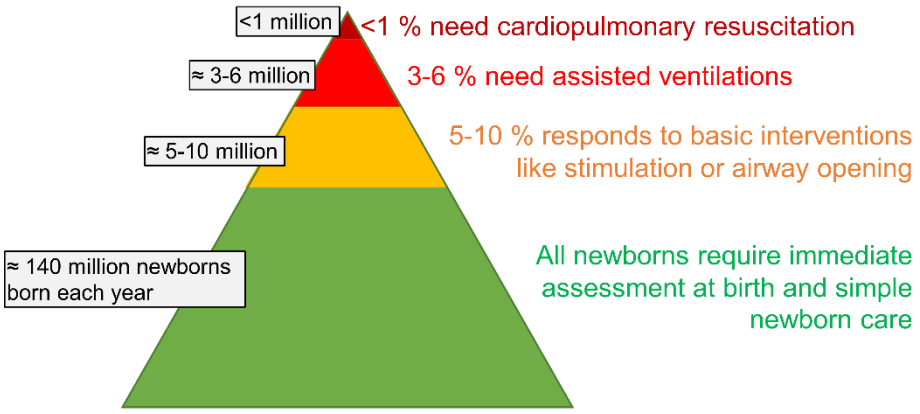


Figure 2 – The figure illustrate the estimated needs for resuscitation at birth in numbers per year and percentages of all newborn infants. Modified from Wall et al.[3]

About 6,700 newborns died every day in 2019, corresponding to an average global neonatal mortality rate (death before 28 days of life) of 17 per 1000 live births.[2] The mortality was unevenly distributed across countries and regions. The highest burden was in sub-Saharan Africa and Central and Southern Asia, together accounting for almost 80% of all

global neonatal deaths. The newborn mortality rate in the United Republic of Tanzania in 2019 was 20 per 1000 live births, lower than the average of 27 for sub-Saharan Africa. For comparison, the Norwegian neonatal mortality rate, one of the lowest in the world, was 1.2 per 1000.[12]

1.1.1 Perinatal deaths and stillbirths

The first days of life are the most critical for the survival of children. Pooled results from 22 studies in a systematic review performed in 2016, indicated that 62% of all neonatal deaths occurred within the first 3 days of life, 44% within the first 24-hours.[13] The leading causes of early neonatal deaths are intrapartum-related hypoxic events (birth asphyxia, page 10), prematurity and sepsis, with an estimated share of approximately 1/3 in each group.[14,15]

Adding to the burden of early neonatal deaths, an estimated 1.2 million babies, counted as stillborn, die during labour globally each year.[16] Fresh stillbirths and severely asphyxiated neonates share a common hypoxic-ischemic pathway.[17] Deaths due to intrapartum-related events may be underreported due to misclassification as fresh stillbirths.[18-20] More than a million children who survive birth asphyxia each year develop cerebral palsy, learning difficulties and other disabilities.[21,22] Around 42 million disability-adjusted life years are estimated to be lost each year due to long-term disabilities caused by intra-partum related complications.[14].

1.1.2 International goals for newborn survival

The estimated global number of neonatal deaths per year declined from 5.0 (4.9, 5.2) million in 1990 to 2.4 (2.3, 2.7) million in 2019.[2] International efforts to improve newborn health were catalysed by the Millennium Development Goals (MDG), which were agreed upon by the leaders of 189 countries in the United Nations, and signed in year 2000.[23] MDG 4 was to reduce deaths in children under five years of age by two thirds from 1990 to 2015. Newborn mortality during this period declined at a slower rate than the mortality for children of 1 month to five years of age. Consequently, in 1990 neonatal deaths accounted for around 40%, in 2019 for 47% of the under-five mortality.[2] The Sustainable Development Goals (SDGs) signed by 193 nations in 2015 are more specific than the MDGs regarding newborn deaths, aiming to reduce neonatal mortality in all countries of the world to <12/1000 before 2030.[24]

1.1.3 Strategies to reduce intrapartum-related deaths

Neonatal deaths are largely preventable by reaching high coverage of quality antenatal care, skilled care at birth, postnatal care for mother and baby, and care of small and sick newborns. Strategies to prevent intrapartum-related adverse outcomes can be divided into three phases:[25]

1) Primary prevention by delivery of high-quality antenatal and obstetric care.
2) Secondary prevention by immediate and adequate resuscitation of the non-breathing baby.
3) Tertiary prevention by advanced neonatal care.

Primary prevention has a high potential to reduce birth-related deaths and disabilities.[26-29] Advanced neonatal care may save very small and sick newborns.[30] However, such interventions rely on complex health systems. Aiming to achieve the MDGs and SDGs, secondary prevention by having a skilled and equipped birth attendant present at every birth, has been identified as the most realistic and effective intervention to reduce perinatal deaths within a short time frame.[25,31-34] Assessments in six African countries (2003-2008) revealed that only 2–12% of health personnel conducting births had been trained in neonatal resuscitation and only 8–22% of facilities had equipment for newborn respiratory support.[3] Setting research priorities to improve global newborn health and birth outcomes, questions related to delivery received the highest scores among international experts.[14,35] To develop low-cost, high quality equipment for resuscitation and monitoring of newborns, and training programs for birth attendants in how to prevent and manage complications, were among the highest rated priorities.

1.1.4 Availability of basic newborn resuscitation

During the last decade, learning programs and low-cost equipment for basic newborn resuscitation have been rolled out on a large scale in low- and middle- income countries to meet the MDGs and SDGs. One such program, which has been widely implemented, is the Helping Babies Breathe (HBB) program. More details on this are given in chapter 1.8.

1.2 Physiology of neonatal transition

Knowledge about how healthy newborns adapt to life outside the uterus, is essential to understand the physiology of newborn resuscitation.

1.2.1 Foetal gas exchange and circulation

Prior to delivery, the human foetus depends upon the placenta for gas and nutrient exchange with the maternal circulation. The lungs develop in a fluid-filled, distended shape with a volume of lung-liquid at least equivalent to the functional residual capacity (FRC) after birth.[36-38] Breathing movements are initiated around 11 weeks of gestation, and becomes more vigorous and organized towards the end of pregnancy.[39] The foetal pulmonary vascular resistance is high. Only an estimated 10-15% of the cardiac output go to the lungs, the rest of the right ventricular output is shunted through the ductus arteriosus to the descending aorta (Fig. 3, next page).[40,41]

Deoxygenated blood is transported through the umbilical arteries to the placenta, where it releases CO_2 and waste products and collects oxygen and nutrients. Blood with up to 80% oxygen saturation (SpO_2) returns to the foetus via the umbilical vein.[42] A directed blood flow to prioritize vital organs, ensures a relatively high oxygen concentration to the brain, heart and liver. Blood from the placenta passes through ductus venosus and foramen ovale to fill the left ventricle, and is pumped to the brain and heart through the ascending aorta. The umbilical vein also drains oxygenated blood through the portal sinus to the liver. The placenta receives around 30% of the foetal cardiac output in the second half of

pregnancy, 20% near term.[43] The large vascular bed of the placenta results in a low systemic resistance. A high rate of tissue perfusion, high haemoglobin level, and increased oxygen affinity in foetal compared to adult haemoglobin, facilitates oxygen transport.

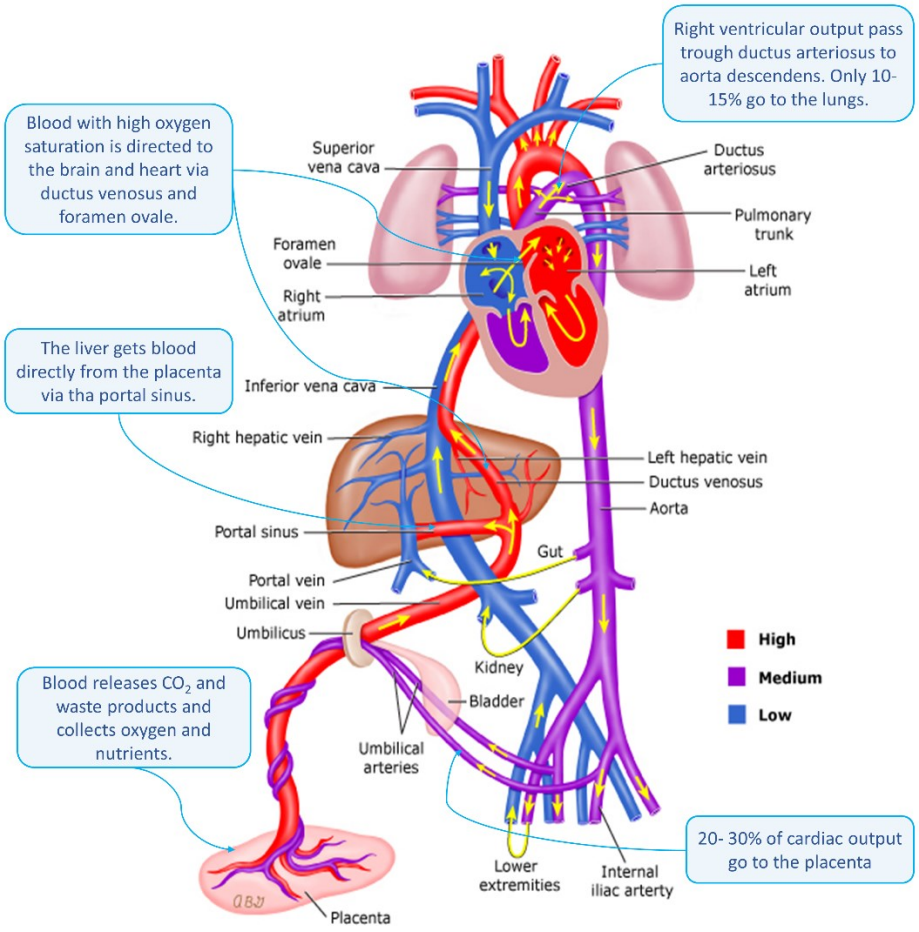


Figure 3 – Illustration of the foetal circulation. Blue textboxes added by K.Holte. Reproduced with permission from: Fernandes CJ. Physiologic transition from intrauterine to extra uterine life. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on March 10th 2021.) Copyright © 2021 UpToDate, Inc. For more information visit www.uptodate.com.

1.2.2 Lung adaption at birth

At birth, liquid must be cleared from the newborn lungs to allow pulmonary gas exchange. Multiple mechanisms before, during and after birth facilitate the process of lung-liquid clearance (Table 1).

Table 1 – Mechanisms contributing to lung liquid clearance at birth.

Active transport of sodium	Glucocorticoids, catecholamines and oxygen are involved in activating Na+ reabsorption through the pulmonary epithelium promoting liquid uptake from the airways into the interstitium.[44-47]
Mechanical forces	Uterine contractions during labour compress the foetal thorax and abdomen causing expulsion of lung liquid.[48-51]
Inspiratory pressure gradients	Negative intrathoracic pressure during active inspiration promote movement of liquid from the alveoli into the interstitial tissue compartment.[52-54]
Clearance of fluid from the pulmonary interstitium	Liquid is gradually cleared from the pulmonary interstitium by the pulmonary circulation and lymphatic vessels.[55,56]
Expiratory braking manoeuvres	Crying and expiratory grunting where the newborn expires actively against a partly closed glottis, help maintain FRC.[57-61]
Role of the chest wall and surfactant	The chest wall partly oppose and surfactant reduce lung recoil generated by surface tension and tissue elasticity, both helps to prevent lung-collapse and maintain FRC.[62-65]

Liquid movement from the airways into the interstitial tissue can occur rapidly, usually within 3-5 breaths, however liquid clearance from the tissue can take hours.[51] The normal FRC of about 30 ml/kg is usually achieved 2-3 hours after birth in vaginally delivered term newborns, 5-6 hours in newborns delivered by caesarean section.[37]

1.2.3 Cardiovascular adaptions at birth

Lung aeration at birth triggers the activity of vasodilating agents (in particular endothelium-derived Nitric Oxide and Prostaglandin I_2) and mechanical effects that reduce pulmonary vascular resistance and increase pulmonary blood flow.[66,67] Clamping of the umbilical cord, removing the low resistance vascular bed of the placenta, leads to a rise in systemic blood pressure. When systemic blood pressure exceeds the pressure in the pulmonary artery, the foetal right-to-left shunt at the ductus arteriosus is reversed. Lung aeration should optimally happen before cord-clamping to maintain left ventricular preload.[68-70]

Mean SpO_2 just before birth in term foetuses is 58%, and can decrease to 30% during labour.[71] The median SpO_2 at 1, 5 and 10 minutes of age in term newborns are 68%, 92% and 97%, respectively.[72] Median time to achieve SpO2 ≥90% is around 8 minutes.

The increase in SpO_2 after birth stimulates closure of the ductus arteriosus. Due to increasing pulmonary blood flow and pulmonary venous return, the left atrial pressure increases, and right-to-left shunting across the foramen ovale decreases.[66] Theoretically, the foramen ovale closes when the pressure in the left atrium exceeds right atrial pressure.

Median heart rate at 5 seconds after birth is around 120 bpm, increasing rapidly to peak around 170 bpm at 1 minute of age, and stabilizes at approximately 150-180 bpm around 5 minutes after births.[73,74] Heart rate measured by pulse oximetry may give lower values than ECG, early cord clamping is associated with lower heart rate.[75,76]

1.3 Hypoxic-ischemic events

Foetal/newborn organ damage due to intrapartum-related events causing poor oxygenation, is commonly called "birth asphyxia". "Asphyxia" is derived from ancient Greek: *"a"– without, "sphuxis"– heartbeat*. Intrapartum complications causing perinatal asphyxia may occur before, during or immediately after birth (Table 2).

Table 2 – Potential causes of perinatal asphyxia (the list is not complete).[77]

Before birth	**During birth**	**After birth**
Maternal conditions *(anaemia, hypotension, preeclampsia, trauma)* Foetal conditions *(anomalies, infection)*	Interruption of placental blood flow Compression of the cord *(abruption placenta, cord prolapse)* Severe impairment of maternal oxygenation *(massive haemorrhage, anaesthetic complications)*	Obstructed airway Pneumothorax Persistent pulmonary hypertension Acute blood loss Sepsis Prematurity

Biochemical diagnostic criteria for severe birth asphyxia with increased risk for neurologic sequela, include an umbilical artery pH <7 and base deficit ≥12 mmol/l.[78] The incidence is 3/1000 live births in high-resourced settings.[79] In absence of blood gasses and pH measures of umbilical blood, diagnostics become less precise in low-resourced settings. The World Health Organization has simply defined birth asphyxia as "failure to initiate or maintain regular breathing at birth."[80] Apgar score <7 at 5 minutes of age, is a commonly used indicator.[81]

1.3.1 The risk of death and brain damage in asphyxiated newborns

Death or brain damage with permanent neurodevelopmental sequela (hypoxic-ischemic encephalopathy), are feared consequences of birth asphyxia. However, even with severe foetal acidaemia, the likelihood of subsequent brain injury or mortality is low.[32] More than 60% of newborns with cord pH <7.00 have a normal labour and delivery course, initiate breathing shortly after birth and are discharged home by normal routine.[82] Among newborns admitted to intensive care units with severe acidaemia, only a small percentage presents with moderate to severe encephalopathy.[83-85]

A disruption of oxygen delivery, initiates several circulatory and biochemical adaptive mechanisms protecting the foetus or newborn from permanent damage.[77] The remarkable ability of newborns to withstand perinatal asphyxia, has been known for ages.[1]

The risk of death or brain injury increases with anoxic time. An isolated respiratory acidosis implies a low risk for brain injury; an elevated arterial pCO_2 may even have protective effects.[86] However, with prolonged hypoxia, increasing metabolic acidosis develops. With an umbilical artery base deficit of 12-16 mmol/L, moderate or severe complications will occur in 10% of newborns. With a base deficit >16 mmol/L at birth, the risk increases to 40%.[87]

1.3.2 A basis for understanding the physiological responses during asphyxia and resuscitation

Geoffrey Dawes (1918-1996) is considered the father of modern newborn resuscitation. In his classical monograph "Birth Asphyxia, Resuscitation and Brain Damage" from 1968, he described responses to disruption of oxygen supply and positive pressure ventilation in newborns of a variety of species, based on animal experiments performed both by himself and other researchers in the 1950 and -60s.[1]

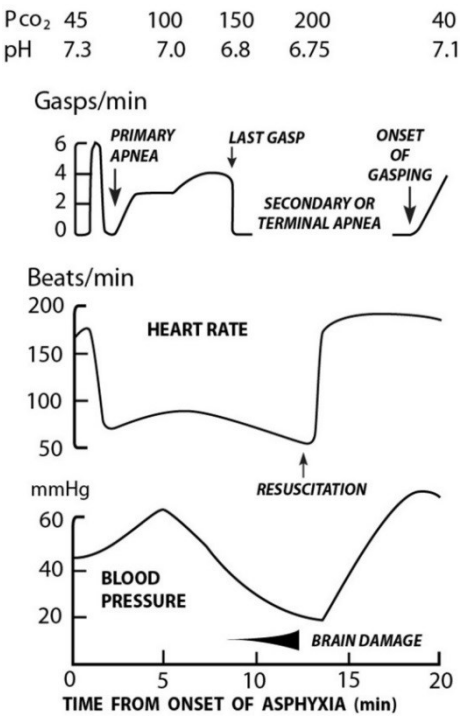


Figure 4 – Physiological parameters during asphyxia and resuscitation in newborn Rhesus monkeys. Adapted from Dawes monograph, 1968.[1]

In his most famous experiment, Dawes blocked the airways of newborn Rhesus monkeys by covering the heads with a bag of warm saline just after cutting the cord (Fig. 4). Around 30 seconds after birth, a brief period of respiratory efforts was observed. This was interrupted by an abrupt and profound fall in heart rate. The animals then went into *"primary apnea"* with cyanosed skin and no muscular tone. Within 0.5-1 minute, the newborn monkeys started gasping, with a temporary increase in frequency after

around 4-5 minutes, before the gasping gradually became weaker. "*Secondary"* or *"terminal apnea"* occurred when gasping stopped completely. If positive pressure ventilation were not started within few minutes after this point, the animal would die.

According to Dawes, the same pattern of primary and secondary apnea interrupted by a period of gasping occurs in several mammal species. Interestingly, the researchers observed large variations in time span depending on species, gestational age, temperature, umbilical artery pH and glycogen stores in the heart. If the arterial pH was low (around 7.0-7.1) on delivery, no breathing movements were observed before the primary apnea. With pH <6.8, "there may be no gasps at all."

Resuscitating his animals with positive pressure ventilation, Dawes described that in still gasping animals, re-admission of air would usually be sufficient to ensure rapid recovery. For animals in secondary apnea, the first sign of recovery would be an increase in heart rate and a gradual increase in blood pressure. Dawes found that time to recovery of respiration depended on the duration of asphyxia beyond the last gasp.

Dawes classical experiments form the base for today's understanding of the physiological responses to birth asphyxia and positive pressure ventilation at birth. Babies vary greatly in degree of asphyxia at birth, but may clinically look the same: Blue/pale, floppy and non-breathing with low heart rate. Newborns in *primary apnea*, will usually respond to basic interventions like drying, stimulation and airway opening. Those in *secondary apnea* may require prolonged positive pressure ventilation.

1.4 International recommendations for newborn resuscitation

Several methods to resuscitate newborns who do not breathe at birth have been applied through history.[88] There is evidence that Hebrew midwives used mouth-to-mouth breathing to resuscitate newborns around 1300 BC. Other methods like tongue pulling, alternate immersion in cold and hot water, slapping, rectal dilation and oxygen administration to the stomach described as late as in the 1960s, were likely less effective. Positive pressure ventilation was identified as key to save newborn lives in the 1960s.[1] Virginia Apgar introduced her scoring system for structured evaluation of the newborn in 1952-53.[89] However, up to late in the twentieth century, newborns were often resuscitated by a hit-or-miss repertoire of strategies based on hunch and theory instead of evidence-based practice.[88]

A more systematic approach to establish evidence-based guidelines for newborn resuscitation, was started in the 1970s and 80s by formation of the Neonatal Resuscitation Program in the US, and the Newborn Life Support course in the UK.[88] The International Liaison Committee on Resuscitation (ILCOR) was formed in 1992 as a forum for cooperation between the principal resuscitation organizations worldwide.[90] Since 2000, the ILCOR has published reviews on resuscitation science and made treatment recommendations approximately every fifth year.[91-93] In questions with insufficient scientific evidence, the committee makes recommendations based on consensus of best available knowledge.

1.4.1 Current recommendations and guidelines

The most recent edition of International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations (CoSTR) for Neonatal Life Support was published in 2020.[94] The algorithm for resuscitation (Fig. 5, next page) was kept unchanged compared to the 2015 version.

Systematic reviews and recommendations from ILCOR form a knowledge basis when regional and national resuscitation committees make guidelines. There are few controversies regarding the key elements, which are practically the same in all guidelines for newborn resuscitation globally.[80,95-98] The goal is to achieve lung aeration and establish pulmonary gas exchange to reverse the asphyxiation process. Initial stimulation and drying is recommended, and will often be sufficient for the newborn to start breathing. For more severely asphyxiated newborns, positive pressure ventilation is central. This should be started without delay, and within 60 seconds after birth.

Systematic reviews by the ILCOR commonly state that "no studies were identified" and available evidence is often classified as "low-certainty". Many details regarding issues like ventilation technique, volume, frequency and devices, differences depending on gestational age, and optimal principles for monitoring have not been sufficiently studied. Thus, differences occur between regional and national guidelines dependent on local preferences and expert opinions, and more research is needed to close the knowledge gaps.

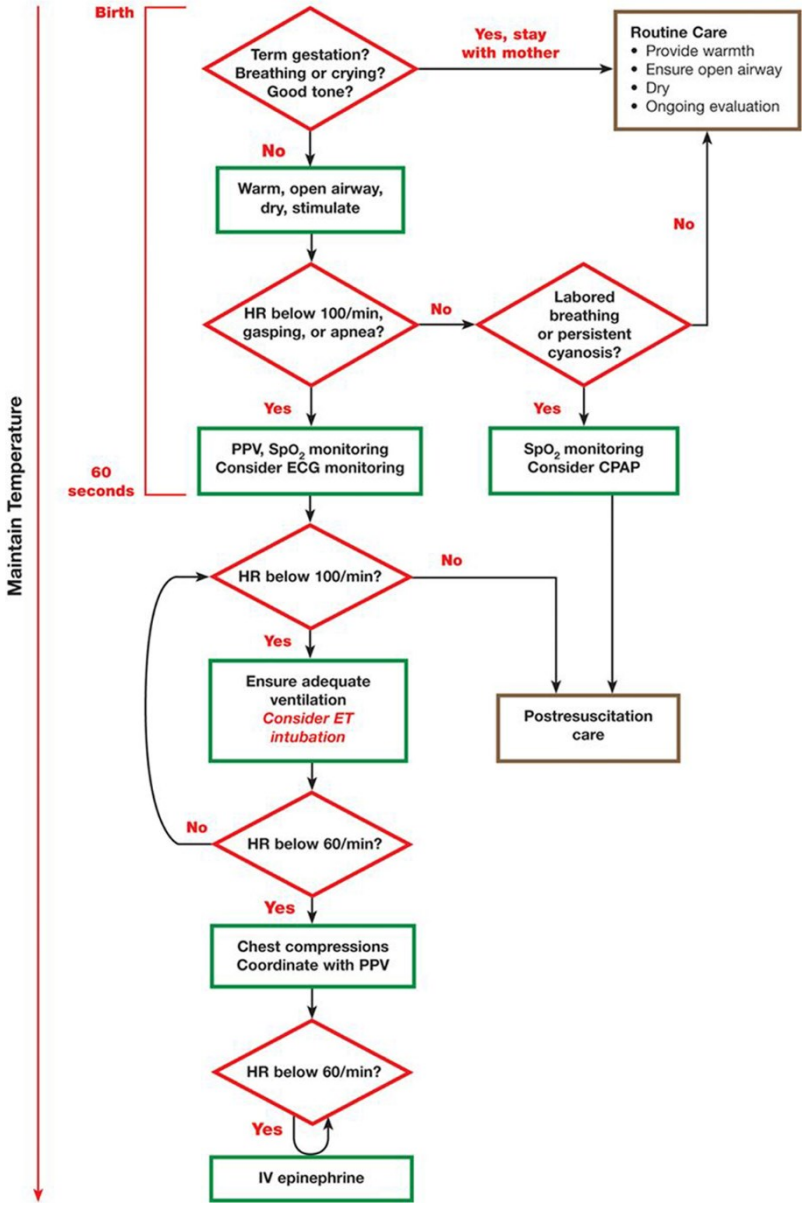


Figure 5 –Neonatal Resuscitation Algorithm according to ILCOR 2020. CPAP indicates continuous positive airway pressure; ECG, electrocardiographic; ET, endotracheal; HR, heart rate; IV, intravenous; and PPV, positive-pressure ventilation.

1.5 The impact of gestational age and birth weight

Babies born at gestational age (GA) 37-42 weeks are defined as "term newborns" (Fig. 6). Birth within 34-36 gestational weeks is commonly regarded as "late preterm" or "near-term".[99] In low-resourced settings, estimates for GA are often imprecise, thus newborns defined as "near-term" in this thesis may also include term newborns who are small for GA, or more preterm newborns who are large for GA. The limits for viability of preterm infants, depend on the availability of advanced neonatal care. Birth before GA 28 weeks is considered an abortion in many low-resourced settings. In high-resourced settings, great efforts will often be done to save extremely preterm newborns down to GA 22 weeks.[30]

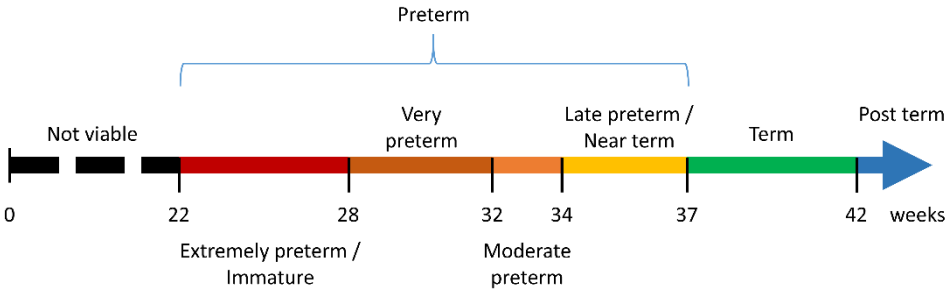


Figure 6 –Different expressions are used to describe degrees of prematurity. The figure is based on WHO definitions by full gestational weeks at birth.[100]

An immature respiratory system causes difficulties for lung aeration (Table 3),[37,51] and preterm lungs are prone to injury caused by positive pressure ventilation.[101-104] Preterm newborns also have increased risk for hypoglycaemia, hypothermia, infections, intracerebral haemorrhages and other complications with potential implications for ventilation, 24-

hour survival and long-term outcomes on long-term. Due to differences in pathophysiological mechanisms and risk factors, results of research done on preterm or immature newborns, may not be generalizable to babies born at or close to term.

Table 3 – Physiological differences in the respiratory system between term and preterm newborns with implications for lung aeration.

	Term	**Preterm**
Endocrinological factors	Increased sensitivity of the pulmonary epithelium to endocrine factors (e.g. cortisol, adrenaline) increasing sodium /water reabsorption	Lung tissue is less responsive to mechanisms to increase sodium /water reabsorption.[44]
Respiratory musculature	Strong. Able to generate high inspiratory pressure gradients.	Weak. Often unable to generate sufficient inspiratory pressures to achieve effective lung aeration.
Chest wall	Compliant, but partly able to oppose lung recoil.	Soft and highly compliant, unable to resist lung recoil.
Surfactant	Present, reduces surface tension at the air/liquid interface of the alveoli.	Insufficient, resulting in high surface tension and increased risk of lung collapse at end-expiration.
Lung volume	Total lung capacity is considerably higher than FRC. Lower risk for volutrauma.	Low difference in volume between FRC and total lung capacity.[104] High risk for ventilation induced lung injury.

1.6 Aerating the lungs

Different equipment is available to ventilate non-breathing newborns, and knowledge gaps exist regarding optimal ventilation strategies.

1.6.1 Equipment

Self-inflating bags

The self-inflating bag (SIB) was introduced in 1956, and is still the most commonly used equipment for newborn resuscitation globally.[80] SIBs consist of a flexible air chamber attached to a face mask (alternatively airway tube or laryngeal mask) via a shutter valve. When the bag is squeezed, the device forces air into the patient's lungs (if the airway is open and the leak is <100%). When the bag is released, it self-inflates to be filled with air or oxygen for the next inflation. Typical bags for neonates vary in volumes from 220 to 320 ml and have a pressure-release valve to avoid unintended delivery of pressures >35-40 cmH_2O.

The SIB is the only ventilation device that can deliver positive pressure ventilations without an external gas source, and thus is the favoured option of ventilation device in low-resourced settings. It is regarded as an essential commodity for basic neonatal resuscitation.[105]

T-piece resuscitators

T-piece resuscitators (TPR) are flow-dependent devices requiring a constant gas inflow to enable provision of positive pressure ventilation. Delivered PIP is adjustable via an airway pressure limit valve. The

device can deliver positive end-expiratory pressure (PEEP) and may be used to support spontaneous breathing by delivering continuous positive airway pressure (CPAP). PEEP/CPAP is adjustable via an expiratory flow resistor. Initial use of CPAP to support breathing during transition at birth is recommended for preterm infants with respiratory distress.[106] Despite a lack of data from term newborns, TPR is currently used as a primary resuscitation device for newborns of all gestational ages many places in resource replete settings.[97,107-111]

In low-resourced settings, TPRs are seldom available due to lack of pressurized air. Table 4 (next page) displays a comparison of advantages and disadvantages of TPRs compared to SIBs.

Flow-inflating bags

Flow-inflating bags require pressurized air to refill the bag between ventilations. The equipment may deliver PEEP, but is difficult to use and requires a high degree of training and experience. Delivered pressures and volumes are highly user dependent.[112] The equipment is mentioned for completeness, but is not considered an alternative for routine use in newborn resuscitation.[106]

Table 4 – Comparison of advantages and disadvantages with self-inflating bags (SIBs) compared to T-piece resuscitators (TPR).

	Advantages	**Disadvantages and risks**
Self-inflating bag	Independent of pressurized gas. Widely available. Low cost.[113] Relatively easy to use. Delivered pressure may be changed quick and easily. [114,115] The resistance in the bag may provide some tactile "feedback" on compliance and air-entry.[116]	Less consistent pressures and tidal volumes compared to TPR.[117-119] Cannot deliver continuous positive pressure to support spontaneous breathing. PEEP-valves for SIBs are available, but concerns have been raised about the ability to deliver reliable PEEP.[120-122]
T-piece resuscitator	Perceived as easy to use.[123] Can deliver PEEP, and provide CPAP to support spontaneous breathing.[124-126] Provides more consistent pressures and tidal volumes compared to SIB.[117-119] May shorten time to initiation of spontaneous breathing.[119,127] May lower risk for BPD in preterm newborns.[128]	Dependent on pressurized air. Difficult to set up and use correctly.[129,130] Risk of inadvertent PEEP generation.[123] Changing delivered pressures takes time compared to SIBs.[114,115] No "tactile feedback" to the provider. Increased risk for pneumothorax, especially in term newborns with high lung compliance.[131-133]

1.6.2 Obstacles and strategies for ventilation

Optimal ventilation strategies during newborn resuscitation to balance the need for a fast lung aeration and re-oxygenation of asphyxiated tissue against the risk for ventilation induced lung injury have not been determined.[94,134] Important obstacles for effective positive pressure ventilation in non-intubated newborns, include mask leak and obstructed airways.[135-137] Lung-compliance varies dependent on pathophysiological mechanisms, and is lower in fluid-filled compared to aerated lungs.[138]

Ventilation induced lung injury

Ventilation induced lung injury is a well-known complication of positive pressure ventilation, and is observed in all age groups.[139] Animal studies point to over-distention due to high tidal volume (V_T) rather than pressure as the dominant risk factor for harm.[102,103,140] Barotrauma by high pressures and atelectotrauma due to repeated collapse and refilling of distal airways, likely contribute.[141] Immature preterm lungs are especially prone to injury. Inflammatory processes initiated by positive pressure ventilation are important in the pathways leading to respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD).[142] BPD mainly affects very preterm infants, and thus is of less relevance for newborns born at or close to term.[143] Using appropriate V_Ts and positive end-expiratory pressure (PEEP) are regarded to be lung-protective ventilation strategies.[101,144,145]

Mask leak and airway obstruction

Considerable leak has been shown to occur during real and simulated newborn mask ventilation.[136,146-149] Large leaks may lead to inadequate V_{TS} during PPV and result in ineffective ventilation. In clinical studies using respiration function monitors to measure leak during ventilation of preterm newborns, median mask leaks between 20-60% has been reported.[150,151] The degree of leak is often underestimated by the provider and not corrected.[150]

Airway obstruction is another cause of inadequate PPV. Using a colorimetric CO_2-detector, airway obstruction has been found to occur in around 75% of newborns ventilated in the delivery room.[152] Arbitrary defining significant obstruction as >75% reduction in expired volumes (V_{TE}), this was found to occur in 26% of newborns in another study.[136] Trigeminal reflex mechanisms (diving reflex) causing apnea and/ or closure of the larynx with application of a facemask, may contribute to high incidence of airway obstruction during PPV in the delivery room.[153]

Degrees of mask leak and obstructed airway vary widely between equipment and providers.[150,151] Training to optimize mask grip may be helpful.[147,148,154] Looking for chest rise is still recommended to guide ventilations during newborn resuscitation in ERC guidelines.[96] This has been shown to be a poor method for estimating tidal volumes.[106,155] Use of respiratory function monitors (RFMs) or CO_2-detectors have been suggested to detect and correct unfavourable ventilation technique during resuscitation.[137,156-159]

Tidal volume

Tidal volume (V_T) during positive pressure ventilation, is the volume of air displaced per inflation. Delivered V_T depends on pressure applied, inflation time, mask leak, lung and chest wall compliance, airway resistance and possible presence of spontaneous breaths.[53,101] Expired tidal volume (V_{TE}) has been found to be a good measure to estimate V_T.[137] During spontaneous breathing at birth, te Pas et al found a mean ± SD V_{TE} of 6.7 ± 3.9 ml/kg in preterm and 6.5 ± 4.1 ml/kg in term newborns, [61] however term infants may use significantly larger V_Ts of 11 ± 5 ml/kg for their first breaths.[160-162] During initial ventilation, some inspired air is kept inside the lungs to form FRC.[53] To clinically assess delivered V_T during PPV is difficult, nevertheless, V_{TE} is rarely measured in clinical practice.[116,150,155,163] Vilstrup et al reported a total lung capacity (TLC) of 43-52 mL/kg in term infants, compared to around 19 ml/kg in preterm infants with RDS by 10 hours of age, with a simultaneous FRC of around 11 ml/kg. Based on these data, some authors have warned that V_T >8ml/kg, may distend the lungs above total lung capacity (TLC) and cause damage, especially in preterm newborns.[101,164]

On the other hand: Insufficient V_T can diminish gas exchange and prolong tissue hypoxia, potentially increasing the risk for brain damage and death.[165,166] Studying the associations between V_{TE} and HR responses during newborn resuscitation, Linde et al found that V_{TE} <6 ml/kg hardly improved HR, while a V_{TE} of median 9.3 ml/kg was associated with the largest positive change in HR.[134]

Ventilation frequency

Observational data on breathing patterns, frequency and tidal volumes in term and preterm newborns, have shown that different ventilation patterns are used, including crying, expiratory hold, grunting and unbraked expiration patterns.[61,167] Ventilation frequency vary greatly dependent on breathing pattern. In 1955, Cook et al reported a ventilation frequency of around 34 breaths/ minute in spontaneously breathing newborns.[168] With unbraked breathing patterns, te Pas et al reported frequencies around 60 breaths/ minute.[61]

The US guidelines for newborn resuscitation recommend 40-60 inflations/min, referring to normal ventilation frequency at birth by spontaneously breathing newborns.[61,95] In European guidelines a ventilation frequency of around 30 inflations/ minute is recommended.[96] Ventilation frequency may have potential impact on lung aeration and affect ventilation efficacy both directly and by indirect effects on other ventilation parameters as V_T, mask leak and inspiration/ expiration times. To my knowledge, no studies have been done to determine the optimal ventilation frequency to achieve a fast and effective lung aeration during BMV in the newborn period.

Prolonged inflation times

During the last few years, there has however been great interest in using prolonged inspiration time in initial inflations during PPV to achieve a fast lung aeration. Inflations where the inflation pressure is maintained for 5 seconds or longer are called *sustained inflations*.

In 1981, Vyas et al found that a prolonged inspiratory time of approximately 5 seconds during PPV facilitated spontaneous respiration in term newborns.[169] Sustained inflations have appeared to be beneficial in animal models.[170-172] However, a large multicentre RCT performed to investigate whether two sustained inflations could improve outcomes compared to standard PPV in preterm infants with GA 26-28 weeks, was stopped after interim analyses due to increased risk of early death in the intervention group.[173] In the latest CoSTR, ILCOR suggest against routine use of initial sustained inflations > 5 seconds.[106] However, the ERC recommends using 5 *opening ventilations* maintaining the inflation pressure for 2-3 seconds.[96]

Peak inflation pressure

Using too high pressures during ventilation, may be a contributing mechanism for ventilation induced lung injury.[140] Ventilation pressures of around 30 cmH_2O has been shown to be sufficient to provide adequate lung-ventilation in most full term newborns.[174] In current guidelines for newborn resuscitation, starting peak inflation pressures (PIP) of 20-25 cmH_2O for preterm and 30 cmH_20 for term newborns are suggested.[95,96] There is weak correlation between PIP and delivered V_{TE}s.[116,150] With low lung-compliance, higher than the recommended initial pressures may be needed to aerate the lungs.[138,165,175] If there is no response to initial inflations despite an open airway, current guidelines state that inflation pressure should be gradually increased.[95,96,106]

1.6.3 Positive end expiratory pressure

Positive end-expiratory pressure (PEEP) is a low positive pressure delivered during expiration in positive pressure ventilation (Fig. 7A).[106] The rationale behind using PEEP is to prevent airway collapse. This may reduce the risk of atelectotrauma by repeated collapse and refilling of distal airways, and improve oxygenation by keeping air inside the alveoli to allow for more effective gas exchange.[37,51] Studies of preterm animals have suggested positive effect of PEEP to assist establishment of FRC and reduce lung injury.[176,177]

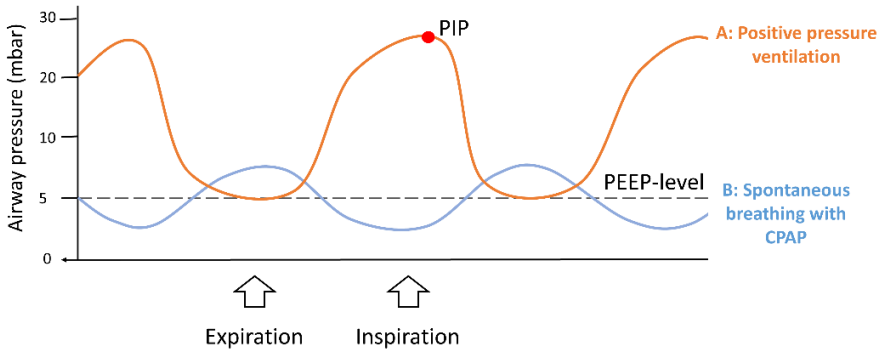


Figure 7 – Pressure curves to illustrate PEEP in positive pressure ventilation (A) versus spontaneous breathing with continuous positive airways pressure (B). In PPV external pressure is applied to "pump" air into the lungs, and PEEP is a low positive pressure at expiration. With CPAP, the pressure fluctuates around the PEEP-level with slightly higher pressures at expiration and lower pressures at inspiration.

Continuous positive airways pressure (CPAP) refers to methodologies of applying a gas flow during spontaneous breathing to generate a positive pressure during the whole ventilation cycle (Fig. 7B). A reduced mortality rate of preterm infants treated with compared to without CPAP, was reported by Gregory in 1971. Nasal CPAP has been widely used in neonatal intensive care units since the early 1970-ties.[178-180] The range of indications include RDS, transient tachypnea, meconium aspiration

syndrome, pulmonary hypertension, pulmonary oedema and respiratory infections.[181,182] CPAP reduce the work of breathing, and the frequency of apnea in preterms.[179] The need for intubation, mechanical ventilation and surfactant administration is reduced.[181] Animal studies have indicated positive effects on oxygenation, FRC, lung compliance, surfactant, lung injury and inflammation.[183] Compared to mechanical ventilation, use on non-invasive respiratory support CPAP may reduce the risk for BPD in preterm newborns.[184]

Despite convincing evidence for positive effects of CPAP in treatment of spontaneous breathing newborns, the evidence for positive effects of PEEP from human studies during PPV at birth is limited. In 2010 the ILCOR stated that PEEP is likely to be beneficial during newborn resuscitation, and should be used if suitable equipment is available.[92] In the 2015 revision, PEEP was still recommended for preterm newborns.[93] However, for term newborns the committee concluded that no recommendation could be given because of insufficient data.

When the work of this thesis was started, PEEP delivered by different devices had been studied in 3 RCTs.[119,185,186] Two studies included term in addition to preterm newborns, but did not report the effects for term newborns alone.[119,186] One study included newborns ventilated with a SIB with PEEP-valve.[119] Serious concerns had been raised about the ability of PEEP-valves for SIBs to deliver reliable PEEP.[120,121,187] Studies to document effects of PEEP in term newborns, and equipment able to deliver reliable PEEP without pressurized air was sought after.[93]

1.7 Monitoring during resuscitation at birth

Stabilization and resuscitation of babies at birth is stressful and requires considerable skills.[188] Assessment of clinical condition and cardiorespiratory monitoring may help adjust and optimize treatment. A selection of methods are mentioned below, with HR monitoring by ECG and ECO_2 monitoring as the two most relevant for this thesis.

1.7.1 Apgar scores

The Apgar scoring system was made to standardise evaluation of newborns' condition at birth (Table 5). [89]

Table 5 – The Apgar scoring system.

	0	1	2
A ppearance (skin color)	Blue / pale	Pink body, blue extremities	Pink
P ulse	Absent	< 100 bpm	≥100 bpm
G rimace (reflex irritability)	Floppy	Minimal response to stimulation	Prompt response to stimulation
A ctivity (muscle tone)	Absent	Flexed arms and legs	Active
R espiration	Absent	Slow and irregular	Vigorous cry

Apgar scores are routinely assessed and recorded at 1, 5 and 10 minutes of age. It is simple and does not require additional equipment. Low Apgar scores have been associated with neonatal mortality and neurologic disability, including cerebral palsy and epilepsy.[189,190] However, most infants with low Apgar scores will have normal

neurodevelopmental outcomes. [191] In a study from Tanzania, 5-minute Apgar score was >7 in 50% of infants who died secondary to birth asphyxia.[192] Despite the standardized system, Apgar scores are subjective, and the inter-observer variability is high.[193,194]

1.7.2 Heart rate

Heart rate assessment is currently considered the most important measure to evaluate clinical condition and response during newborn resuscitation and is central for decision making.[106] Both clinical and technical methods are used (Table 6).

Table 6 – Methods for heart rate monitoring during newborn resuscitation.

	Advantages	**Disadvantages and risks**
Auscultation	Cheap and easily available, requires only a stethoscope. Keeps the focus on the patient. Often the only method available in low resourced settings.[80]	Inaccurate.[195] Done intermittently and gives no continuous feedback. May lead to pauses in ventilation.[4,196,197]
Pulse oximetry	Also provides information on oxygen saturation. Only pulse giving heart beats are counted. Continuous recording and feedback	Takes time to achieve reliable recordings.[198-200] Frequently underestimates heart rate.[201] Loss of signals due to contact disturbances or low peripheral circulation.[198-200]
ECG[1]	Reliable and accurate recordings.[202] Fast to apply. [73,74,198,199] Can distinguish pulseless electric activity from asystole.[203] Continuous recording and feedback.	Pulseless electric activity counted as heart beats. Moves focus from patient to screen.[204]

[1] ECG=Electrocardiogram

1.7.3 Monitoring of ventilation

Adequate ventilation is the cornerstone to successful newborn resuscitation.[106,205] A variety of methods are used or suggested to evaluate whether effective ventilation is achieved (Table 7).

Table 7 – Methods for ventilation monitoring during newborn resuscitation.

	Advantages	**Disadvantages and risks**
Chest rise	Cheap and easily available. Keeps the focus on the patient. Often the only method available in low resourced settings.[98]	Imprecise and subjective. Frequently underestimates V_T.[155] Potentially increases risk for delivery of too high V_Ts, over distention and lung injury.
Pressure display	Widely available and easy to apply on ventilation equipment. Enables detection of large mask leaks. May reduce risk of barotrauma.	Due to variations in lung compliance the appropriate PIP will vary between infants and in the same infant over time.[138,165,206] Does not detect airway obstruction. Does not detect too low or high delivered V_T.[116,207]
Volume display	Enables detection of too low and too high V_{TE}s.[116,207,208] May potentially reduce the risk for lung injury due to volutrauma.[103,142,209,210]	Requires advanced equipment. Measured values include air expressed from upper respiratory tract mask.[211,212] Optimal V_Ts are not known. Gives no information on degree of gas exchange. Moves focus from patient to screen.
RFM[1]	Simultaneous display of pressure, V_{TE}, leak and ventilation frequency. May be used to detect and correct mask leak or obstructed airway.[157] May help avoid injury due to barotrauma, volutrauma, over- or under-ventilation. Learning and improved technique.	Requires advanced equipment. Misinterpretation of signals. Flow sensor adds dead space to the resuscitation equipment and alters hand grip.[157] May not improve clinical performance.[213] Moves focus from patient to screen.

[1] RFM=Respiratory function monitoring

1.7.4 Expired CO_2-monitoring

Pulmonary gas exchange cannot occur before air reaches the alveoli. An increase in expired CO_2 (ECO_2) has been found to indicate degree of lung aeration immediately after birth.[214] In spontaneously breathing term newborns, it has been reported to take on average 9 seconds before ECO_2 was detected.[215,216] Maximum ECO_2 was obtained after 143 seconds. Results from clinical studies have shown an increase in ECO_2 before HR response during PPV in the delivery room.[214,217,218] High mask leak or airway obstruction will lead to a prompt reduction in ECO_2, and thus ECO_2 is promising as an indicator for patent airway and effective ventilation.[219] In addition to ventilation, ECO_2 depends on metabolism and pulmonary circulation.[220] This adds complexity to the interpretation as low levels of ECO_2 do not always indicate that lung aeration has not been achieved, but may also be a sign of a more severe clinical condition. Linde et al found that median ECO_2 in the first minute of bag-mask ventilation at birth was lower in newborns who died before 24 hours of age compared to survivors.[221]

The 2015 CoSTR from ILCOR mentioned ECO_2 as a potentially more sensitive marker of effective ventilation than HR, and stated that more research is needed to determine whether ECO_2 monitoring is useful to assess response to resuscitation.[93]

1.8 Helping Babies Breathe

Helping Babies Breathe (HBB) is an evidence-based curriculum in basic neonatal care and resuscitation for use in resource-limited areas.[98] It was developed by the American Academy of Pediatrics in cooperation with several stakeholders to meet the challenges of MDG 4.[23] The scientific basis is the neonatal evidence evaluation of ILCOR.[106]

The HBB educational program is simulation based, and was designed in order to train large numbers of birth-attendants in the basic steps of newborn resuscitation. The goal is that a skilled and equipped person should be present at every birth to provide adequate care for the baby. Birth-attendants should be able to assess the clinical condition of the newborn, provide temperature support, dry and stimulate the baby, and perform timely assisted ventilation if needed.

Only very few (<1%) newborns will need chest compressions, medication or prolonged assisted ventilation,[3] and the chances for these newborns to survive in low-resourced settings are very small in absence of advanced medical care. Thus, the HBB-curriculum does not include instructions for chest compressions, medication or intubation.

Equipment and educational material for the HBB-program were developed and designed in cooperation with Laerdal Global Health (Stavanger, Norway). The action plan and course material are largely pictorial with simple text (Fig. 8, next page).

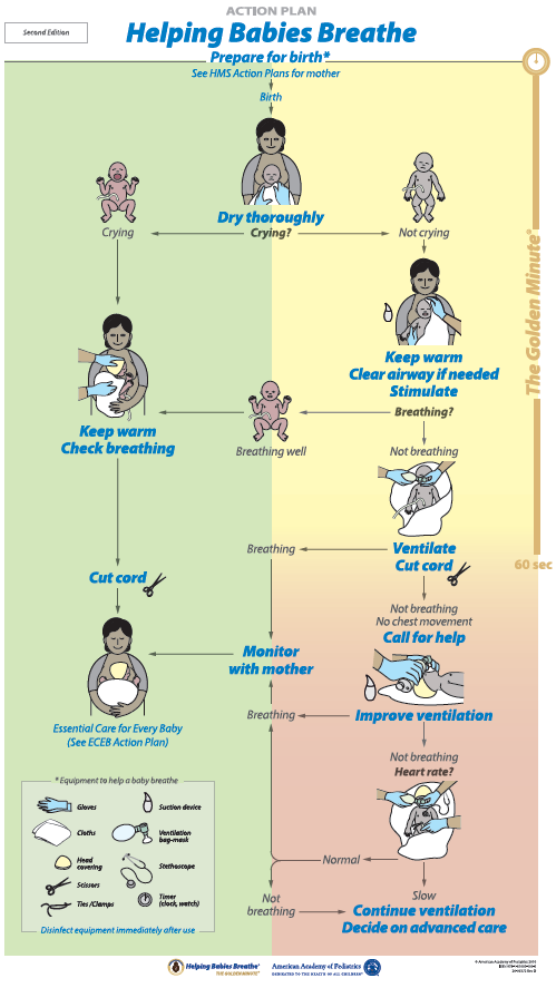


Figure 8 - Helping Babies Breathe action plan for newborn resuscitation, second edition (Published with permission from the American Academy of Pediatrics)

The Helping Babies Breathe learning program for newborn resuscitation, has been implemented in more than 80 countries. More than 750 000 health care workers have been trained and equipped.[98]

Following introduction of HBB in eight Tanzanian hospitals, 24-hour newborn mortality was reduced by 47%, stillbirth rates by 24%.[10]

In a review article from 2011, it was estimated that neonatal resuscitation training in facilities, reduces term intrapartum-related deaths by 30%.[222]

1.9 The Safer Births project

Safer Births is a group of researchers, research staff and engineers, today counting more than 100 people representing 12 international institutions.[223] The ambitious goal is to contribute to improve newborn survival globally. Safer Birth was formally established in 2012 as a collaboration between Haydom Lutheran Hospital and Muhimbili National Hospital in Tanzania, Stavanger University Hospital in Norway and Laerdal Global Health. The project was preceded by a research collaboration associated with the national implementation and evaluation of the HBB program initiated in Tanzania in 2009.[10] Hege Ersdal did her PhD on a work linked to the implementation of HBB in Tanzania.[224] She is the principal investigator for the Safer Births study group and a supervisor for the present work.

The Safer Births project aims to support prevention, detection and management of perinatal asphyxia through sustainable, feasible and adaptable solutions for training and therapy. The public-private partnership with Laerdal Global Health allows for development of new equipment designed for use in low-resourced settings. Laerdal Global Health also delivers equipment and education material for the HBB-program on a non-profit basis. Safer Births aims to evaluate and improve equipment and learning methods used with the HBB-curriculum. [98]

The research in the Safer Births focus on primary prevention of birth asphyxia by methods to monitor foetal heart rate during labour,[29] and secondary prevention through studies on methods, equipment and

training for newborn resuscitation, stabilisation and monitoring. Through years of continuous data collection, the project has established an impressive database with observational data from around 30 000 deliveries, and heart rate and ventilation data from more than 1600 bag-mask ventilated newborns.[223] The large database offers possibilities to study a wide range of questions related to newborn survival and resuscitation in low-resourced settings using a variety of methods. Papers published by the group range from epidemiological studies and studies to evaluate cost effectiveness of interventions[192,225-229] via studies of machine learning for automatic interpretation of data[230-232] to studies to describe practise,[196] evaluate effect of training methodologies,[233-236] studies to improve understanding of the basic physiology of newborn transition and resuscitation[74,134,138,221,237] and RCTs to compare new equipment to existing standards.[238,239]

1.10 Summary of the introduction

The global burden of newborn mortality and morbidity due to hypoxic ischaemic events during labour is high and largely preventable. Having a skilled and equipped birth attendant present at every birth is central to save newborn lives. Positive pressure ventilation is the key to newborn resuscitation. There are knowledge gaps regarding optimal ventilation strategies and monitoring during resuscitation. Clinical benefits of using PEEP to term newborns are poorly documented. Optimal ventilation volumes and frequency are not known. Measuring ECO_2 during resuscitation adds interesting possibilities.

2 Aims and hypotheses

The overall aims of this thesis were to investigate potential benefits of ECO_2-monitoring and a new PEEP-valve in bag-mask ventilation during resuscitation of mainly term newborns.

2.1 Specific aims

1. To study how ventilation factors (V_{TE}, ventilation rate, leak and PIP) and clinical factors (initial HR, Apgar scores) affect ECO_2 during bag-mask ventilation in newborn resuscitation.	**Paper I**
2. To compare the relative impact of ventilation factors and clinical factors on ECO_2 during bag-mask ventilation in newborn resuscitation.	
3. To explore ECO_2 as a marker of positive clinical response to bag-mask ventilation during newborn resuscitation.	**Paper II**
4. To compare the predictive information of ECO_2 and HR as indicators of 24-hour survival during newborn resuscitation.	
5. To determine whether adding a new PEEP-valve to the bag-mask device, compared to no-PEEP, can improve HR response in term and near-term newborns during resuscitation.	**Paper III**
6. To study the impact of PEEP compared to no-PEEP, on 24-hours mortality and ventilation parameters during bag-mask ventilation in newborn resuscitation.	

2.2 Hypotheses

Ventilation factors (V_{TE}, ventilation rate, leak and PIP) and clinical factors (initial HR, Apgar scores) affect measured values of ECO_2 during newborn resuscitation.	**Paper I**
ECO_2 can predict survival during newborn resuscitation and is an earlier indicator for positive response to bag-mask ventilation than HR	**Paper II**
Adding a new PEEP-valve to the bag-mask device during newborn resuscitation improves HR response in term and near-term newborns.	**Paper III**

2.3 Proposed clinical benefit

Better understanding of the relative impact of ventilation factors (V_{TE}, ventilation rate, leak and PIP) and clinical factors (initial HR, Apgar scores) on ECO_2 may improve interpretation of ECO_2 measurements during newborn resuscitation and help determine optimal ventilation strategies.	**Paper I**
ECO_2 may be used as an early marker for severity of clinical condition, ventilation quality, treatment response and prognosis during newborn resuscitation.	**Paper II**
If the new PEEP-valve is effective to improve HR response, it may have potential to improve clinical outcomes of newborn resuscitation, especially in low-resourced settings where ventilation equipment dependent on pressurized air is unavailable.	**Paper III**

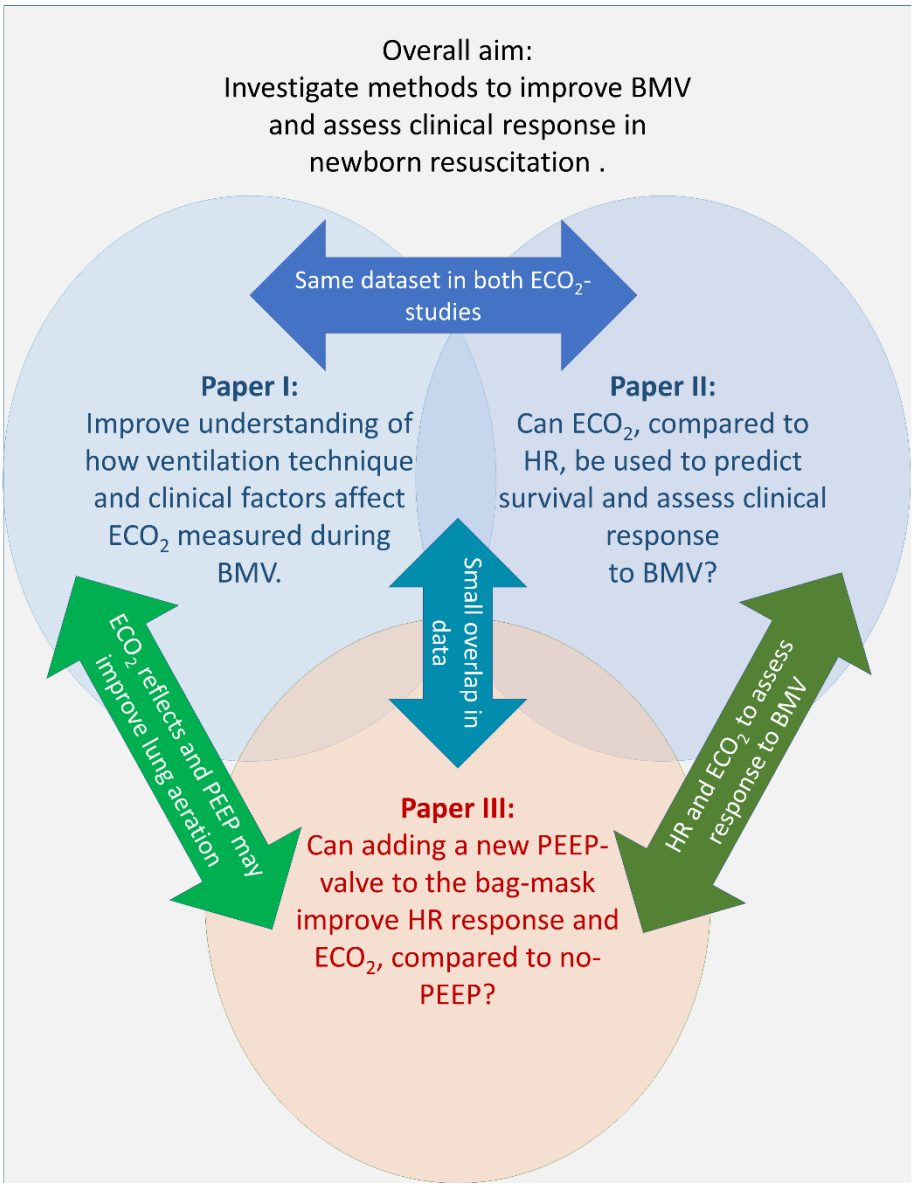


Figure 9 – The figure illustrates connections between aims, hypotheses and study population in the papers included in this thesis.

3 Methods

3.1 Setting and study population

All data for the studies included in this thesis, were collected at Haydom Lutheran Hospital, a rural referral hospital located in the Manyara province of Tanzania (Fig. 10). Around 900 000 people live in the primary catchment area, 5.7 million in the greater reference area.[240] The hospital was founded by Norwegian Missionaries in 1955, integrated in the national health plan of Tanzania in 1963 and recognized as a level 2 referral hospital by the Government of Tanzania in 2010.

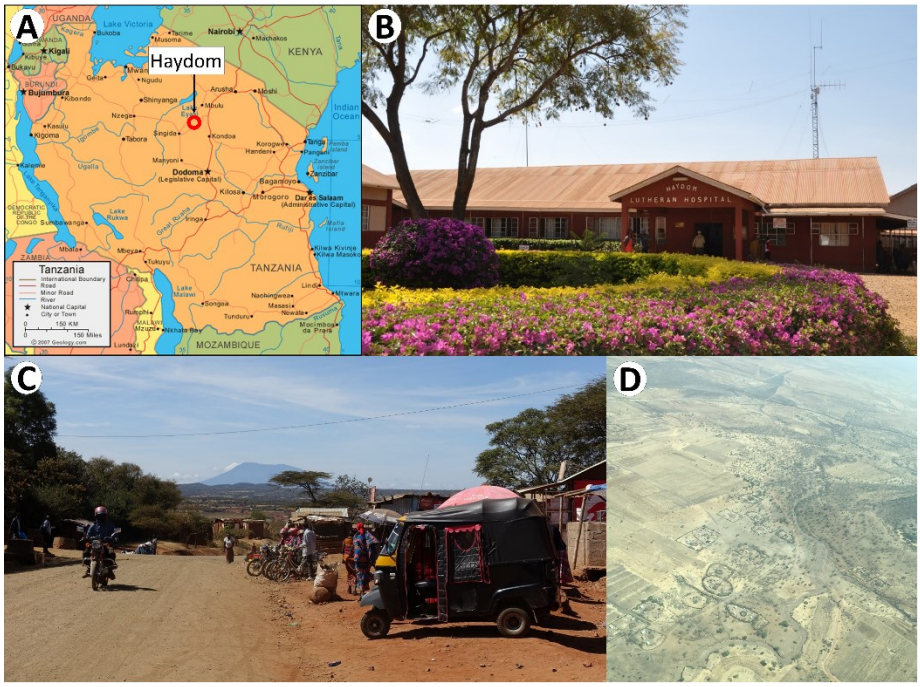


Figure 10– A: Map of Tanzania. B: Haydom Lutheran Hospital. C: Haydom main road. D: Farmland of the Manyara region in dry season. Photos: Kari Holte.

The area around the hospital is mainly farmland with a poor, rural population. Local roads have a low standard, and for many people, getting to the hospital is a long and uncomfortable travel. Home delivery is common, with an estimated proportion of about 50% in the region.[241] Childbirths are also conducted in governmental Health Centres and Dispensaries (level I) in the reference area. Poor infrastructure, long transport and low income cause delay for complicated deliveries to be assisted, mothers often arrive to the hospital in late stage labour. After introduction of user fees for ambulance transport and delivery from January 2014, the monthly number of deliveries in the hospital was reduced by 17% within few weeks, within 5 years the reduction was 30%.[225,227] The frequency of labour complications increased.

The hospital provides comprehensive emergency obstetric care and basic newborn care. Midwives conduct most deliveries, with doctors on 24-hours call. There are seven single bed labour rooms and one operation theatre for caesarean section, all equipped with a resuscitation table. Newborn resuscitation is mainly the responsibility of midwives. The local procedure for newborn resuscitation follows the HBB algorithm emphasizing stimulation and early initiation of BMV, but does not include chest compressions or medication.[98] After resuscitation the midwives decides, based on the clinical condition, whether to keep the newborn with the mother or transfer to a neonatal ward offering antibiotics, phototherapy and intravenous fluids, but no respiratory support except supplemental oxygen by nasal cannula.[229]

3.2 Study designs and timeline

Paper I and **II** are descriptive and analytic observational studies using data collected prospectively in the Safer Birth study at Haydom Lutheran Hospital between March 1st 2013 and June 1st 2017. The two studies are based on the same cohort of live-born bag-mask ventilated newborns with first recorded HR <120 bpm. **Paper III** is a non-blinded randomized controlled trial performed at Haydom Lutheran Hospital between September 26th 2016 and June 30th 2018.

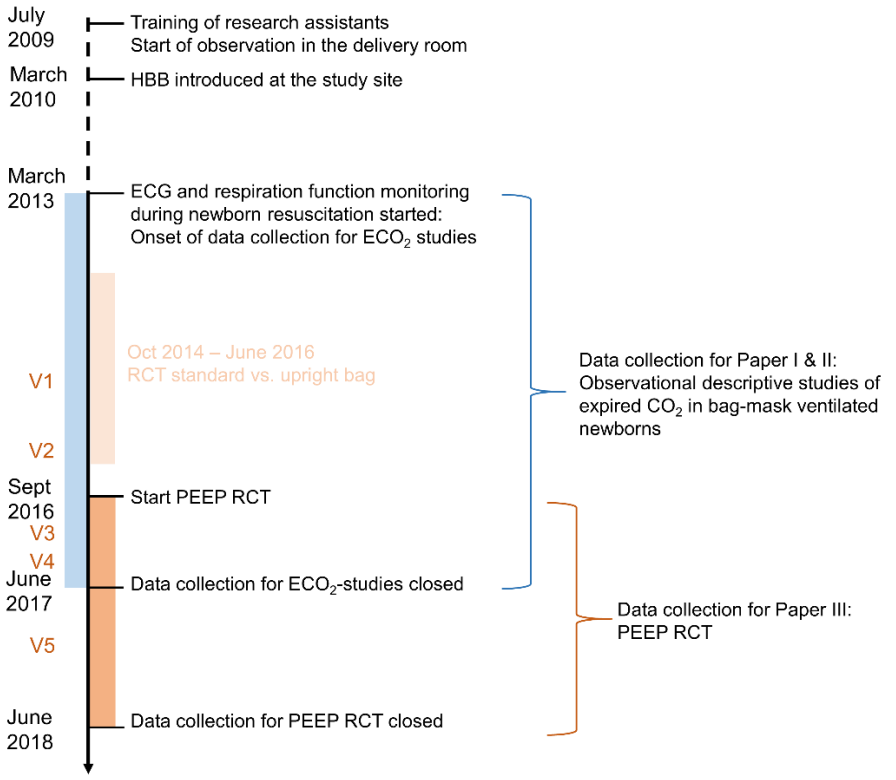


Figure 11 – Timeline of data collection for the studies included in the thesis and central time points in the build-up of the Safer Births study. V1-5 marks visits to the study site by the PhD-candidate. Information on other studies in the Safer Birth project is given in the introduction.

3.3 Data sources, equipment and training

The studies included in this thesis were all done taking advantage of the unique research infrastructure in the labour ward of Haydom Lutheran Hospital.

3.3.1 Data sources

Three main data sources were available:

1. Systematic, direct observational data
2. ECG and ventilation data
3. Video data

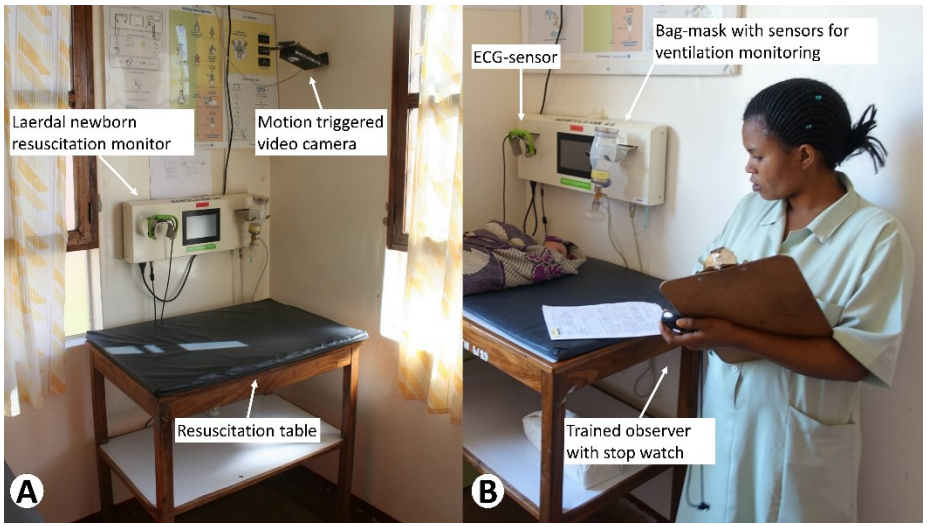


Figure 12 – A: Resuscitation table with Laerdal Newborn Resuscitation Monitor and motion triggered camera. B: Research assistant observing newborn after birth. Photos: Kari Holte

Trained non-medical research assistants observed all deliveries (Fig. 12).[9] They recorded perinatal information included gestational age,

labour complications, exact timing of the birth, delivery mode, birth weight, gender and Apgar scores. If resuscitation was attempted, they documented time intervals using stop watch and noted whether stimulation, suction or bag-mask ventilation was done, what equipment was used and the outcome at 30 minutes and 24 hours. The form used by the research assistant to record information, is enclosed in Appendix 1.

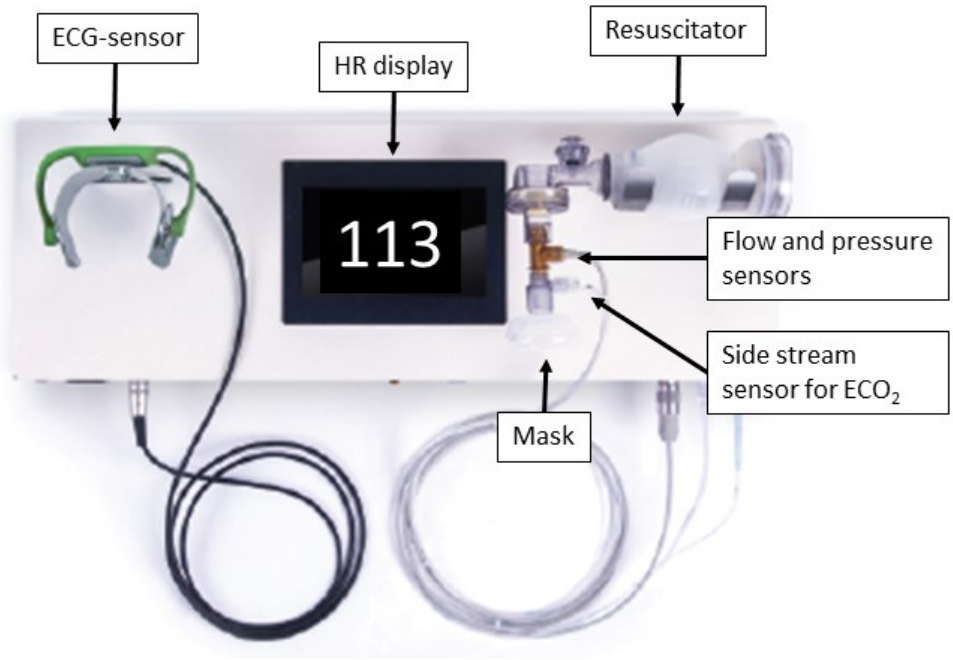


Figure 13 – Laerdal Newborn Resuscitation Monitor.

A newborn resuscitation monitor (Fig. 13) developed for research by Laerdal Global Health (Stavanger, Norway) was mounted on the wall above all resuscitation tables.[242] Each monitor was equipped with a self-inflating bag and a dry-electrode ECG sensor to be easily placed around the newborns' trunk. Sensors for side-stream CO_2 (ISA^{TM}, Masimo,

Irvine, CA, USA), pressure (piezo resistive pressure sensor, MPXV5010, Freescale semiconductor, Austin, TX, USA) and flow (hotwire anemometer flow sensor, MIM, Gmbh, Krugzell, Germany) to record ECO_2 and ventilation parameters were placed between the mask and bag. The attachment device added a dead space of 1 ml. The monitors provided visual HR feedback on the screen. ECO_2 and ventilation parameters were not displayed.

Motion triggered video cameras were mounted above all resuscitation tables. Videos were used for quality control, but not as a primary data source in the present studies.

3.3.2 Ventilation devices

For the studies in Paper I and II, 230 ml standard (Fig. 14) or 320 ml Upright resuscitator (Figure 15, Laerdal Global Health, Stavanger, Norway) were used for BMV.

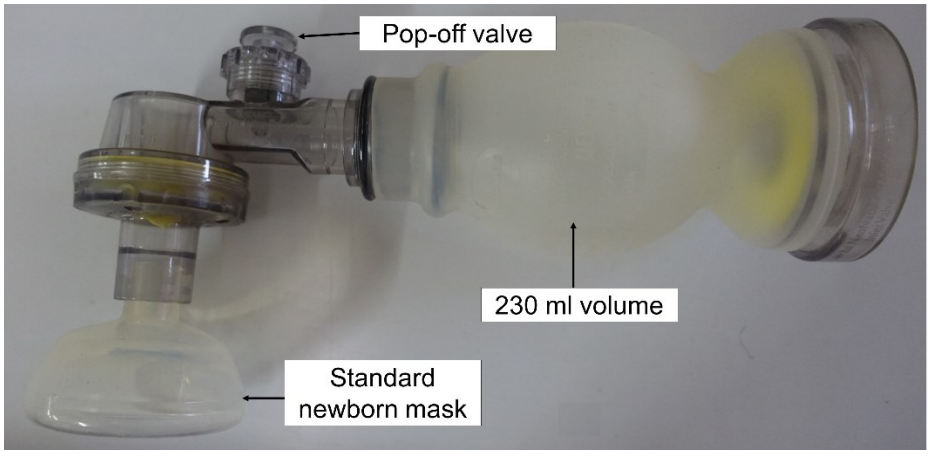


Figure 14 – Laerdal standard resuscitator.

The newborns included in Paper III were ventilated by 320 ml Upright resuscitator (Fig. 15, Laerdal Global Health, Stavanger, Norway) with or without a new PEEP-valve. Except for the PEEP-valve, the two resuscitators were identical.

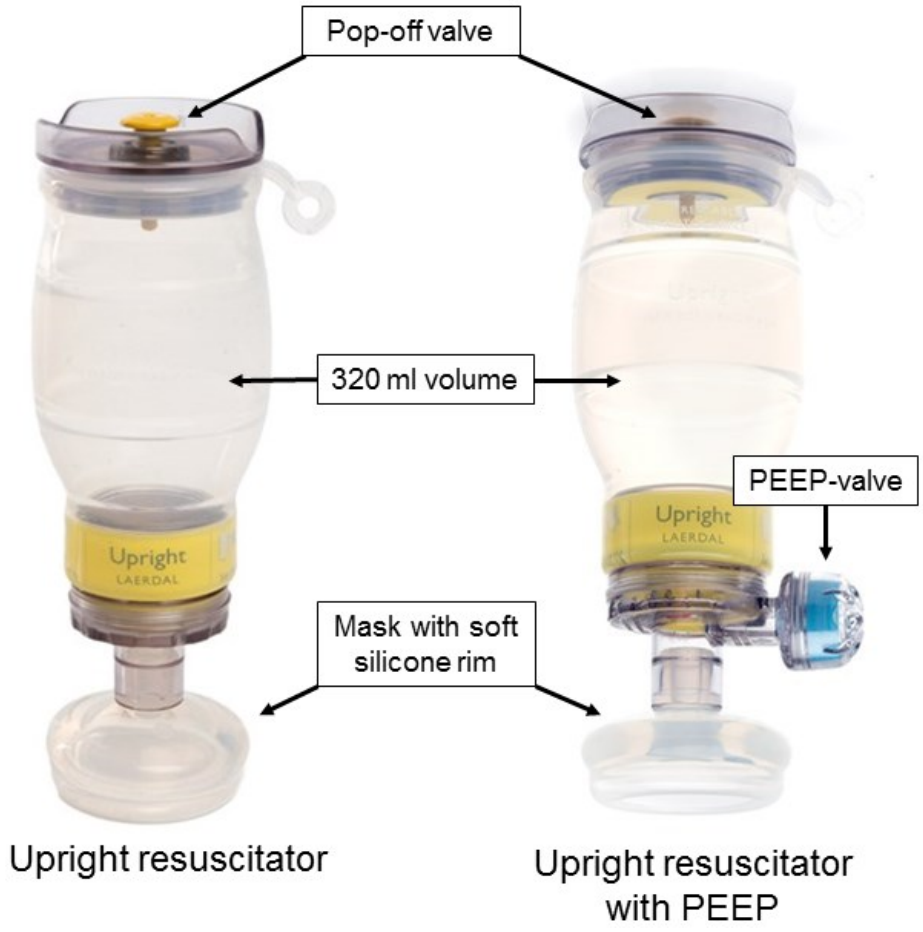


Figure 15 – Laerdal Upright resuscitator without and with PEEP-valve.

The PEEP-valve in Laerdal Upright bag with PEEP, consists of a convex silicone membrane with a slit connected to the expiration channel (Fig.16). When pressure during expiration exceeds approximately 6 mbar, the membrane inverts and the slit opens to let air escape. At lower pressures, the valve is closed. This enables PEEP to be generated without an external gas source. The PEEP-valve and expiration channel were dimensioned to fit the normal expiration volumes of newborns.

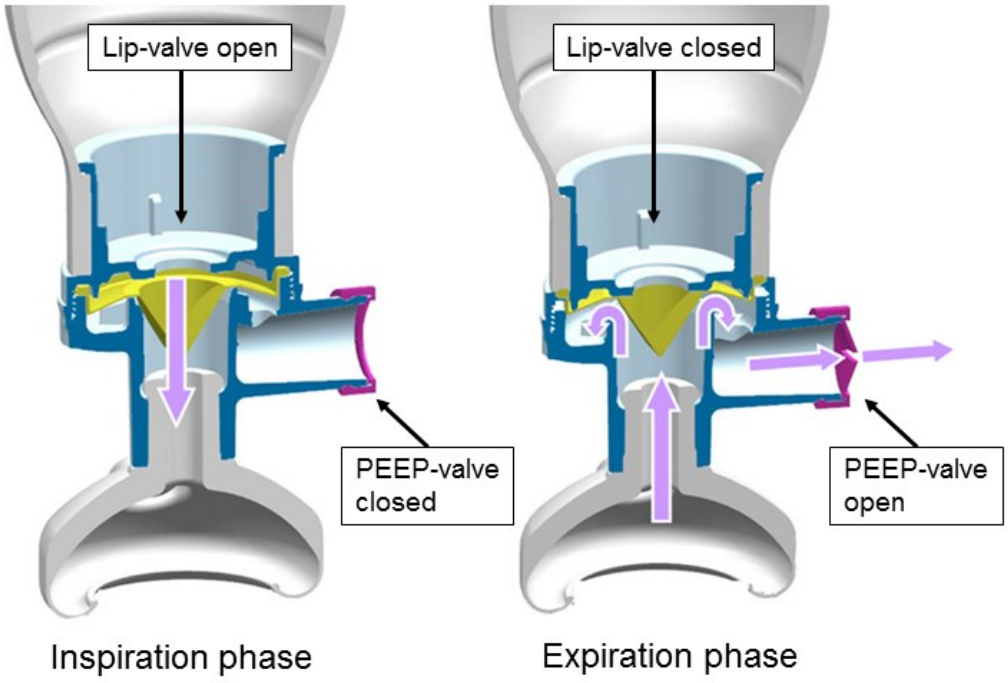


Figure 16 – Cut-through illustration of Laerdal Upright resuscitator with the new PEEP-valve. (Figure: Øystein Gomo.)

3.3.3 Training

Since introduction of high frequency, low dose HBB-training at Haydom Lutheran Hospital in 2011,[228,235,236] manikins for skills training have been available in the labour ward, and midwives have been encouraged to practice. Focus on training has varied over time, depending on ongoing studies. One-day HBB courses for midwives, nurses in neonatal and maternity ward and anesthesiology nurses have been arranged approximately once a year. HBB-trainings were combined with giving information to the health care personnel about planned and ongoing studies.

No special trainings were arranged for Paper I and II. Data collection was done in parallel with concurrent studies. During the RCT comparing ventilation performances using Laerdal standard resuscitator or Laerdal Upright bag in October 2014 to May 2016, two one-day HBB-training courses plus ten-minute weekly practical simulation trainings were arranged.[239] Preparing for the PEEP RCT, one-day HBB-training courses for all personnel involved in deliveries and newborn care were arranged in May 2016. Information about the study was given simultaneously. Further training-sessions and motivation meetings related to the PEEP RCT were arranged when the PhD-candidate visited the study site (Table 8). Local HBB master trainers were responsible for keeping a constant focus on training between these visits. In January 2017 new training equipment including a more advanced manikin able to give feedback on ventilation technique and an iPad with an App for team training was introduced at the study site.

Table 8 – Visits to the study site for training and follow up related to the PEEP-study.

Visit	**Month/Year**	**Purpose of visit**
V1	Aug 2015	Introduction of the PhD-candidate to the study site and team.
V2	May 2016	One-day HBB-training courses. Information to personnel about the planned PEEP-study. Meetings with team.
-	Sept 2016	Start of PEEP-study. The PhD-candidate could not come due to death of sister. The main supervisor Ketil Størdal went to Haydom in her place.
V3	Jan 2017	Visit to follow up data collection. Introduction of new training equipment including more advanced manikin and app for team training at the study site. Sessions with skills training and simulation training in the labour ward.
V4	May 2017	Visit to follow up data collection and improve inclusion. Motivation and information. Individual training sessions.
V5	Oct 2017	One-day HBB-training courses. Meetings with team.

3.4 Inclusion and randomization

For paper I and II we included all live-born newborns with initial HR <120 bpm and available data for both ECO_2 and HR. The choice to exclude newborns with initial HR (iHR) ≥120 bpm was based on a prior study finding that normal HR is around 120 in the first seconds of life.[74] As low iHR is a known risk factor for unfavourable outcome,[221] we proposed that newborns who received BMV, but had higher HR at the onset of recordings, were likely different in pathophysiology and prognosis. Stillborns, defined as Apgar score 0 at 1 and 5 minutes or GA <28 weeks, were excluded. We also excluded newborns ventilated with PEEP, as we expected PEEP to affect lung aeration with potential impact on ECO_2. Exclusions due to missing data were mainly related to technical problems with the resuscitation monitors or delayed download which a few times resulted in overwriting of data.

For paper III, all live-born bag-mask ventilated newborns without major deformities were eligible for inclusion. Randomization was done by weeks. The first and last author prepared a randomization schedule in advance, using www.randomizer.org. Research nurses changed all resuscitators weekly so that only the bag-mask resuscitator according to randomization (Upright resuscitator without or with PEEP-valve) was placed at the resuscitation tables. Randomization per patient was not feasible in this setting where mothers frequently arrive in late stage labour. Blinding was impossible, as the presence of PEEP-valve was visible on the bags.

3.5 Data collection, management and control

Observational data were noted from the time of admission to 24 hours after birth in all deliveries (Fig. 17). The resuscitation monitor automatically started data collection when HR-sensor or bag-mask was used. The video cameras were motion triggered. Thus, data were collected for all newborns born in the data collection period.

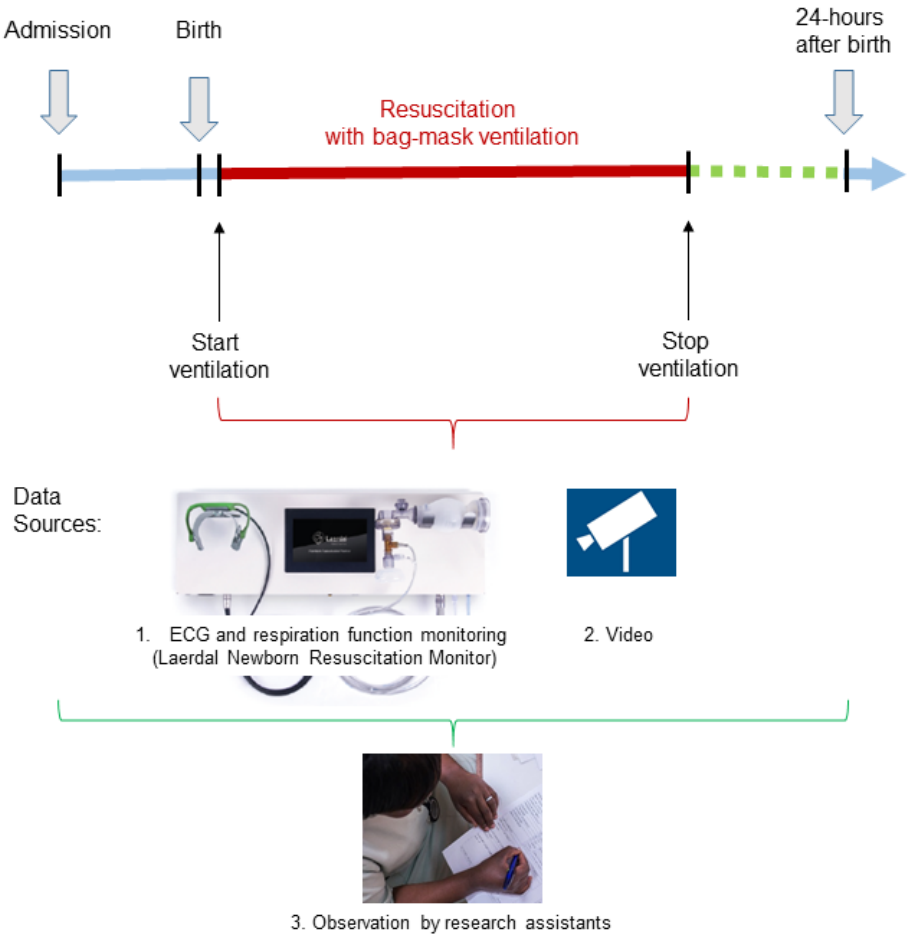


Figure 17 – Timeline of data collection for bag-mask ventilated newborns.

Observations done by research assistants, were noted on data collection forms (Appendix 1). Finished forms were kept in a locked drawer, collected by a research nurse the following day, and brought to the research department where data were double entered into a database by two data clerks. If discrepancies between the entered data were seen, the original data form was rechecked. The original forms were stored in locked, fire safe cabinets. Signal data from the resuscitation monitor and video-data were downloaded on a weekly basis.

All data were sent to a server at Laerdal Strategic Research, Stavanger, Norway, where it underwent subsequent quality control. Each patient dataset from the monitor was checked manually for signal integrity by Joar Eilevstjønn. Crosschecks of data from different sources were done by the PhD-candidate, Hege Ersdal and other members of the Safer Birth study group. If inconsistences were found, the original data were double checked and mistakes corrected.

Research nurses did daily rounds in the labour ward during the data collection period to check the monitors, clean used equipment and collect data collection forms (Fig. 18, next page).

During the data collection period for the PEEP RCT, a weekly check of delivered PEEP was performed using a manometer, and the PEEP-valves were visually inspected to make sure that they kept working as intended. None of the PEEP-valves needed replacement during the data collection period. In the PEEP-study, data were excluded if consent from the mother was not obtained.

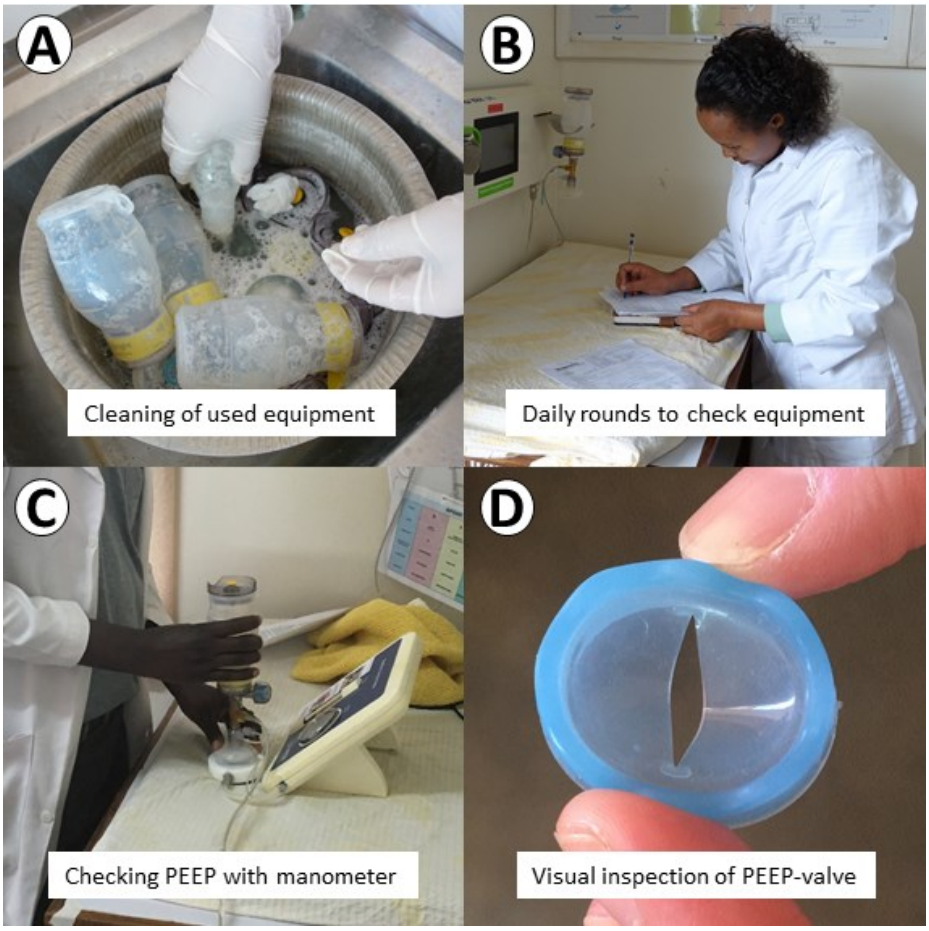


Figure 18 – Examples of control routines during the data collection period. A+B: Research nurse Anita Yeconia on daily rounds to check equipment and keep everything clean and ready for use. C+D: Weekly check of delivered PEEP and inspection of PEEP-valves during PEEP RCT. All photos: Kari Holte.

3.6 Data analysis and statistics

All statistical analyses for the papers included in this thesis were done by the PhD-candidate using Stata SE version 16 (StataCorp, Texas, USA). Ketil Størdal, Hege Ersdal and Claus Klingenberg supervised choices of outcome measures, covariates, methodology and presentation of results. For paper I, help and advice was provided by statistician René Holst at Østfold Hospital Trust. For Paper II and III, Hein Stigum at the Norwegian Institute of Public Health was an important collaborator to discuss and solve statistical issues.

3.6.1 Sample size calculation

Paper I and II were descriptive and analytic observational studies. Due to the large sample of data collected, and the explorative nature of the studies, no sample size calculations were considered necessary.

Sample size calculation for Paper III was done by Ketil Størdal based on HR changes found in a study by Linde et al.[74] To detect a clinical relevant difference of 25% with a two-sided significance level of 0.05 and a power of 0.80, we found that a minimum of 882 ventilation sequences (definition on next page) from approximately 300 newborns would be necessary. Accounting for 10% missing data, we aimed to enrol a minimum of 330 newborns, 165 in each group. Due to frequently missing HR data at the start of BMV, we expanded the data collection period to 4 months after reaching the target of 330 included newborns. Dependency between ventilation sequences was not accounted for in the sample size calculation.

3.6.2 Definitions of parameters used for analyses in the thesis

ECO_2	Maximum concentration of carbon dioxide as percent of expired air per ventilation, collected side-stream by continuous sampling between bag and mask.
HR	Heart rate measured by dry-electrode ECG. Values were smoothed as means per approximately 12 beats per algorithm in the monitor.
24-hour survival	Binary parameter for 24-hour outcome; survival versus death.
V_{TE}	Expiratory tidal volume calculated based on expiratory flow measured between bag and mask. May underestimate true values slightly due to minimal leak during expiration.
VR	Ventilation rate (frequency) calculated based on time between ventilations. The threshold to detect a ventilation was set to PIP >5 mbar.
ML	Mask leak calculated per ventilation based on the difference (percent, %) between inspired and expired volumes.
PIP	Peak inflation pressure measured in mbar as the highest registered pressure per ventilation.
MIP	Mean inflation pressure calculated for individual ventilations based on integration of the pressure curve.
PEEP	Positive end-expiratory pressure defined as the pressure in mbar measured at the end of the expiration curve just before the next ventilation began.
BW	Birth weight in grams, commonly rounded up or down to nearest 50 grams by the midwives.
iHR	Initial heart rate calculated as the mean of first five recorded HR values per newborn.
Apgar scores	Apgar scores given by the midwives at 1 and 5 minutes of age. Subjective parameter.
Time	Time in seconds calculated from the first ventilation per newborn or per ventilation sequence as specified.
Ventilation sequence	Periods of minimum 10 seconds with continuous ventilation and no pauses > 5 seconds.

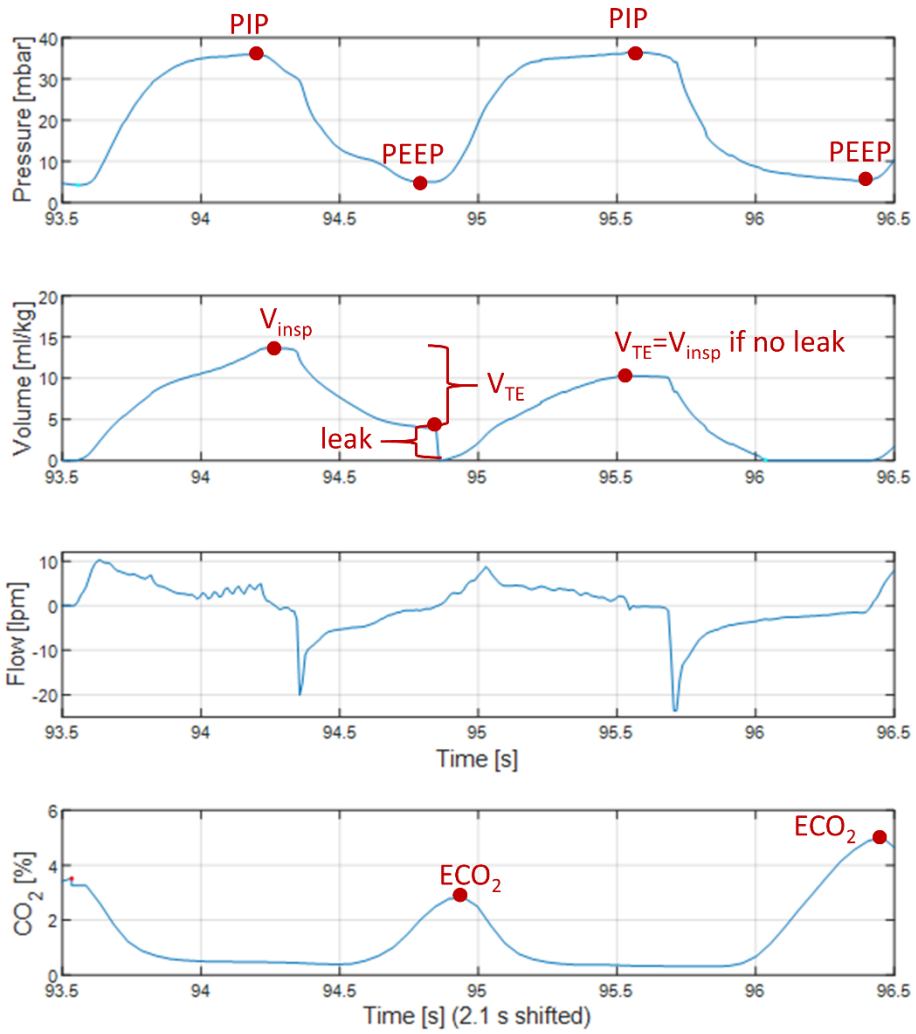


Figure 19 – Section of pressure-, volume, flow, and CO_2-curves from one of the included newborns who received bag-mask ventilation with PEEP. The measuring points for PIP, PEEP and ECO_2 are marked. A delay in ECO_2-recording due to side-stream sampling causes a time-shift of 2.1 seconds for the CO_2-curves compared to the other curves. Expired volumes were used as estimates for tidal volumes (V_{TE}). The leak was estimated as the difference between inspired volume (V_{insp}) and V_{TE}. The volume curve was set to baseline with each new inspiration. In absence of leak $V_{insp} = V_{TE}$

3.6.3 Calculations and exclusions done before analyses in each paper

Paper I	ECO_2, V_{TE}, VR, ML and PIP were smoothed as floating means per 5 ventilations within ventilation sequences. One value per ventilation were included in mixed models. Time to ECO_2 >2% was calculated as the time from first delivered BMV until the first smoothed ECO_2-value >2%. Ventilations with V_{TE} >30mlkg or VR >120/min were considered unlikely to be correct measurements and excluded. For the random intercept analyses, we included observations from the first 5 minutes of ventilation.
Paper II	ECO_2 was calculated as medians and maximums of per ventilation maximums per individual per time intervals (0-30, 30.1-60 and 60.1-300 seconds) HR was calculated as medians and maximums per individual per time intervals (0-30, 30.1-60 and 60.1-300 seconds) V_{TE} was calculated as per individual medians per time intervals (0-30, 30.1-60 and 60.1-300 seconds). Ventilations with V_{TE} >30mlkg or VR >120/min were considered unlikely to be correct measurements and excluded.
Paper III	All observations of HR, ECO_2, V_{TE} and ML per individual newborn were used in mixed models. PIP, MIP and PEEP were calculated as medians of per individual medians per first 10 minutes of BMV.

3.6.4 Statistical methods

For descriptive statistics, all quantitative parameters were checked for normality by Shapiro Wilks test and plotting the distributions in histograms. Normally distributed parameters were displayed as means with standard deviations (SD). Parameters with skewed distributions were displayed as medians with interquartile range (IQR). Categorical data were presented as numbers and percent. Differences between groups were tested with student t-tests for normally distributed parameters, Wilcoxon Rank sum tests to compare medians, and Pearson Chi^2 tests for categorical data.

Heart rate and ventilation parameters were sampled continuously during bag-mask ventilation. Thus, we had a large number of repeated observations collected per newborn. Several of the parameters showed systematic trends of increase or decrease by time, likely due to complex physiological changes related to birth, reflex mechanisms and clinical responses to the treatment. Analysing the data, we had to account for variation at multiple levels (per newborn, per ventilation sequences and between newborns), changes by time and dependency between parameters. Ventilation pauses and variations in duration of bag-mask ventilation added to the complexity.

Table 9 – Overview of outcome parameters, covariates and statistical methods used in each paper.

	Paper I	Paper II	Paper III
Outcomes	Primary outcome: ECO_2 per ventilation Secondary outcome: Time from first BMV to ECO_2 >2%	24-hour survival	Primary outcome: HR-response Secondary outcomes: ECO_2, PEEP, MIP, PIP, V_{TE}, leak, duration of BMV, 1- and 5-min Apgar, 24-hour outcome
Covariates	Ventilation parameters: V_{TE}, leak, VR, PIP Clinical parameters: iHR, 5-min Apgar, BW Other: Time	Main model: ECO_2* and HR * Secondary models: Time to ECO_2 >2% and HR >100 bpm, V_{TE}, BW	Ventilation without or with PEEP-valve
Statistical methods	Linear random intercept regression models Cox-regression Kruskal-Wallis test Pearson Chi^2 tests Wilcoxon rank sum tests	Logistic regression ROC curves Pearson Chi^2 tests Wilcoxon rank sum tests	Linear random effect regression models (with splines) Pearson Chi^2 tests Wilcoxon rank sum tests

* Maximums and medians per time intervals; 0-30, 20.1-60 and 60.1-300 seconds.

In **Paper I**, the aim was to explore the relative impact of ventilation factors (V_{TE}, VR, ML, PIP) compared to clinical factors (iHR BW, Apgar scores) on ECO_2 measured during bag-mask ventilation of term and near-term newborns. ECO_2 showed a large variation between individual ventilations. Due to side-stream sampling, there was a delay of approximately 2.1 seconds between registration of ventilations by pressure- and flow-sensors, and ECO_2 registration. Joar Eilevstjønn matched the ECO_2 per ventilation with observations of other ventilation parameters, perfect match was unlikely. To even out variations between ventilations, we smoothed ventilation parameters as means per 5 ventilations. After smoothing the variation per newborn was still large. To display this, summary measures of ventilation parameters were calculated both as medians of per individual medians of repeated observations (due to skewed distribution), and as means in mixed models with display of intercorrelation coefficients showing the proportion of the total variance assigned to variance between newborns.

To explore associations between ECO_2 and the covariates in the first 5 minutes of ventilation, we used linear random intercept regression models taking variation at two levels into account. ECO_2 was first plotted as a function of all the covariates in scatter plots. The smoothed local polynomial function in Stata was used to look for linear and non-linear trends of associations. We also inspected the residuals. We found non-linear associations with ECO_2 for time, V_{TE} and PIP. We performed log-transformation for time and added a quadratic term for V_{TE} and PIP, guided by Akaike's information criteria, to achieve linear associations.

Random intercept linear regression was performed both in univariate and multivariate models to explore the associations with ECO_2, first for the covariates one by one, then in a complex interplay taking all available data into account. To compare the associations with ECO_2 for covariates measured at different scales, we calculated the explained variance (R^2) for each covariate in the univariate models, and for ventilation factors compared to clinical factors in the multivariate models. As complex associations with transformed variables are difficult to interpret by beta-coefficients and p-values, we also made graphs using smoothed local polynomial plots for predicted ECO_2 per covariate.

To account for potential build up effects with continuous ventilation, compared to ventilation with pauses, we also analysed the first three ventilation sequences with duration >10 seconds in secondary models.

Immediately after birth, ECO_2 is an indicator of degree of lung aeration.[214] A successful lung aeration is critical for survival. Thus, factors associated with a rapid increase in ECO_2, may also be associated with a more favourable outcome. To explore associations between the covariates and time to achieve an increase in ECO_2, we also analysed the data with Cox-regression for time to ECO_2 >2%. Hazard ratios were calculated both per unit of the covariates, and by standardized values (subtracting mean and dividing by standard deviation) to enable comparison between covariates measured on different scales.

Hypothesising that newborns who had ECO_2 >2% in the first ventilation (and thus excluded from the Cox-regression), or never reached the

threshold, may have different characteristics compared to those who reached the threshold during ventilation, we added a simple comparison of groups by medians of clinical factors and ventilation factors in the first 30 seconds of ventilation using Kruskal-Wallis test.

In **Paper II**, the aims were to explore ECO_2 measured during BMV in newborn resuscitation as a predictor of 24-hour outcome and compare the predictive information of ECO_2 and HR.

We analysed the data using logistic regression models. As there was only one outcome, survival or death, per newborn, using all observations of ECO_2 and HR in mixed models, would not give meaningful results. Thus, we had to find representative summary measures for the covariates. However, we considered changes by time to be likely relevant and highly interesting for potential differences in the predictive information of ECO_2 and HR. To balance the need for analysing only one value per covariate per newborn, and to explore changes of predictive information by time, we decided to do repeated analyses of summary measures calculated by time intervals.

To select relevant time intervals, we made graphs to display variation in ECO_2 and HR by time. Finding a rapid increase in ECO_2 and HR in the first minute before reaching a more constant level, we chose 0-30 seconds, 30.1-60 seconds, and 60.1-300 seconds as time intervals for calculating summary measures to use in logistic regression.

As commented in the description of Paper I, ECO_2 varied largely between ventilations. We hypothesised that maximum values per time

interval were likely more representative for the newborns clinical condition at birth than medians, while medians would be more affected by the ventilation technique. We proposed that maximums would be more practical in clinical use, as remembering the highest value observed within a time interval is feasible compared to estimating a median in a stressful situation. To explore whether maximums and medians gave different results as predictors for survival, we decided to analyse both.

All analyses were performed in both univariate models, and in mutual adjusted models including ECO_2 and HR per time intervals. Mutual adjustment is not considered a good method in causal models where one covariate is expected to affect the other, and not the other way around. Directed acyclic graphs (DAGs) are used to assess causal relationships and identify confounders. However, our models were not causal models, but prediction models designed to explore whether ECO_2, compared to HR, could be used to foresee the chances for survival. For this purpose, we considered mutual adjustment useful to evaluate if both parameters would give more information than each parameter alone.

Due to the finding of a close association between ventilation factors, especially V_{TE}, with ECO_2 and time to ECO_2 >2% in Paper I, we suspected that V_{TE} might also be relevant for survival. Higher V_{TE} was associated with higher ECO_2. We therefore performed secondary analyses adjusting for median V_{TE} within time intervals. Expecting pathophysiology and causes of death to be potentially different

depending on GA/ maturity, we also performed stratified analyses for newborns with BW < vs. ≥ 2500 g.

Severely asphyxiated newborns have high levels of arterial CO_2.[86] ECO_2 measured in an open system during BMV, is very likely to underestimate arterial CO_2, overestimation is unlikely. Thus, high ECO_2 could theoretically indicate more severe acidosis. HR above normal range may also be a sign of stress. We used categorical logistic regression models to check for potential non-linear effects with reduced survival associated with high values of ECO_2 and HR.

Receiver operating characteristics (ROC) curves graphically display sensitivity as a function of 1-specificity for all possible cut off values of the covariates in diagnostic tests with binary outcomes.[243] The area under the ROC curves (AUC) is thus a measure for the total predictive information of the covariates. We made ROC curves and calculated AUC for predicted sensitivity and specificity of the covariates, based on the results of the unadjusted logistic regression models. AUCs for maximum ECO_2 and HR within each time interval were compared by Pearson Chi Square tests. To display selected cut-off values for ECO_2 in the ROC-curves, we plotted the sensitivity and specificity for maximum ECO_2 ≥1, 2 and 4% and HR ≥60, 100 and 120 bpm.

To further explore the impact of time, we compared the time intervals from first ventilation until ECO_2 ≥2% and HR ≥100 bpm, and studied time from first delivered ventilation until ECO_2 reached ≥2% and HR ≥100 bpm as covariates in secondary logistic regression models among

newborns with initial ECO_2 <2% and HR <100 bpm. We performed post hoc analyses using Wilcoxon rank sum tests to assess for differences in initial HR, Apgar scores, BW and ventilation factors (V_{TE} and mask leak) depending on which threshold was reached first.

Paper III is a randomized controlled trial aiming to study whether adding a PEEP-valve to the bag-mask during resuscitation of term and near term newborns could improve HR response. Secondary outcomes included ventilation parameters and 24-hour mortality. Per protocol, the plan was to study HR-response per ventilation sequences. Due to large variations in duration of ventilation sequences, studying changes from the first to the last measured value, was not considered appropriate. This would also be an oversimplification of available data, with potential for losing important information, since both HR and ventilation parameters were collected continuously during BMV. After statistical expert advice, we decided to analyse parameters with repeated observations and systematic changes by time in linear random effect models.

For the primary outcome HR-response, we fitted a three-level model (with robust standard errors due to skewed distributions) taking repeated observations per newborn and dependency between ventilation sequences into account. We allowed for individual HR slopes within ventilation sequences. The analysis was performed with splines for time (3 knots) to optimize model fit. The effect of PEEP was tested as a binary variable. The results were displayed graphically in margin plots, both for

all ventilation sequences combined and per ventilation sequence. We included up to 5 ventilation sequences per newborn.

Similar random effect models and margins plots were used to analyse differences in ECO_2, V_{TE} and ML by groups. We included only the first 60 seconds of ventilation for these analyses. To reduce the complexity, we used two level models not taking ventilation sequences into account.

We performed stratified analyses of the primary outcome for newborns with iHR < vs. ≥ 100 bpm. Expecting the benefit of PEEP to be potentially different dependent on lung maturity, we also stratified by BW < vs. ≥ 2500g. Finding lower delivered V_{TE} in the PEEP-group, we added post hoc analyses for HR and ECO_2 with adjustment for V_{TE}.

We also performed more direct comparison of summary measures using Pearson Chi^2 tests, Wilcoxon rank sum tests and Cox-regression as appropriate. Where possible, we aimed to display the results in ways comparable to prior studies of PEEP in the delivery room.[119,185,186] To explore factors associated with high or low PEEP, we compared ventilation factors and clinical factors in groups by median PEEP per newborn < vs. ≥ 4mbar in newborns ventilated with PEEP.

3.7 Ethical approval, consent and safety issues

Ethical approvals for the studies were granted by the National Institute for Medical Research in Tanzania (Ref. NIMR/HQ/R.8a/Vol.IX/1434 and NIMR/HQ/R.8c/Vol.I/325) and the Regional Committee for Medical and Health Research Ethics for Western Norway (Ref.2013/110).

All mothers of the newborns included in paper I and II were informed about ongoing research. Consent was not considered necessary by the ethical committees for these observational studies. No interventions except standard care were done.

For the PEEP RCT, midwives approached mothers for informed oral consent at admission for labour. If pre-delivery consent was considered inappropriate, usually due to late stage labour at arrival, research nurses sought deferred consent on the day after delivery (Fig. 20).

Figure 20– If pre-delivery consent was not obtained, the mother's observation form was marked with "Pending consent". Research nurses visited the mother the day after delivery to inform her about the study and ask for deferred consent. Photo: Kari Holte

Before the PEEP-study was started, we discussed potential hazards. Testing on manikins was performed by Monica Thallinger and other researchers in the study group to assess the performance of the PEEP-valve before taking the new equipment into clinical use.[244] Thorough quality control was also done by the manufacturer Laerdal Global Health, and Upright bag with PEEP was CE-marked before study start.

As PEEP around 5-6 delivered by T-piece is already in routine use several places, the risk for complications with PEEP in the intended area was considered to be low. However, if higher then intended PEEP was given, we speculated that there might be an increased risk of pneumothorax or reduced venous return to the heart. Due to low availability of X-ray at the study site, routine X-ray to look for pneumothorax could not be done. To reduce potential hazards of unintended high PEEP, we implemented routines to check the PEEP-valve with weekly visual inspection and control of pressures using a manometer. Data were inspected regularly to look for extreme PEEP-values.

An external data and safety monitoring committee conducted pre-planned interim analyses in the PEEP RCT with stopping rules for the clinical endpoint death at 24 hours after enrolment of approximately 100 and 200 newborns.

4 Main results

In the study period between March 1st 2013 and June 30th 2018, Haydom Lutheran Hospital had 3600 - 4600 deliveries annually.[225] A total number of 21 131 newborns were born, including 611 stillbirths (2.9%). Around 7% of newborns received bag-mask ventilation at birth (Table 8).

Among 17 476 newborns born between March 1st 2013 and June 1st 2017, 434 were included in Paper I and II. Among 6 225 newborns born between September 26th 2016 and June 30th 2018, 417 were included in Paper III. Due to overlapping data collection periods, a few newborns were eligible for inclusion in all studies, 37 newborns were included in all three papers. A joint flow chart for the whole thesis is displayed on the next page (Fig. 21).

Table 10 – Characteristics for the 21 131 newborns born at Haydom Lutheran Hospital between March 1st 2013 and June 30th 2018.

	n*	Value
Birth weight, median (IQR), grams	20 729	3 300 (3000 – 3600)
Birth weight <2500 g, n (%)	20 729	1 422 (6.8%)
Gestational age, median (IQR), weeks	19 762	38 (37 – 40)
Gestational age < 34 weeks, n (%)	19 762	493 (2.5%)
Gender, n (%) females	21 130	9 927 (47%)
Delivery mode, n (%) caesarean sections	21 130	4 790 (23%)
Bag-mask ventilation performed, n (%)	20 917	1 540 (7.4%)
24-hour outcome, n (%)	21 129	
Normal		19 597 (93%)
Admitted		740 (3.5%)
Dead		181 (0.86%)
Fresh stillborns		281 (1.3%)
Macerated stillborns		330 (1.6%)

*The n per parameter is lower than 21 131 due to missing data. BW was not recorded for macerated stillborns. No estimate for GA was available for 1 324 liveborns and 45 stillborns.

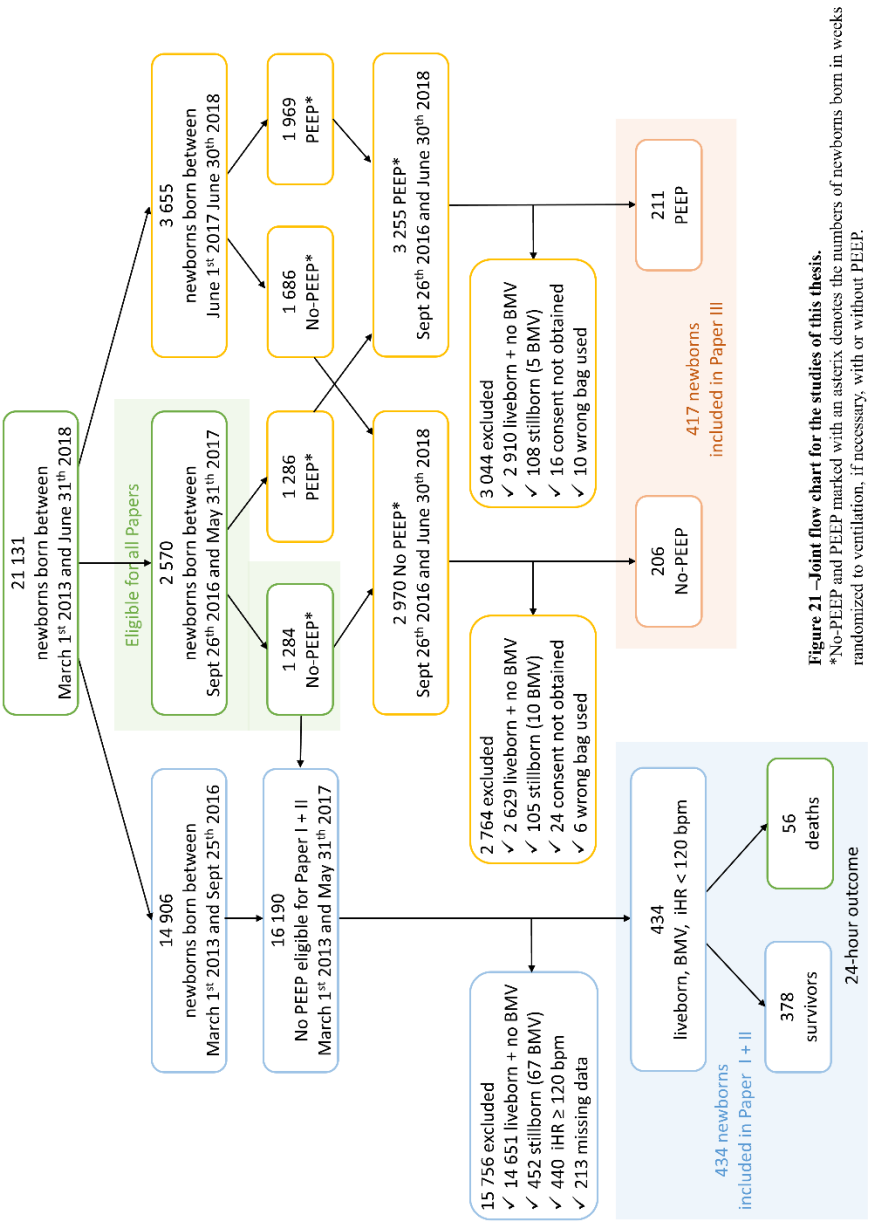


Figure 21 –Joint flow chart for the studies of this thesis.
*No-PEEP and PEEP marked with an asterix denotes the numbers of newborns born in weeks randomized to ventilation, if necessary, with or without PEEP.

4.1 Expired CO_2 reflects both ventilation quality and clinical condition

In **Paper I**, we found that both ventilation factors and clinical factors were significantly associated with measured levels of ECO_2 in the first 5 minutes of bag-mask ventilation at birth (Fig. 22). The ventilation factors (V_{TE}, VR, ML and PIP) together explained 31 % of the variance in ECO_2, while the clinical factors (BW, iHR, 5-min Apgar) explained 11 % of the variance.

4.1.1 Ventilation factors

Expired volume: V_{TE} showed the closest association with ECO_2, alone explaining 19% of the variance in measured values. Higher V_{TE} up to 15-20 ml/kg was associated with higher levels of ECO_2. Higher V_{TE} up to 14 ml/kg was also associated with a shorter time to reach ECO_2 >2% with standardized hazard ratio 3.75 (2.56-5.48).

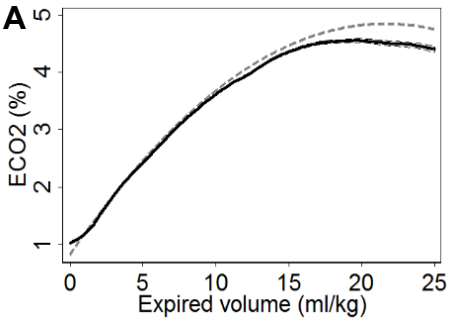
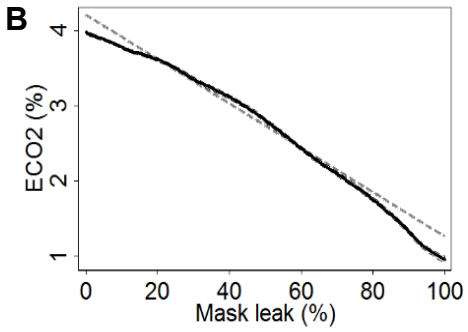
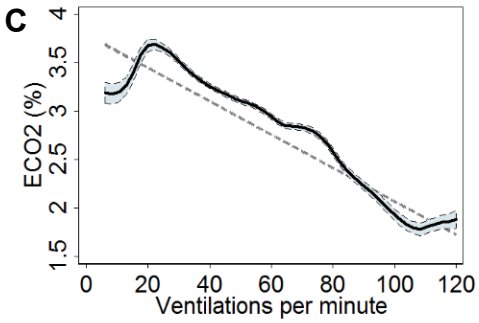


Figure 22 – The graphs embedded in the text on the next pages display smoothed local polynomial plots for predicted values of ECO_2 by the covariates based un the univariate (dashed, grey line) and multivariate (solid, black line) models. A: ECO_2 by V_{TE}.. B: ECO_2 by ML. C: ECO_2 by VR. D: ECO_2 by PIP. E: ECO_2 by BW.F: ECO_2 by iHR. G: ECO_2 by 5-min Apgar scores

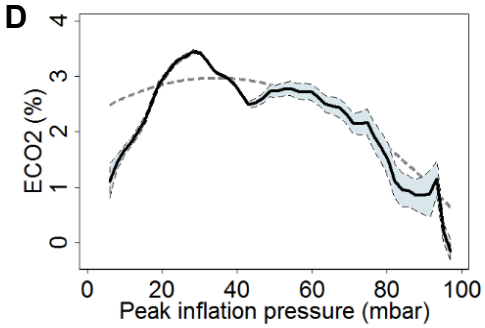
Mask leak: ML was correlated with V_{TE} (Spearmans Rho -0.65), thus an independent interpretation of the two parameters cannot easily be done. In random intercept models including both V_{TE} and ML, ML was still significant indicating independent effects. In the Cox-regression models, ML lost significance when adjusted for V_{TE}.



Ventilation rate: VR explained 7.5% of the variance in ECO_2 in univariate and 16% in multivariate models. An interaction term for V_{TE} and VR was significant with p <0.001. VR around 30/min was associated with the highest ECO_2. We found no association between VR and the time to reach ECO_2 >2%.



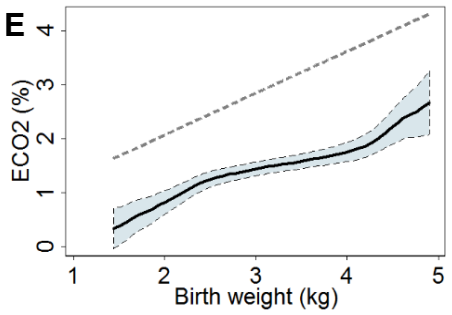
Peak inflation pressures: We found a non-linear association between PIP and ECO_2 in the first 5 minutes of ventilation, with low ECO_2 associated with both low and high PIP. The highest ECO_2 was found for ventilations with PIP around 30



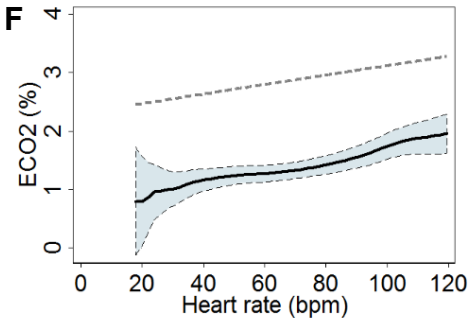
mbar. Higher PIP was associated with a shorter time to reach ECO_2 >2% with standardized hazard ratio 1.36 (1.24-1.50). In analyses per ventilation sequence, we found a linear association between PIP and ECO_2 in the first sequence, non-linear in the second, and no association in the third (Supplement, Paper I).

4.1.2 Clinical factors

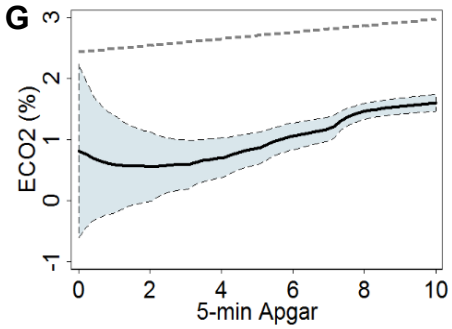
Birth weight: Higher BW was associated with higher levels of ECO_2. BW explained 4.4% of the variance in ECO_2 in univariate models, 6.8% in multivariate models. Increasing BW was also associated with a shorter time to reach ECO_2 >2% with standardized hazard ratio 1.23 (1.10-1.38).



Initial heart rate: Newborns with higher iHR also had slightly higher levels of ECO_2, and reached ECO_2 >2% faster with standardized hazard ratio 1.17 (1.05-1.30). iHR explained only 0.6% of the variance in ECO_2 in univariate models, and 1.3% in multivariate models.



Apgar scores: Higher 5-min Apgar scores were weakly associated with higher levels of ECO_2. 5-min Apgar scores explained 0.3% of the variance in ECO_2 in univariate models, 2.9% in multivariate models. Substituting 5-min Apgar scores with 1-min Apgar scores did not affect the main conclusions. The standardized hazard ratio for time to reach ECO_2 >2%, was 1.42 (1.25-1.61).



4.2 Expired CO_2 can predict survival at 24 hours

In **Paper II**, we found that ECO_2 measured during the first 5 minutes of bag-mask ventilation at birth, could predict 24-hour outcome in resuscitated newborns. Higher levels of ECO_2 were associated with a higher probability to survive. ECO_2 increased earlier than HR in a majority of newborns (Fig. 23). ECO_2 reached >2% before HR reached >100 bpm in 70% of newborns with lower initial values.

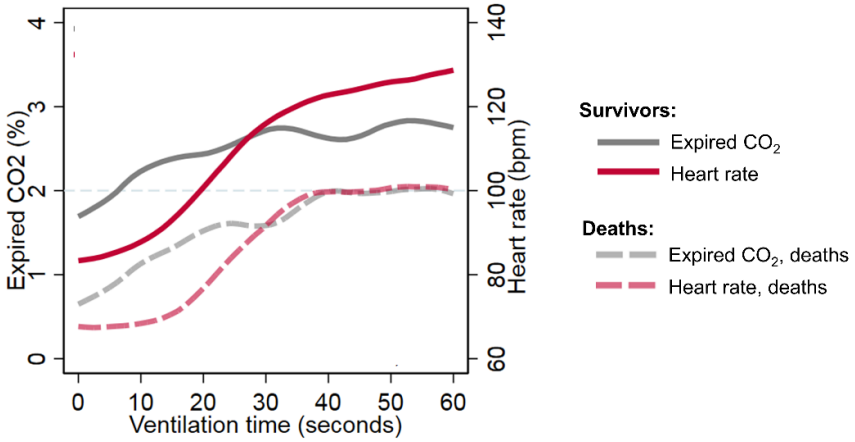


Figure 23– Illustration of the increase in ECO_2 and HR in survivors compared to deaths in the first minute of BMV. ECO_2 increased before HR, survivors had higher levels of ECO_2 and HR than non-survivors. This figure display smoothed local polynomial plots of all measured values of ECO_2 by time.

The predictive information of ECO_2 was not significantly different when compared to HR in any of the time intervals 0-30 seconds, 30.1-60 seconds and 60.1-300 seconds. However, the direction of trends and the earlier increase in ECO_2, suggested that ECO_2 may serve as an earlier predictor for survival, while HR seems more sensitive and specific after the first minute of BMV. Maximum and median ECO_2 and HR within

the selected time intervals gave similar predictive information. As maximums are likely more feasible as prognostic information in a clinical setting, further description focus on maximums.

4.2.1 The first 0-30 seconds of BMV

The maximum ECO_2 measured within the first 0-30 seconds of BMV was a non-significantly better predictor for 24-hour survival than maximum HR (Fig. 24). AUC (95% CI) for maximum ECO_2 compared to maximum HR were 0.72 (0.65, 0.79) vs. 0.67 (0.58, 0.76), p=0.21. Both ECO_2 and HR were significant predictors for 24-hour survival in mutually adjusted models, indicating independent predictive effects. The total AUC for ECO_2 and HR combined, was 0.73.

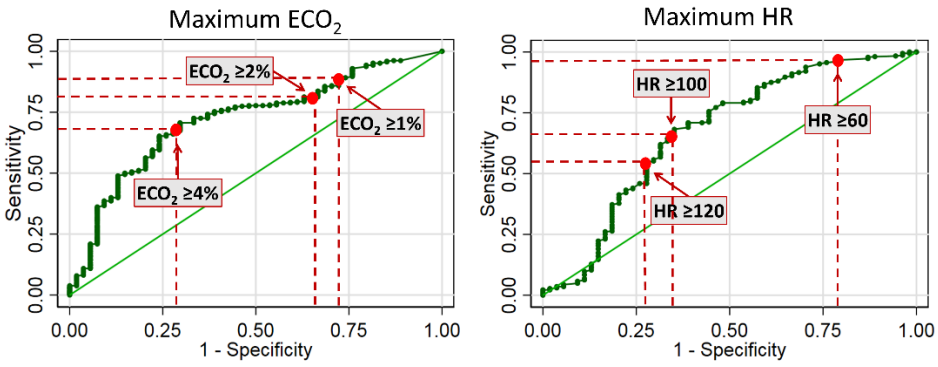


Figure 24– ROC-curves for maximum ECO2 and HR in the first 0-30 seconds of ventilation.. The ROC-curves display sensitivity plotted against 1-specificity for all possible cut-off values when using the covariate of interest as a "diagnostic test". AUC is the area under the ROC-curves, and may be used as a measure for the total predictive information of the test. Sensitivity and specificity for selected cut-off values of maximum ECO_2 and HR measured in the first 0-30 seconds of BMV are plotted in the curves.

4.2.2 Within 30.1 - 60 seconds of bag-mask ventilation

Maximum ECO_2 and HR measured after 30.1-60 seconds of BMV gave very similar ROC-curves for 24-hour survival (Fig. 25). AUC (95% CI) for maximum ECO_2 was 0.69 (0.60, 0.78), compared to 0.66 (0.56, 0.76) for maximum HR, p=0.56. ECO_2 and HR were both significant predictors for 24-hour survival in mutually adjusted models, thus ECO_2 still added extra predictive information compared to HR alone. The total AUC for ECO_2 and HR combined, was 0.69.

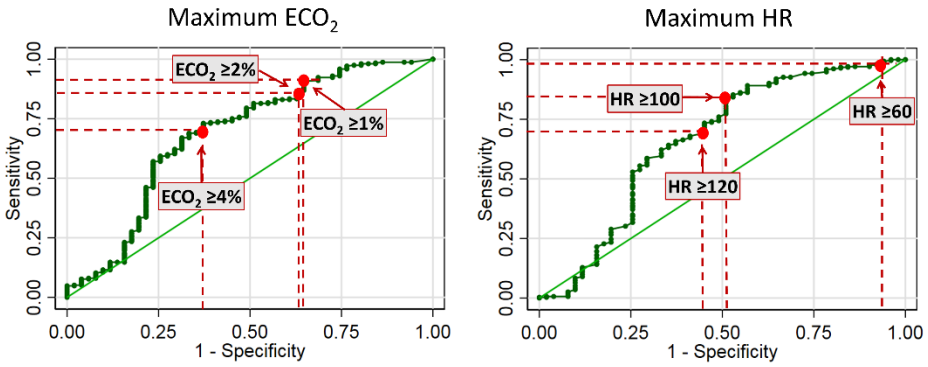


Figure 25– ROC-curves for maximum ECO_2 and HR measured within 30.1-60 seconds of BMV at birth. Selected cut-off values for maximum ECO_2 and HR are plotted to indicate estimated sensitivity and specificity when used as a prognostic test for 24-hour survival.

4.2.3 Within 60.1 - 300 seconds of BMV

After 60 seconds of bag-mask ventilation the predictive information of maximum ECO_2 and maximum HR, were at the same level with AUC (95% CI) for maximum ECO_2 = 0.62 (0.53, 0.71) compared to 0.64 (0.54, 0.64) for maximum HR, p=0.74. In mutually adjusted models, ECO_2 lost

significance, indicating that ECO_2 did not add extra predictive effect after one minute of ventilation compared to HR alone. The total AUC for ECO_2 and HR combined, was 0.64. Using thresholds of ECO_2 >2% or >4% and HR >100 bpm or >120 bpm, had high sensitivities as predictors of 24-hour survival, however, specificities were low (Fig. 26).

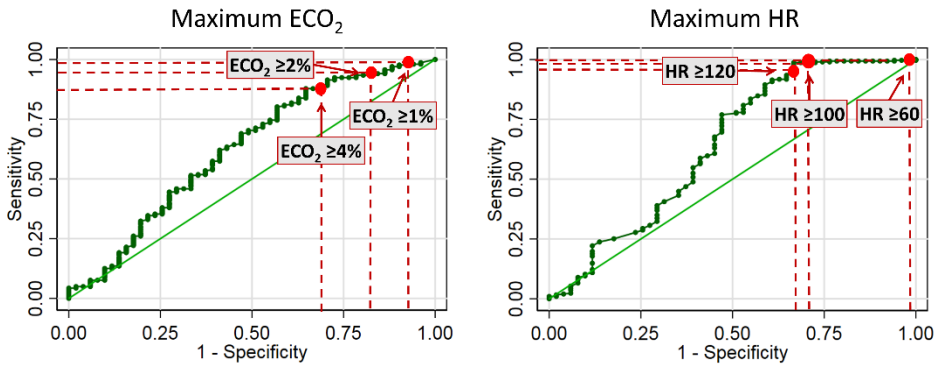


Figure 26– ROC-curves for maximum ECO_2 and HR measured within 60.1-300 seconds of BMV at birth. Selected cut-off values for maximum ECO_2 and HR are plotted to indicate estimated sensitivity and specificity when used as a prognostic test for 24-hour survival.

4.2.4 The impact of V_{TE} and BW

Adjusting for V_{TE} did not reduce the predictive information of ECO_2 or HR. In stratified analyses by BW, the direction of trends suggested slightly better predictive information for 24-hour survival by ECO_2 and HR during BMV at birth for newborns with BW ≥2500 g compared to <2500 g.

4.3 PEEP did not improve heart rate response or expired CO_2

In **Paper III**, we found no clinical benefit of adding a PEEP-valve to the bag-mask device during resuscitation of term and near term newborns.

4.3.1 HR-responses and clinical parameters

The HR-responses were similar in the two groups (Fig. 27), HR at 2 minutes of age and time from first BMV until HR reached ≥100 bpm, ≥120 bpm or ≥140 bpm did not differ. We found no difference in secondary outcomes 1- and 5-minute Apgar-scores, ventilation time or 24-hour outcome.

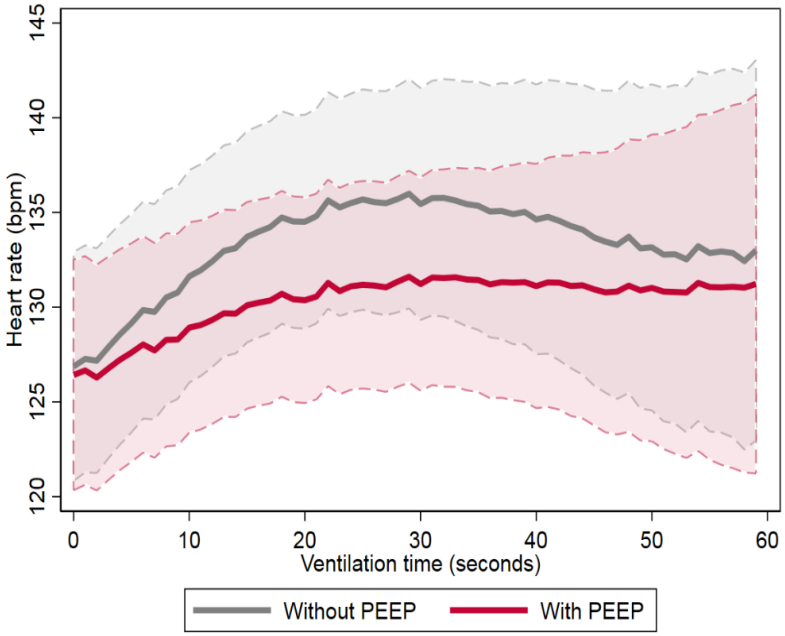


Figure 27– HR-response for all ventilation sequences combined in newborns ventilated with compared to without PEEP. Up to 5 ventilation sequences were included per newborn. The graphs are margin plots with 95% Confidence intervals based on the results of a three level random effects regression model testing including PEEP/no PEEP as a binary variable.

4.3.2 Expired CO_2

Newborns ventilated with a PEEP-valve on the bag-mask, had borderline significant lower ECO_2 in the first 10 minutes of ventilation compared to newborns ventilated without PEEP (Fig.28). Median (IQR) of medians was 2.9 (1.5-4.3) % in newborns ventilated with PEEP compared to 3.3 (1.9-5.0) % in the no-PEEP group, p=0.05. Time to reach ECO_2 ≥2% was 8.6 (3.6-23.1) seconds in the PEEP group compared to 7.9 (3.8-19.5) seconds in the no-PEEP group, p=0.27.

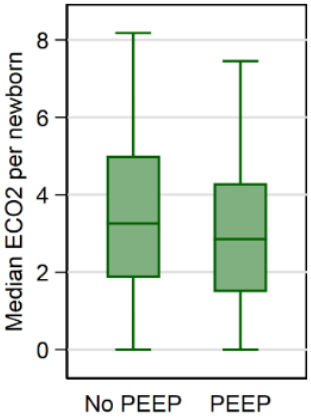


Figure 28a –Median ECO_2 in the first 10 minutes of BMV

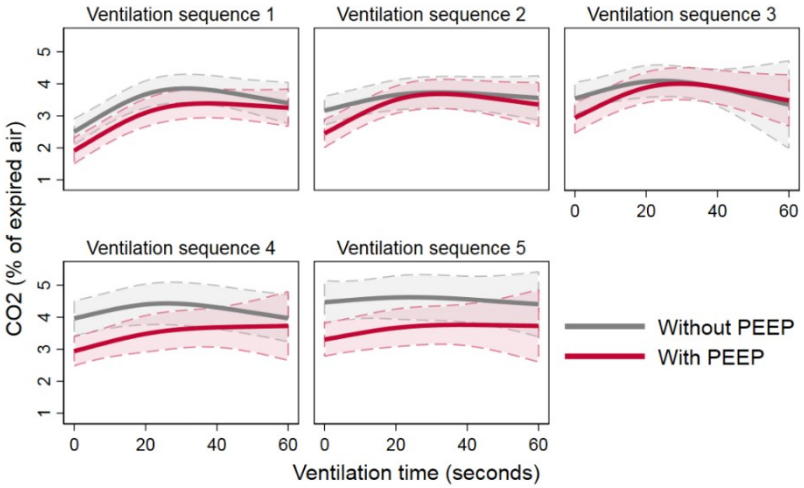


Figure 28b – ECO_2 per ventilation sequences for newborns ventilated with compared to without PEEP. The graphs are margin plots with 95% confidence intervals based on a the results of a three level random effects regression model testing including PEEP/no PEEP as a binary variable. These per sequence results for the increase in ECO_2 were not displayed in Paper III.

4.3.3 Ventilation parameters

Pressures: The PEEP-valve delivered PEEP as intended, with a median (IQR) of per newborn median PEEP of 4.7 (2.1-5.5) mbar in the first 10 minutes of ventilation in newborns ventilated with PEEP, compared to 0.1 (0.1-0.2) mbar in newborns ventilated without PEEP, p<0.001. There was no difference in PIP, median (IQR) of medians 39 (37-41) mbar.

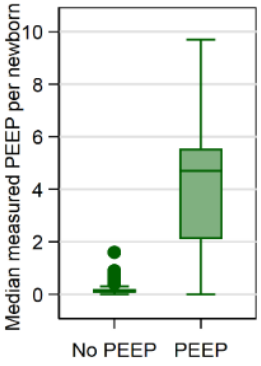


Figure 29 –Median PEEP per newborn

Expired volume: Median (IQR) of per newborn median V_{TE}s in the first 10 minutes of ventilation was significantly lower in newborns ventilated with compared to without PEEP with 4.9 (1.9-8.2) ml/kg in the PEEP group versus 6.3 (3.0-10.5) ml/kg in the no-PEEP group, p=0.02.

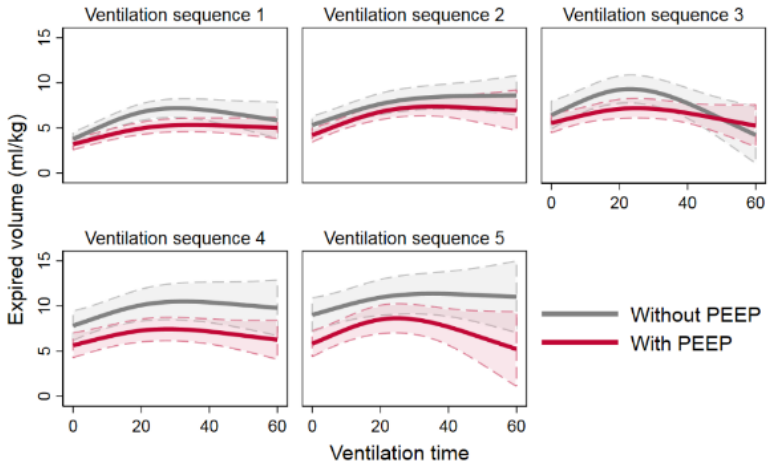


Figure 30– V_{TE} per ventilation sequences with compared to without PEEP. The graphs are margin plots with 95% confidence intervals based on the results of a three level random effects regression model. These per sequence results for V_{TE} were not displayed in Paper III.

Mask leak: ML decreased with time while V_{TE} increased. ML was borderline significantly higher in newborns ventilated with compared to without PEEP, with median (IQR) of per newborn median leak 46 (22-64) % in the PEEP group versus 40 (18-60) % of expired air in the no-PEEP group, P=0.06 (Fig.31).

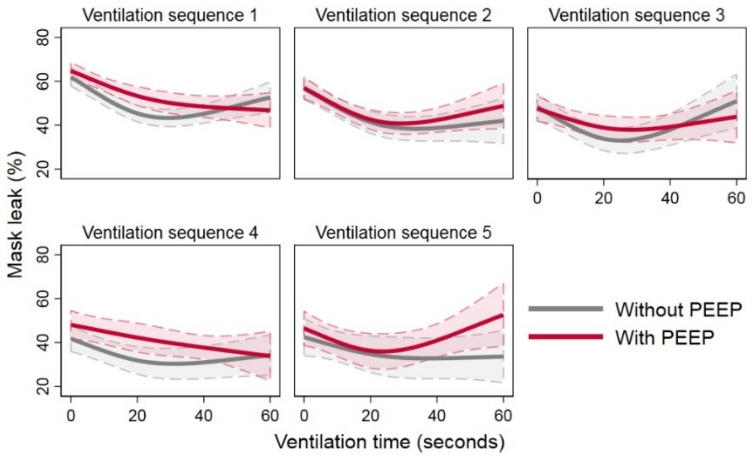


Figure 31– ML per ventilation sequences for newborns ventilated with compared to without PEEP. The graphs are margin plots with 95% Confidence intervals based on a the results of a three level random effects regression model testing including PEEP/no PEEP as a binary variable. These per sequence results for the decrease in ML were not displayed in Paper III.

5 Discussion

In this thesis, I have presented three studies designed to explore measures to improve bag-mask ventilation of term and near-term newborns at birth, with focus on ECO_2 and PEEP. This discussion will consider methodological aspects of the thesis and discuss the main findings in the light of the current scientific literature.

5.1 Methodological considerations

Searching for new knowledge rises philosophical questions: What is true? This thesis builds on a biomedical scientific tradition claiming that truth exists. However, associations found in a sample of study objects may not disclose causation. Results found in one group may not be valid in a different population. The studies of this thesis have strengths and weaknesses in a scientific perspective.

5.1.1 Study design

The thesis includes two prospective observational studies and one RCT, all performed at one study site; Haydom Lutheran Hospital (HLH) in Tanzania. Large sample sizes and a combination of observational data and automatically recorded biomedical signal-data are major strengths of all the included studies.

Paper I and II: The two CO_2-studies had analytic and descriptive aims. We wanted to explore associations between parameters in a sample of bag-mask ventilated newborns without doing interventions besides

standard treatment, and thus observational study designs were considered appropriate. A prospective compared to retrospective design was chosen as this allows for studying associations by time, and reduce the risk of bias because the study objects are recruited and data collection performed before outcomes are known.

Paper III: For the PEEP-study, a randomized controlled design was chosen, as we wanted to study the effect of a single exposure variable: PEEP. By randomizing study objects into two groups that differ only by the variable of interest, causal relationships can be investigated with low risk of confounding, and thus RCTs are often considered the "gold standard" of medical research.

Different *outcome measures* have been used to evaluate clinical effects of resuscitation at birth. In the PEEP-study, HR was selected for primary outcome. The choice was done partly because HR is central to evaluate clinical response to ventilation.[106,119,185] Among secondary outcomes, we included 24-hour mortality, total ventilation time and ventilation parameters. It must be noted that a trial cannot tell anything about outcomes that are not studied. For the PEEP-study, it may be considered a weakness that we did not study long-term lung-function or neurodevelopmental outcomes, and did not register the incidence of pneumothorax. Sample size calculation was based on the primary outcome, and the power to assess differences for infrequent outcomes like 24-hours mortality may not have been present.

5.1.2 Internal validity

The accuracy of a result is determined by the degree of systematic variation from the true value (*validity*) and the degree of absence of random variation (*precision*). The term *internal validity* encompasses how accurate a study describes what it aims to measure. *Bias, confounding* and *random errors* are the three major threats to internal validity and will be discussed below.

Bias

Bias results from trends in selection or measurements that can lead to conclusions that are systematically different from the truth. Bias are often classified into *selection bias* and *information bias*.

Selection bias

Selection bias may occur if participants in a study population are not randomly selected from the target population of interest. This makes the study population potentially less representative and induction of results to the target population may not be valid.

Paper I and II: For observational studies, the ethical committees allowed inclusion of all newborns at HLH without consent from the mother. This reduced the risk of selection bias. A number of newborns were excluded due to missing data. The reasons were mainly related to technical issues, however we cannot rule out a possibility for systematic differences between newborns with or without complete data. Exclusion

of newborns ventilated with PEEP likely did not affect the sample, as these newborns were selected by randomization.

Paper III: Comparing perinatal characteristics of the enrolled newborns, we found that more preterm/ small newborns had been included in the PEEP group compared to the no-PEEP group. We found no reasonable explanation for this, and concluded that this must have happened by chance. Stratified analyses by BW were done to explore potential differences by group. For newborns with BW ≥2500g, the BW was similar within groups. For newborns with BW <2500g, a higher share of smaller newborns, including 7 cases with maternal preeclampsia/ eclampsia, were noted in the PEEP group and none in the no-PEEP group. This may have biased the results in the <2500g group, but as the main results were the same in both strata, we found it unlikely to have affected the main conclusions.

We were allowed to use deferred consent from mothers who arrived to the hospital in late stage labour. This was likely important to include newborns with a high risk of complications, is generally well accepted by parents, and was a strength of the trial.[245,246] However, research nurses who sought consent from mothers the day after delivery, reported that in cases with a fatal outcome, asking for consent felt uncomfortable. The number of mothers who refused to participate in the study was very low. There may however, be a risk that some mothers were deliberately not asked. This could skew the selection of included newborns by groups if the risk of fatal outcome differed.

Information bias

Information bias is also called *observation bias* or *measurement bias*. This refers to systematic errors between groups that arise in collection, recall, recording and handling of data. Information bias also includes bias due to missing data.

Paper I: Apgar scores are subjective,[193] and systematic errors by clinical condition may have occurred. Similarly, the first detected HR defined as *initial HR* (iHR) was collected with variable delay after birth depending on when the HR-sensor was applied. Systematic differences in delay dependent on clinical condition is a possibility. Due to a time lag of approximately 2.1 s for ECO_2 compared to pressure/flow/volumes, the match of data per ventilation may not have been perfect. This is more likely to have affected ventilations given with at a high inflation rate, and thus may be a source of bias.

Paper I and II: The dry-electrode method for ECG recording is sensitive to disturbance by movement, and bias may have occurred due to different frequency of loss of signals dependent on clinical condition. Pulseless electric activity may have been present in some of the most compromised newborns.

Paper I-III: Different occurrence of missing data between groups was a possibility in all studies in the present work. Ventilation pauses occurred at different time points per newborn, HR signals were sometimes lost, total time with ongoing resuscitation varied. Thus, the number of newborns contributing with data, changed by time with systematic

differences by clinical condition. To address this issue, we have specified numbers of newborns included at different time points.

Other biases

Performance bias may occur in RCTs if the intervention is not blinded. In the PEEP study, the choice of SIB could not be kept secret, as the PEEP-valves were visible on the bag. Theoretically, this could have affected the midwives performance both when asking mothers for consent and during resuscitation. However, only one choice of SIB was immediately available at the resuscitation table per week, and if alternative should be used, the option was standard bag (not Upright). This was only used twice in the study period. Among the other 14 cases excluded because of wrong SIB used according to randomization, 12 occurred within a period of two weeks. This was due to a misunderstanding by a newly employed research nurse, resulting in wrong SIB available at the resuscitation tables. As newborn resuscitation is a lifesaving and stressful procedure, the attention of the midwives were likely fully concentrated on saving the newborn during BMV, and not on the choice of SIB. Thus, we find it very unlikely that the lack of blinding affected inclusion or efforts during BMV.

Reporting bias occurs when selected outcomes from clinical trials are chosen for publication. This problem can be mitigated by pre-registration of planned outcomes. Registration in *clinicaltrials.gov* was done for Paper III. Paper I and II were observational studies and more explorative in nature and no pre-registration of planned outcomes were done.

Hawthorne effect refers to changes in behavior or performance due to awareness of being observed. The midwives at Haydom hospital have been observed by research assistants since 2009 and video-filmed since 2013. The observation was done in the same way for all newborns, thus bias due to observation in the present studies is unlikely.

Confounding

Causal relationships are often multifactorial. In observational studies, the effect of a particular exposure on groups can often not easily be detangled from effects of other associated factors. This is called *confounding.* Confounding can be adjusted for statistically if identified and properly measured. Unmeasured factors can produce confounding bias if associated with the studied exposure and outcome simultaneously.

Paper I: All the included covariates affected ECO_2. Each covariate could also modify the effects of other covariates in a complex manner, and thus act as mutual confounders. To address this, we analyzed the data in both univariate and multivariate models. Interaction and correlation between the covariates further complicated the picture. Meticulous analyses were done to explore this, though due to high complexity in the data, getting a full overview was likely not feasible. Changes in lung compliance, airway obstruction and muscle tone are among unmeasured confounders that may have affected the results. For the comparison of explained variance (R^2) between clinical and ventilation parameters, I suspect that the impact of clinical condition may have been underestimated. Blood gas analyses could have added more objectivity.

Paper II: Clinical factors and ventilation factors, affected both HR, ECO_2 and 24-hours outcome, and may be seen as confounders. In this study, however, the aim was not to study *causal effects*, but to investigate whether ECO_2, compared to HR, could *predict* the risk of death. An alternative way to see this is that we explored if the exposure variables could be used to represent the sum of confounders affecting both the newborns clinical condition and the outcome (Fig. 32).

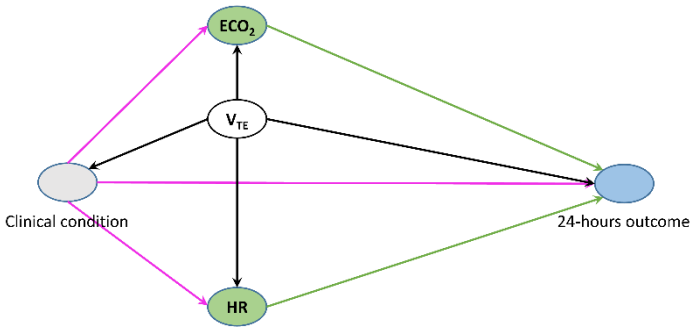


Figure 32 – The study in Paper II was not designed to *estimate* a causal effect of HR or ECO_2 on 24-hours, but to explore the ability of each parameter to *predict* the outcome. The figure above is not an ordinary direct acyclic graph (DAG), but inspired by DAGs to illustrate the reasoning. Clinical condition and ventilation quality are illustrated as confounders affecting ECO_2, HR and 24-hours outcome. HR and ECO_2 were used as proxy-variables to represent the combined effect of clinical condition and ventilation quality on 24-hours outcome. We adjusted for V_{TE} to assess whether ventilation technique was central for the outcome or not.

Random errors

The results from one study may differ from another purely because of random sampling variation. A broad distribution due to individual variation and measurement errors, decrease the precision of the results. The risk of errors due to sampling variability decreases with increasing sample size, and thus the large sample sizes in this thesis are major strengths. Statistical methods to display and handle random errors have been thoroughly discussed in the methods section (page 58).

Association versus causality

Association does not imply causation. The existence of an association between parameters may be due to bias or chance. Moreover, the direction of cause and effect relationships may not always be clear. Real life newborn resuscitation allows low possibility to control experimental conditions. An obligatory prerequisite for causal associations is that the cause must precede the effect. When several parameters change at the same time, the possibilities to distinguish between causes and effects are low. Furthermore, when changes are studied by time, the effects of a change in one parameter, may again reversely affect parameters related to the cause for the change. This is relevant for Paper I and II where central questions were how clinical condition and ventilation quality affected ECO_2, and whether ECO_2 could predict death. A complex interplay between ventilation parameters and clinical parameters occurred, with likely improvement in both lung compliance and clinical condition by time. To distinguish clearly causes and effects between clinical parameters and ventilation parameters with this study set up is not possible. In fact, the associations found in Paper I likely simultaneously describe both *causation* and *reverse causality* between parameters. Nevertheless, studies done in real life are needed to describe the full, complex picture that meets health care providers during newborn resuscitation. We used prior studies and logic based on physical and physiological principles to speculate on directions of causality. However, this must be interpreted with care.

"Comparing apples and oranges"

In clinical studies, variation between study objects will naturally occur. For all studies included in this thesis, it is likely that the effects of different exposures were not the same on all individuals. The clinical condition varies largely between newborns with insufficient spontaneous breathing at birth. This issue was also mentioned by Dawes in his monography from 1968[1]: *Human babies vary greatly in the degree of asphyxia with which they present at birth, and this has not been easy to estimate quantitatively.* He further wrote: *The results on a small number of babies in severe asphyxia was swamped by those on a larger number resuscitated in primary apnoea. And from a statistical point of view the numbers, and hence numbers of deaths, are inadequate for valid comparison.* The same problem may be relevant for the present studies, and may be seen as a kind of *misclassification bias*. Did all ventilated newborns actually need PPV? Were the included newborns representative for the newborns we intended to study?

We addressed this issue by doing comparisons between groups based on time to thresholds in Paper I and II and stratified analyses by BW < vs. ≥ 2500g and initial HR < vs. ≥ 100 bpm in paper III. Variations in clinical condition with a share of less severely compromised newborns than anticipated in the sample size calculation could impose a risk for *type II error* (accepting a false *null hypothesis* of no difference) in Paper III. However, trends in the data rather suggested a better clinical response in newborns ventilated without than with PEEP.

5.1.3 External validity

Induction of results found in a *study population* to a larger *target population*, is only acceptable when there are reasons to believe that the populations are similar in terms of associations between the studied exposures and effects. If this is the case, the results are said to be *generalizable* or to have a high *external validity*.

Several factors may limit the external validity of the studies in this thesis.

Table 11 – Factors potentially affecting the external validity of the studies in this thesis.

Risk	**Potential consequence**
All data were collected at one site.	Results may not be generalizable to other study sites.
The setting was rural with high morbidity, long transport and potential delay for complicated deliveries to be assisted.	Higher incidence of severe birth asphyxia than in regions with better access to obstetric care, routine hospital delivery and free transport.
Advanced neonatal care, including chest compressions, intubation, medication and more and respiratory support after initial resuscitation, was not available.	Make results potentially less generalizable to high-resourced settings. Especially outcomes related to survival are likely to be different in settings with higher availability of advanced care.
The midwives were exposed to regular training and persistent focus on newborn resuscitation.	The resuscitation skills of birth attendants at HLH may be better than in many low-resourced settings.

Especially for Paper I and II, the generalizability of the results may be questioned. In Paper I we have analysed associations of several covariates in a complex interplay. The results may not be the same in a population with different prevalence of severe birth asphyxia, a higher

or lower frequency of airway obstruction or mask leak, different praxis for estimating Apgar scores or other methodologies for measuring initial HR, ventilation factors or ECO_2. For Paper II, HR and ECO_2 may be less closely associated with 24-hour mortality in settings with higher availability of advanced care, but are still likely to be useful to identify newborns at risk for complications. For Paper III the single study site with potential differences in clinical presentation of the newborns and ventilation skills among midwives compared to other places, may also limit the external validity.

Despite potential flaws to the generalizability of the present studies, the criteria to start BMV at HLH follow international recommendations. Even if the incidence of birth asphyxia is higher in low-resourced settings due to a weak system for primary prevention, we find no reasons to believe that the physiology of asphyxiated newborns differs by nation or geography. The interpretation of ECO_2 and the general effects of PEEP should be the same. Variation in clinical condition between newborns and experience between providers will naturally occur in all real-life situations. Very few newborns receive medications or chest compressions during resuscitation at birth, no matter where they are born. Thus, we find no obvious reasons limiting the validity of the main findings in a global context. Opposite, we believe that the results from term and near-term newborns at HLH, are likely more representative for newborns born with similar GA other places in the world than manikins, extremely preterm newborns or animals.

5.2 Discussion of the main findings

5.2.1 Expired CO_2 during bag-mask ventilation at birth

Interpretation of expired CO_2

In Paper I, we found ECO_2 to be associated with both ventilation and clinical factors, with V_{TE} as the most dominant predictor for ECO_2. ECO_2 showed a gradual increase during initial ventilation, corresponding well with a simultaneous increase in V_{TE}. The findings are well in line with the results of Hooper et al, who found a highly significant relationship between ECO_2 levels and the immediate preceding end-inflation lung gas volume in intubated preterm newborn rabbits.[214] Schmölzer et al[215] and Blank et al[216] have also described a pattern of increasing ECO_2 with simultaneously rising V_{TE} by time in spontaneously breathing term newborns. Hooper et al elegantly demonstrated that ECO_2 might be used as an indicator of lung aeration in the immediate newborn period.[214] An increase in ECO_2 with increasing minute volumes found in Paper I differs from the normal physiological pattern seen with fully aerated lungs, and further underpins that ECO_2 is diffusion limited during initial ventilation of fluid-filled newborn lungs.[214]

Prior studies of ECO_2 in the newborn period, have commonly excluded ventilations with low V_{TE} or high leak. [214-216,220] As no exclusions can be done when interpreting measured values during ongoing resuscitation, we decided to retain all observations. This may explain the large

variation in ECO_2 between ventilations found in Paper I and II, and a lower median ECO_2 in our results than in other studies.

The significant associations with decreasing leak and non-linear associations with increasing PIP harmonize well with studies showing that ECO_2 responds to airway obstruction and mask leak on a nearly breath-to-breath basis.[219,247] The significant associations with initial HR and Apgar scores found in Paper I further indicate that the degree of clinical compromise also affects ECO_2. This is in line with prior studies describing low ECO_2 as a potential marker of low pulmonary circulation.[166,248-250]

Taken together, the findings in Paper I suggest that ECO_2 during BMV in the immediate newborn period may be seen as a combined indicator of lung aeration, airway patency, pulmonary circulation and metabolism in a complex interplay. Finding ventilation factors to explain substantially more of the variance in ECO_2 than clinical factors, we proposed that, despite the complexity, ECO_2 is likely to be useful to assess lung aeration and ventilation quality also in a population of bag-mask ventilated newborns. Following this reasoning, we induced that ventilation volumes and frequencies associated with higher levels of ECO_2 may be favorable to achieve a fast lung aeration.

Expired CO_2 as indicator of effective ventilation

In Paper II, we found that 70% of newborns reached ECO_2 ≥2% before HR ≥100 bpm. The finding is well in line with the physiological principles explored in Paper I, and underpins ECO_2 as an early marker

for lung aeration and effective ventilation. Time to ECO_2 >2% was also used as a secondary outcome measure in Paper III.

Three prior studies of mainly preterm newborns, have shown a significant increase in ECO_2 preceding HR response during mask ventilation in newborn resuscitation: Hooper et al found that ECO_2 >10 mmHg occurred median (IQR) 28 (21-36) seconds before HR>100 bpm in 10 preterm infants (mean ± SD GA 27 ± 2 weeks).[214] Mizumoto et al reported a median delay between detection of ECO_2>15 mmHg to HR>100 bpm of median (range) 15 (8-73) seconds in 7 non-intubated newborns with GA 31-37 weeks.[217] Blank et al observed gold colour change by colorimetric CO_2 detection prior to HR and SpO_2-response during PPV in 41 newborns with median (IQR) GA 29 (25-34).[218] Different from the three mentioned studies, our study included a substantially higher number of mainly term newborns. The main results were the same, strengthening ECO_2 as a sensitive marker for effective ventilation independent of GA.

We also found a group who reached HR ≥100 bpm before ECO_2 ≥2%. A lower V_{TE} and higher leak in this group, suggest suboptimal ventilations as explanation for the slower rise in ECO_2. Because there were no differences in time to HR ≥100 bpm for those who reached HR ≥100 bpm first compared to those who reached ECO_2 ≥2% first, we speculated that these newborns were likely less severely asphyxiated, despite the low initial HR, and may have had some spontaneous breathing, intact airway reflexes and a high leak/ closed glottis to explain the low ECO_2.

The comparison of times to thresholds by 24-hours survival in table 3 in Paper II, may be seen in relation to table 4 in Paper I, as the study population was the same. A number of newborns had ECO_2 >2% in the first ventilation, some never reached this threshold. These were excluded from comparison of time to thresholds. The data does however still provide interesting information. First, ECO_2 >2% in the first ventilation, suggests that the process of lung aeration and pulmonary gas exchange was initiated before PPV was started. The newborns were however still regarded as in need of PPV by the midwives. Second, among newborns who did not reach ECO_2≥2% while observed, 15 survived to 24 hours, while 8 died. Surviving to 24 hours without lung aeration is impossible. Thus, the result suggests that this group comprised some vital newborns who survived despite low-quality ventilations. Third, combining information on V_{TE}s from Paper I with 24-hour survival in Paper II, may rise a question of whether some of the 8 newborns who died without reaching ECO_2>2% received insufficient tidal volumes. Curiously inspecting individual measures among the 8, I found that most of these newborns did not reach HR ≥100 bpm despite appropriate volumes. However, one had HR >100 bpm while observed, but median V_{TE} <2ml/kg for all ventilations recorded. This underpins that persistent low ECO_2 may be due to either severely compromised clinical condition or ineffective ventilation. For a small number of newborns, insufficient tidal volumes may have been a contributing cause of death.

Expired CO_2 as predictor of outcome

Paper II documented for the first time that ECO_2 measured during the first 5 minutes of BMV at birth may, similar to HR, serve as a predictor of 24-hours survival. An association between low ECO_2 in the first minute of BMV with 24-hours mortality during newborn resuscitation, has prior to our paper been briefly described in a study from HLH by Linde et al.[221] In cardiopulmonary resuscitation in adults and children, a rise in ECO_2 is used as a marker for return of spontaneous circulation.[251,252] In the newborn period, however, low ECO_2 is rarely due to cardiac arrest.

Due to the high variability in measured values, ECO_2 may be difficult to interpret during ongoing PPV. Our results indicated that maximum ECO_2 was as good as medians ECO_2 to predict 24-hour outcome. This simplifies the interpretation for prognostic purposes, as only the highest observed value is needed.

Used as prognostic tests for 24-hour survival, we found that reaching a maximum $ECO_2 \geq 2\%$ or HR $\geq$ 100 bpm before 5 minutes of age had sensitivities of >95% to predict survival at 24 hours. However, the specificities were relatively low for both parameters, meaning that a number of newborns survived despite not reaching the thresholds. Thus, relying on low ECO_2 or HR alone to discontinue resuscitation is highly problematic. However, reaching one or both thresholds should encourage further efforts. Using lower threshold values, would improve specificity, but reduce sensitivity.

5.2.2 The impact of PEEP

Clinical effects of PEEP

In the PEEP-study, we found no substantial difference in HR and a borderline significant lower ECO_2 in the PEEP-group. There was no significant difference in time from first to last ventilation. We further found no difference in 24 hours survival.

The effects of PEEP compared to no PEEP during newborn resuscitation, have been studied in 5 other RCTs with variable sample sizes, methods to deliver PPV and PEEP and different main outcomes.[119,127,185,186,253] Table 12 (next page) provides key information on each study. In addition to the mentioned RCTs, a large prospective cohort study by Guinsburg et al is central.[128] The study included 1962 preterm newborns with GA 23-33 weeks and BW 400-1499g, 1456 were ventilated with TPR, 506 with SIB. The choice of equipment was done by the neonatologist for each patient. The main finding, was that TPR compared to SIB was associated with improved survival to hospital discharge without major morbidities (BPD, IVH III-IV, PVL), OR 1.38 (95% CI 1.06-1.80).

As the methods of the available studies are so different, the results are not directly comparable. Szyld et al[119] is the only study in addition to our PEEP-trial including newborns who received PPV performed with SIBs with a PEEP-valve. They did however not display a direct comparison of newborns ventilated with a SIB with or without PEEP. Szyld, Thakur and Kookna included term newborns, however Kookna is the only study reporting results from term and near-term newborns separately.

Table 12 – RCTs comparing PPV with or without PEEP.

	Patients	**Clinical outcomes**
Dawson[185]	80 newborns, GA<29 weeks *41 TPR PEEP 5* *39 SIB PEEP 0*	**Main outcome** No difference in SpO_2 at 5 min **Secondary outcomes:** Lower HR with SIB at 1 min, no difference by 5 min. Interventions: Trends of more CPAP within 5 minutes in TPR-group, not significant. No difference in intubation, suctioning, O_2 adm
Szyld[119]	1027 newborns, GA≥26 weeks, 63% BW≥2500 g *511 TPR PEEP 5* *526 SIB* *226 PEEP 0* *290 PEEP +*	**Main outcome** No difference in proportion of newborns with HR ≥100 bpm at 5 minutes of age **Secondary outcomes:** Intubation: 17% TPR vs 26 % SIB (P=0.02). More days on mechanical ventilator and O_2 in SIB-group. No difference in Apgar, CPR, time to spontaneous breathing, air leaks, CPAP, HIE. Subgroup analyses for very low BW infants (<1500g): Higher HR ≥100 at 2 min of age with TPR, 88% TPR vs 76% SIB (P=0.04). Less BPD in TPR group, 25% vs 75% (P=0.04) Subgroup analyses for newborns ventilated with SIB +/-PEEP: No direct comparison done between for PPV with SIB +/- SIB. Comparison performed by ILCOR showed no difference (see text)
Thakur[186]	90 newborns, GA≥26 weeks *40 TPR PEEP 5* *50 SIB PEEP 0*	**Main outcome** Shorter duration of PPV in TPR-group, 30s TPR vs 60s SIB (P=0.02) **Secondary outcomes** Resuscitation with room air 38% SIB vs 72% TPR (P=0.01). Intubation 34% SIB vs 15% TPR (P=0.04). No difference in Apgar, NICU adm, RDS, mechanical ventilation, surfactant, mortality. Newborns with GA<34 w: 19 TPR vs. 18 SIB: Larger differences.
Kittsommart[253]	51 newborns, GA≤32 weeks or GA<1500 g *26 TPR PEEP 5* *25 TPR PEEP 0*	**Main outcome** No difference in SpO_2. **Secondary outcomes** No difference in FiO2, air leak, surfactant, BPD or death. *Pilot study, no sample size calculation done. By chance higher BW in PEEP-group (P=0.02). Not mentioned by ILCOR.*
Kookna[127]	90 newborns, GA≥28 weeks *25 TPR PEEP 5* *25 SIB PEEP 0*	**Main outcome** Shorter duration of PPV in PEEP-group, 71s TPR vs 88 s SIB (P=0.003) **Secondary outcomes** Higher 1-min Apgar with TPR, TPR 5.0 vs SIB 4.4 (P=0.02), no difference at 5 and 10 min. RDS higher in SIB-group, TPR 28% vs 60% SIB (P=0.04). No difference in HR, SpO_2, air leak, mortality

Like in our study, no difference in HR response was found by Szyld, Thakur and Kookna. Dawson et al found a lower HR at 1 minute in the SIB-group compared to TPR, Szyld similarly reported a higher proportion with HR ≥100 bpm at 2 minutes of age with TPR compared to SIB in subgroup analysis for newborns with BW<1500g. None of the studies reported on ECO_2. The studies by Thakur and Kookna both found shorter PPV time in the TPR group compared to no significant difference in our study.

Because of the low-resourced study setting, advanced care was not available at our study site. Thus, we could not study outcomes like intubation or days on mechanical ventilator. Dawson, Szyld and Thakur found that more newborns were intubated in the SIB group compared to TPR. Long term outcomes for lung function (except BPD) or neurodevelopment in term and near term newborns, were not available in any of the mentioned studies.

Results from studies comparing ventilation with PEEP delivered by TPR, may not be transferrable to a setting where PEEP is delivered by SIB as the methods differ substantially. Preceding the 2020 update of CoSTR, ILCOR performed a scoping review for studies comparing TPR and SIB.[126] In February 2021, a draft version of a systematic review of devices for administering PPV was posted for public comments.[143] Summing up the results, the conclusion for most predefined outcomes was that benefit or harm could not be excluded based on available data. A benefit with evidence of very low certainty of using TPR compared to

SIB was found for the incidence of BPD and IVH and for the duration of PPV. Subgroup comparison based on GA was not feasible due to limited data and variable inclusion criteria. The draft[143] also summed up results of studies comparing a PPV with a SIB with or without a PEEP-valve, including the study by Szyld et al and Paper III in this thesis. No benefit or harm could be excluded for any of the included outcomes. HR, ECO_2 or ventilation parameters were not discussed. At the time of writing, the final version of this document is still not published.

Taking all available information together, the evidence for clinical benefit or harm with using PEEP during ventilation of term and near term newborns, is still very weak. BPD and IVH are hardly relevant outcomes at term. The finding of shorter PPV time with TPR by Thakur and Kookna, and a lower intubation rate with TPR by Szyld and Thakur, may indicate a benefit of TPR to facilitate spontaneous breathing. However, the risk of bias was large in all studies. Clinical condition among included newborns likely varied. A shorter PPV time with TPR may have been due to CPAP potentially facilitating spontaneous ventilation in the more vital, and does not prove a better efficacy to aerate the lungs in the most severely compromised. Large retrospective cohort studies have reported on increased incidence of pneumothorax, especially in term newborns, after taking delivery room CPAP into routine use.[131-133] Adjusting PIP with TPR takes more time than with SIB.[115]

There is no clear evidence for clinical benefit or harm of using a PEEP-valve during bag-mask ventilation of term and near term newborns.[94]

PEEP and ventilation parameters

Besides studying clinical effect on PEEP, Paper III includes interesting data on ventilation parameters during BMV with and without PEEP-valve. In the following, I will discuss this in relation to existing literature, physical and physiological principles.

Compared to no PEEP, we found that the PEEP-group in our study had borderline lower ECO_2 (P=0.05). The newborns also received lower tidal volumes (V_{TE}, P=0.02) and had borderline higher leak (P=0.06). Median (IQR) PIPs were similar and close to the "pop-off" pressure for the pressure release valve on the bag in both groups, 39 (37-41) mbar. The PEEP-valve delivered PEEP within the intended area (median (IQR) PEEP 4.7 (2.1-5.6) mbar in the PEEP-group compared to 0.1 (0.1-0.2) mbar with no PEEP.

Interpreting the results for ECO_2 in the light of the findings from Paper I and II, a lower ECO_2 in the PEEP group may indicate a less effective lung aeration with compared to without PEEP in this study. This is opposite of expected. As described in the introduction, chapter 1.6.3, the rationale about using PEEP during newborn resuscitation, is to assist lung aeration and facilitate establishment of FRC by preventing airway collapse at expiration.[37]

We speculated that the lower V_{TE} found in the PEEP group may be a key to understand the lower ECO_2 (Figure 33, next page). During PPV, the

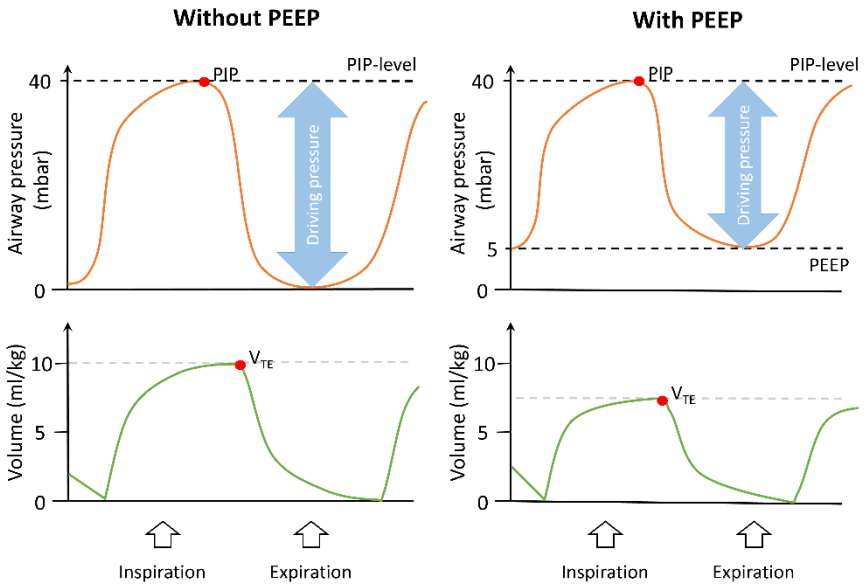


Figure 33 – Drawing to illustrate how a lower difference between PIP and PEEP may affect driving pressure and V_{TE}. *Driving pressure = PIP - PEEP*

driving pressure for a ventilation is the difference between PIP and PEEP. If compliance and airway resistance is kept constant, the tidal volume (V_T) will depend on the driving pressure.

A number of other explanations are possible: During initial ventilation, some air is retained within the lungs to form FRC. Theoretically, this process should be facilitated by PEEP, and lower V_{TE}s / higher "leak" in the PEEP-group could be due to accumulation of FRC. However, if this was the case, I would expect ECO_2 to be higher in the PEEP-group.[214] The larger mean airway pressure (MAP) may increase dead space to dilute the CO_2 concentration due to pressurization of the upper airway and mask.[211,212] The higher MAP with positive pressure in the mask at expiration may also alter mask seal contributing to the observed increase

in leak. It is also thinkable that altering the pressure in the mask potentiated trigeminal reflex mechanisms leading to closure of the glottis among more vital newborns. This phenomenon has been described both in preterm and term newborns.[153,254,255] Furthermore, an increase in MAP may have affected venous return to the heart, which could again affect cardiac output in hearts compromised by asphyxia.[256]

Among the studies mentioned on page 100-102, only Dawson et al report on measured PEEP, which was found to be mean ±SD 5.6 ±1 with TPR and 0.5 ±0.5 with SIB. PIP was around 30 mbar in both groups, however with a larger variation in the SIB group. V_{TE} was found to be similar between the groups, however with a trend of lower V_{TE} and less spread in newborns ventilated with TPR. Szyld et al have reported on PIP, finding significant higher values and larger variation in newborns ventilated with SIB compared to TPR ($P<0.001$). For all groups, the reported PIPs were lower than in Paper III (TPR 25.3 ±1.2, SIB without PEEP 27.3 ±3.9, SIB with PEEP 28.7 ±5.5).

The relatively higher PIP values observed at HLH compared to other studies likely reflect that the midwives often squeeze the bag until the pressure-relief valve opens or even close the valve. A need for higher pressures due to a high share of severely asphyxiated newborns with low lung compliance may be an explanation.[138] Frequent occurrence of obstructed airway and a focus in the HBB-program on looking for chest rise and increase pressure if needed, may have affected the results.[98]

Reliability of the PEEP-valve

The reliability of PEEP-valves for SIBs has been questioned in a number of studies from simulated neonatal resuscitation.[114,120,121,187] The measured PEEP with a variety of PEEP-valves tested on manikins generally was too low compared to the set value. Typically, a mean PEEP of 2-3 cmH_2O was reported with a set PEEP of 5 cmH_2O. Increasing ventilation frequency has been reported to be associated with higher PEEP.[121]

The median (IQR) PEEP of 4.6 (2.1-5.3) mbar in Paper III was well within the intended range of 4-8 mbar. Distribution of measured values is displayed in Supplemental figure 5 in Paper III. Significant difference in clinical parameters for newborns in the PEEP-group who received a median PEEP $<$ vs. $\geq$ 4 mbar with higher Apgar scores and initial HR, suggest that keeping a mask seal to provide adequate PEEP was difficult among more vital newborns.

Gomo et al has further explored the reliability of the PEEP-valve used in Paper III in relation to other ventilation parameters using data from the PEEP-study.[237] PEEP well within intended values was found with mask leak up to 80%, and delivered PEEP was minimally affected by ventilation frequency. The results were significantly different from the results found in the manikin studies mentioned above. This may suggest a better reliability of this novel PEEP-valve compared to other models. This is a possibility as the valve was specially designed for newborns with a smaller diameter optimized for typical neonatal ventilation

volumes. However, as discussed in the study by Gomo, a realistic PEEP cannot be delivered with a PEEP-valve when there is no lung to expire air.[114] The setup in manikin studies often does not realistically simulate newborn airways, and thus the results will often not be transferable to real babies.

Preclinical testing of Upright with PEEP on manikins was done by Thallinger et al.[244] The PEEP-values measured were within the intended range. However, compared to the results in Paper III, V_{TE}s observed on manikins were generally higher and PIPs slightly lower. This further underlines that ventilating newborns differs from ventilating manikins, and results obtained in manikin studies may not be directly transferrable to clinical settings.[121]

Interestingly, recent studies have also raised serious concerns regarding the reliability of PEEP delivered with T-piece resuscitators. A risk of intrinsic PEEP-generation, particularly with a high lung compliance, is of special concern.[123]

Upright with PEEP and prematurity

The cohort of newborns included in Paper III, consisted of mainly term and near term newborns. Due to imprecise estimation of GA in the study population, we used BW <2500 g as a proxy for prematurity. Stratified analyses by BW did not disclose principal differences between ventilations with compared to without PEEP-valve in presumably preterm compared to term newborns, however V_{TE}s were generally higher among the smallest newborns.

5.2.3 Implications for clinical practice and further research

Should expired CO_2 be measured and displayed?

Paper I and II largely confirm ECO_2 as an early and sensitive marker for effective ventilation. A significant increase is seen around 10-20 seconds before HR response.[214,217,218] Measured values change on a breath-to-breath basis dependent on ventilation factors, and ECO_2 monitoring during resuscitation might help to identify airway obstruction and mask leak.[247] As time is critical and effective ventilation is key to intact survival for severely asphyxiated newborns, an early feedback to help correct ventilation technique could potentially make a difference for outcomes.[9]

It must be underlined that in our studies measured values of ECO_2 were not displayed for the midwives. Thus, they could not adjust ventilation technique as response to changes in ECO_2, and we have no documentation of whether this could improve the prognosis.

There are also arguments against introducing ECO_2 monitoring during newborn resuscitation. Table 13 (next page) display an overview of potential advantages and disadvantages. Practical issues regarding availability of suitable equipment are likely among the most important reasons why ECO_2 monitoring is still in limited clinical use. Large variability in measured values and complex associations with clinical and ventilation factors, may impose a serious risk for misinterpretation and distracting the providers attention away from the newborn.[257]

Table 13 – Potential advantages and disadvantages of ECO_2 monitoring during bag-mask ventilation at birth based on literature and the authors reflections. The points given for colorimetric CO_2-detectors are compared to quantitative methods.

	Advantages	**Disadvantages and risks**
Capnography	Adds objectivity to assess lung aeration, airway patency and gas exchange.[214,219] Earlier and more direct feedback on clinical response to ventilation/ changes in ventilation technique compared to HR.[214,217,218] Continuous display of numerical values. Adds information with potential prognostic value.	Requires a spacer between mask and bag, which adds dead space and alters ergonomics for the SIB. Large variation in measured values may confuse providers. Risk of misinterpretation.[257] With low ECO_2 due to severely compromised clinical condition, providers may waste valuable time trying to adjust correctly performed ventilations. Distracts attention away from the patient. Low availability of suitable equipment. Additional costs and need for resources to maintain equipment.
Colorimetric *	Higher availability, lower costs. Does not require electricity or complicated electronics.[218] Less complex interpretation. Display placed close to patient, less distraction of attention away from clinical observation.	Risk of false readings.[258] Adds resistance to flow.[259] Single use equipment, dependent on delivery, more waste.

*Colorimetric CO_2 detectors

Several authors have argued that a display of V_{TE} in combination with CO_2 should be used to reduce the risk of volutrauma and provide a way to distinguish between different causes of low ECO_2. In high-resourced settings there is an ongoing debate about the use of respiratory function monitors (RFM) in the delivery room, especially for preterm newborns.[188,202,213,257,260] Two randomized trials comparing visible versus masked RFM curves during initial ventilations in preterm newborns reported a

significant reduction in V_{TE} and leak in the RFM visible group, and a trend towards less BPD.[261,262] To my knowledge, a significant benefit on long term outcomes for preterm newborns remains to be proven, and similar studies during BMV around term have not been done.

Availability of a combined display of ECO_2 and V_{TE} using RFMs, does not seem like a realistic alternative for 140 million global births per year. Having a skilled and equipped birth attendant present at every birth, should still be the focus for efforts to improve newborn survival globally. The potential utility of the ECO_2-studies in this thesis for low-resourced settings, is more related to better understanding of the physiology of BMV, and not so much to introducing new equipment.

A simple display of ECO_2 < vs. ≥ approximately 2% can be achieved by using colorimetric CO_2-detectors.[218,219] I personally have no experience with these. However, taking the findings in the present studies and literature into account, a display of ECO_2 in combination with thorough clinical observation may have potential to help improve ventilation technique. Further studies are needed to document potential benefit on long term and clinically relevant outcomes. Thorough considerations must be done regarding utility, practical use and costs before introducing such equipment in low-resourced settings.

Should expired CO_2 be used for prognostication?

In the latest CoSTR, ILCOR suggests that a reasonable time frame to consider discontinuing resuscitation efforts is after around 20 minutes with no heart rate.[94] All recommended steps of resuscitation should have

been followed and reversible causes excluded. The recommendation is classified as weak with very low-certainty evidence. The committee underlines that the decision should be individualized, taking into account factors such as GA, other morbidities, the family preferences and availability of neonatal intensive care. The WHO Newborn resuscitation Guidelines,[80] suggest that resuscitation should be stopped if no detectable heart rate after 10 minutes of effective ventilation or HR < 60 bpm and no spontaneous breathing after 20 minutes of resuscitation. Thus, the criteria to stop resuscitation efforts are strict according to guidelines.

Based on the findings in Paper II, I propose that ECO_2 may have a potential to be useful as additional information to support decision making. The presence of ECO_2 measures ≥2% should highly encourage further efforts. However, due to low specificities for prognostic purposes, relying on low ECO_2 alone in decisions to discontinue resuscitation should not be done. If ECO_2 is to be used clinically for prognostication, further studies are needed to establish reasonable stopping rules that include ECO_2. As for HR, the information must be combined with thorough considerations taking clinical responses, duration of resuscitation and availability of advanced neonatal care into account. Due to the dual nature of ECO_2 as an indicator of both clinical condition and ventilation quality, it will be especially important to consider the quality of given ventilations before using a persistent low ECO_2 as supporting information to stop resuscitation efforts.

What are appropriate tidal volumes?

Based mainly on Paper I and partly supported by Paper II and III, I have come to believe that higher tidal volumes (V_T) than the commonly recommended 4-8 ml/kg should be targeted during BMV to newborns at or near term. This may be a controversial suggestion, as large V_Ts have been shown to cause ventilation induced lung injury (see chapter 1.6.2, page 22). Several authors have warned that V_Ts > 8ml/kg should be avoided.[101,164,263]

So, what makes me think that somewhat larger V_Ts may be favourable? First, the findings in Paper I showed that V_{TE}s of 10-14 ml/kg were associated with higher values of ECO_2 and a shorter time to reach ECO_2>2% than lower V_{TE}s. Second, 24-hours survival studied in Paper II improved with higher levels of ECO_2 and a shorter time to reach ECO_2 >2%. Third, using PEEP in Paper III did not result in higher levels of ECO_2. Instead, we found borderline significant lower ECO_2 in the PEEP-group, suggesting a slower lung aeration with compared to without PEEP. We simultaneously found lower measured V_{TE} in the PEEP-group, possibly explaining the lower ECO_2.

Prior findings from our study site have also suggested that higher V_Ts than 8 ml/kg may improve clinical response to BMV. Linde et al found that a V_{TE} of median 9.3 ml/kg was associated with the largest positive change in HR.[134] Thallinger et al found a higher ECO_2, indicating a faster lung aeration, in BMV with Upright compared to standard Laerdal bag. Median (IQR) V_{TE} was 10.0 (4.3-16.8) ml/kg for Upright bag compared

to 8.6 (3.5-13.8) ml/kg for standard bag. For the most compromised newborns, time is critical, and a rapid clinical response is desired.

Ventilation induced lung injury occurs in all ages. A rise in inflammatory parameters has been found after mechanical ventilation in term newborns.[264] However, BPD is not a disease of term newborns, and the risk of lung injury after BMV for infants at or near term is low (Figure 34). For term and near-term newborns, the risk of HIE due to prolonged hypoxia with too low delivered V_Ts, may outweigh the potential risk for lung injury due to hyperinflation.

It is widely accepted that insufficient V_Ts during resuscitation can diminish gas exchange and prolong tissue hypoxia, potentially increasing the risk for brain damage and death.[165,166] The current recommended range of V_Ts of 4-8 ml/kg, is based on measurements performed in spontaneously breathing term infants and intubated preterm infants.[101]

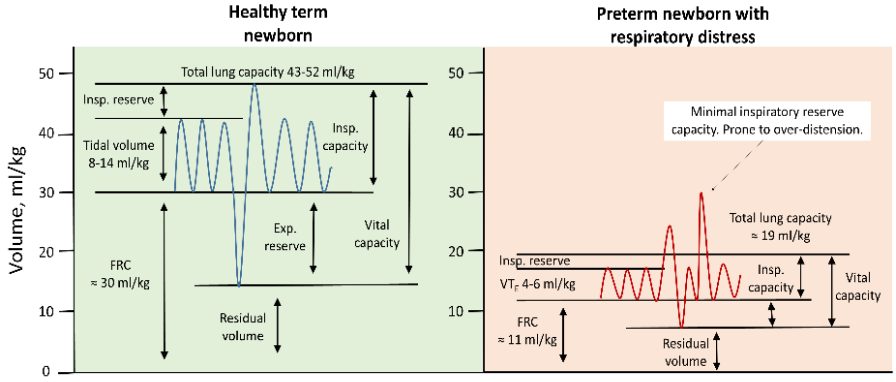


Figure 34 – The figure illustrate differences in V_T, FRC and TLC in normal term newborns compared to preterm newborns with respiratory distress based on volumes reported by Vilstrup et al.[104] The figure illustrates that the higher total lung capacity in healthy term newborns may allow for V_Ts of 8-14 ml/kg with low risk of lung-injury.

Van Vonderen et al compared volumes in facemask vs. intubated PPV, finding that extra volume may be needed to compensate for upper airway distention with facemask ventilation.[212] Mask distension may also contribute to V_{TE}.[211] Thus, some of the delivered volumes may escape from entering the airways, partly explaining a need for higher volumes.

None of the three studies included in this thesis have investigated long-term outcomes. Despite a suggestion of V_{TE}s around 10-14 ml/kg to be potentially favorable for a fast lung aeration, the optimal V_Ts to be recommended during BMV around term remains unclear.

A randomized controlled study targeting V_{TE}s of for example 4-8 ml/kg compared to 8-12 ml/kg during BMV in term newborns, could add valuable information. However, due to a low frequency of lung- or neurodevelopmental injury following resuscitation in the study population, a very large sample size would be needed to detect possible differences in long-term outcomes. Blood gas analyses to enable subgroup analyses dependent of degree of asphyxia could add valuable information.

What is appropriate ventilation frequency?

A ventilation frequency of around 30 inflations/min was associated with the highest ECO_2 in Paper I. This suggests that a ventilation frequency of around 30 inflations/ minute, as recommended by the ERC,[96] may support a faster establishment of FRC compared to the higher ventilation rate of 40-60 inflations/min recommended by the AAP.[95] We have however not studied inspiration and expiration times, and subtle

interactions between ventilation parameters, compliance changes by time and effects on arterial CO_2 levels may complicate the picture. In a study using data from Paper III in this thesis, we found that an increase in ventilation frequency was associated with lower V_{TE}s.[237] Thus, a potential benefit of lower ventilation frequency may be due to slightly longer inspiration times or higher V_Ts.

Prolonged inflations require a low ventilation frequency during initial PPV. Delivering sustained inflations > 5 seconds with a SIB, is hardly possible.[265] Most studies of prolonged inflation have been performed in preterm animals or very preterm newborns using TPRs.[169-172] Ventilation frequency during BMV has received little attention in clinical studies, but may have significant impact on ventilation efficacy.

Despite a suggestion for lower ventilation rates to be potentially favorable in Paper I, optimal inflation rates to achieve a fast lung aeration and avoid injury at or near term are still not known. Even if TPR is now commonly used in high-resourced settings, SIBs are still the only alternative where most newborns in need for resuscitation are born. Further studies are needed to determine the optimal ventilation frequency during BMV around term. An RCT targeting for example 30-40 vs 40-50 inflations/ min could be interesting. As for V_Ts, a very large sample size would be needed to document effects on long-term outcomes. Alternative outcome measures could be ECO_2, HR response, duration of PPV, V_{TE}, inflation times and blood gas analyses pre and post resuscitation.

What are appropriate peak inflation pressures?

According to the results in Paper I, PIP explained only minor parts of the variation in ECO_2. However, a stronger positive linear association with ECO_2 in first compared to later ventilation sequences may support a need for higher pressures in initial ventilations to overcome low compliance. This is in line with prior findings indicating fast changes in lung compliance during initial lung aeration.[138,165]

The PIPs measured in all the studies of this thesis were higher than the currently recommended starting set point for PIP of 30 mbar in term newborns.[95,96] This may suggest that the PIPs used in some cases were unnecessarily high. However, a high share of severely asphyxiated newborns with low lung compliance may also explain a need for higher pressures. The lower ECO_2 and V_{TE} with PEEP in Paper III, potentially due to lower driving pressures, may further strengthen a need for high PIPs to achieve lung aeration with short ventilation times in this cohort of newborns.

Tidal volumes are highly dependent on lung compliance and thus no exact recommendations can be given for PIP. Current guidelines state that PIP should be increased as necessary to achieve appropriate volumes.[95,96] When possible, high PIPs should be avoided. High PIPs may be needed in severely asphyxiated newborns.[138] A high occurrence of obstructed airways may complicate the picture. Improving ventilation technique by focus and specific training on airway opening in the HBB-program may potentially reduce the need for using high PIPs. I speculate

that slightly longer inflation times associated with a reduced ventilation frequency may potentially also enable lower PIPs to be sufficient. A CO_2 display to detect obstructed airway could also potentially be useful.

Should PEEP be used?

We found no clinical benefit of adding a PEEP-valve to the bag-mask in Paper III. A lower ECO_2 and higher leak in the PEEP-group rather suggested a slower lung aeration.

It should be noted that the PEEP-study was not powered to detect differences in mortality. Long-term outcomes were not studied. A possible positive effect on the risk for RDS, lung-injury or HIE cannot be ruled out. To investigate this in a population of term newborns, will require a large sample size and a meticulous system for follow up.

As discussed on page 100-103, the evidence to support using TPR over a SIB for ventilating term and near-term newborns, is very weak. The results in Paper III suggest that a sufficient driving pressure to deliver adequate V_T, may be more important than PEEP for lung aeration at term. This could be and argument for using a SIB without PEEP rather than TPR when ventilating severely asphyxiated newborns, due to potential advantages of being able to adjust the PIP faster. However, this is speculation and not supported by current scarce evidence.

Despite delivering median PEEP within the intended range, adding a PEEP-valve to a SIB cannot provide CPAP. Most newborns in need for resuscitation will start breathing spontaneously when initial lung

aeration is achieved. Using a TPR for resuscitation may have advantages compared to a SIB with a PEEP-valve by facilitating spontaneous breathing.

Our results rather suggest against using a SIB with compared to without PEEP. A large trial including long-term outcomes could improve the evidence.

5.3 Ethical considerations

Practical and ethical issues regarding consent and safety considerations have been described in chapter 3.7. In this chapter, I will concentrate on a more general discussion of emergency research in a vulnerable population and public-private partnership.

The Helsinki declaration is a statement of ethical principles for medical research involving human subjects.[266] Four paragraphs are of particular relevance for the studies of this thesis:

§ 13	Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
§ 19	Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.
§ 20	Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.
§ 28	For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

The research of this thesis was performed in a developing country involving one of the most vulnerable groups, the newborn child, in a potentially life-threatening emergency situation. Doing research in such

settings, raises extra concerns regarding ethical standards. Cultural differences and economic dependency further call for a sensitive approach. However, not doing research in a population with obvious needs is also an ethical problem.

The Safer Births study group mainly focus on research to improve training methodologies and develop better equipment for use in low resourced settings. This has a clear potential to be beneficial for the study population. The research has brought knowledge and resources to the study site, new equipment and a focus on training and skills to save newborn lives. In fact, an improvement in newborn care has been documented at HLH, clearly indicating benefit for the population involved.[225,228] The study group has been able to raise funding for further projects with Tanzanian doctors who have obtained their PhD in the Safer Births in charge, and thus there is hope that the positive effects can be sustained. This is however an ethical dilemma for research in poor regions: What to do when the financing runs out, the project is finished - and the local health care system is still dependent on the research and people involved will lose their income.

The research infrastructure at HLH was built up in close collaboration with local representatives. There is a constant focus on safety and protection of the rights for the included newborns, their families and involved health care personnel. Research assistants and research nurses were employed to take care of data collection. This hindered extra work-load for the midwives and reduced the risk of bias potentially involved

with self-reporting. The research nurses were also responsible for maintaining equipment and keeping everything clean and ready for use, which added extra benefit for patient safety.

A concern for the midwives, was potential risks of being observed and video-filmed. What if someone did something wrong? These issues were thoroughly discussed with the staff and management to ensure that observations done in research should not affect working relationships and not be displayed for colleagues. During data-analyses, harmful praxis or suboptimal treatment have sometimes been uncovered. This raised dilemmas for the researchers regarding intervention. The problem was solved by addressing these issues in training sessions in general terms with no identification of the persons involved.

A question that may be asked, is whether informed consent has the same meaning in a poor and partly illiterate population? Due to language barriers with different tribal backgrounds, informing the mothers was not always possible, and some were not asked to participate due to this. There may however still be a possibility that some mothers gave consent despite not really understanding the information given. A special concern in the PEEP-study, was asking for deferred consent in cases with unfavourable outcome. This has already been mentioned twice (page 67 and 86). The difficulties were thoroughly discussed in the study group, and the research nurses took responsibility for informing and asking the mothers in a sensitive way. To reduce the need for using deferred consent, we aimed to seek consent at admission whenever possible. It

has been debated whether involving community leaders and stakeholders in planning may sometimes be more sensitive to the needs of a study population than asking for individual consent for something that the people involved does not have the prerequisites to understand.[267]

The research in Safer Births is done in close collaboration with Laerdal Global Health and Laerdal strategic research. Doing research in a public-private partnership raises ethical questions as economic interests and personal relationships may affect the work. However, public-private partnerships also open possibilities that are not achievable without cooperation. The Laerdal team has a unique competence to develop equipment designed for the needs in low-resourced settings, and does this work on a non-profit basis. The representatives for Laerdal had a limited role in the scientific work. Study designs, data analyses and presentation were solely the responsibility of researchers with no personal economic interests in the results.

6 Conclusions

The results of this thesis have brought more knowledge on interpretation of ECO_2 and the use of a new PEEP-valve in BMV at birth.

The findings support ECO_2 as an indicator of lung aeration in the immediate newborn period. However, pulmonary circulation and airway patency will also significantly affect the results and must be accounted for in the interpretation. To optimize lung aeration during bag-mask ventilation, our findings suggest that in asphyxiated term and near-term newborns, using tidal volumes of 10-14 ml/kg and a relatively low ventilation frequency of around 30 inflations/minute may be favorable.

An increase in ECO_2 was seen before HR response to ventilation, and thus ECO_2 is a sensitive indicator of clinical effect during resuscitation. ECO_2 may simultaneously be used to assess airway patency. We have documented for the first time that ECO_2 measured during BMV at birth is also significantly associated with 24-hours survival. This also makes ECO_2 potentially useful for prognostic purposes.

Adding a PEEP-valve did not improve HR response during BMV at birth in term and near-term newborns. We also found no better ECO_2 in the PEEP-group, lower tidal volumes, higher mask leak and no difference in survival despite delivery of adequate PEEP. Our study does not support routine use of PEEP during BMV at birth.

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Predictors for expired CO_2 in neonatal bag-mask ventilation at birth: observational study

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ABSTRACT

Background Expired carbon dioxide (ECO_2) indicates degree of lung aeration immediately after birth. Favourable ventilation techniques may be associated with higher ECO_2 and a faster increase. Clinical condition will however also affect measured values. The aim of this study was to explore the relative impact of ventilation factors and clinical factors on ECO_2 during bag-mask ventilation of near-term newborns.

Methods Observational study performed in a Tanzanian rural hospital. Side-stream measures of ECO_2, ventilation data, heart rate and clinical information were recorded in 434 bag-mask ventilated newborns with initial heart rate <120 beats per minute. We studied ECO_2 by clinical factors (birth weight, Apgar scores and initial heart rate) and ventilation factors (expired tidal volume, ventilation frequency, mask leak and inflation pressure) in random intercept models and Cox regression for time to ECO_2 >2%.

Results ECO_2 rose non-linearly with increasing expired tidal volume up to >10 mL/kg, and sufficient tidal volume was critical for the time to reach ECO_2 >2%. Ventilation frequency around 30/min was associated with the highest ECO_2. Higher birth weight, Apgar scores and initial heart rate were weak, but significant predictors for higher ECO_2. Ventilation factors explained 31% of the variation in ECO_2 compared with 11% for clinical factors.

Conclusions Our findings indicate that higher tidal volumes than currently recommended and a low ventilation frequency around 30/min are associated with improved lung aeration during newborn resuscitation. Low ECO_2 may be used to identify unfavourable ventilation technique. Clinical factors are also associated with persistently low ECO_2 and must be accounted for in the interpretation.

What is known about the subject?

- Expired CO_2 (ECO_2) is low immediately after birth before the lung liquid is cleared.
- ECO_2 may serve as a marker for effective ventilations in intubated patients.

What this study adds?

- The quality of ventilations are more important than the clinical condition for measured ECO_2 during the first minutes of bag-mask ventilation in newborn resuscitation.
- Ventilation frequency around 30/min gives the highest ECO_2.
- Tidal volumes of 10–14 mL/kg are associated with the highest ECO_2 and the shortest time to reach ECO_2 >2%.

INTRODUCTION

Around 3%–6% of newborns receive positive pressure ventilation at birth to facilitate transition and establish cardiorespiratory stability.[1–3] Heart rate (HR) response is an important indicator of effective resuscitation,[3 4] but cannot directly assess ventilation. Hooper *et al* found that expired carbon dioxide (ECO_2) indicates degree of lung aeration immediately after birth.[5]

Newborn lungs are liquid filled. Before functional residual capacity is sufficiently established, gas exchange is diffusion limited.[6] To detect ECO_2, liquid must be cleared and air must enter the alveoli. ECO_2 increases rapidly in the first minute of extrauterine life during spontaneous breathing, but slower if positive pressure ventilation is needed.[7–9] Capnography may help identify unfavourable technique and guide ventilations during newborn resuscitation.[10–14] There is currently insufficient evidence that ECO_2 monitoring during newborn resuscitation affects outcome.[3 15] ECO_2 depends, in addition to ventilation, on metabolism and pulmonary circulation.[16]

Optimal ventilation strategies for rapidly establishing effective pulmonary gas exchange in non-breathing newborns have not been fully determined. Recent studies indicate that larger tidal volumes (V_{TE}) than the 4–8 mL/kg currently recommended may cause faster increase in HR.[4 17 18] Guideline recommendations for ventilation frequency vary between

the USA (40–60/min) and Europe (30/min), and evidence for any recommendation is sparse.[19 20]

In this study, we aimed to explore the relative impact of ventilation factors (V_{TE}, frequency, mask leak and pressure) and clinical factors (birth weight (BW), Apgar scores and initial HR) on ECO_2 during bag-mask ventilation (BMV) in resuscitation of term and near-term newborn infants. Better understanding may improve interpretation of ECO_2 measurements and help determine optimal ventilation strategies.

METHODS

Study design and setting

Observational study performed between 1 March 2013 and 1 June 2017 at Haydom Lutheran Hospital, a rural Tanzanian referral hospital with 4–5000 deliveries annually. The study was part of Safer Births, a research consortium on labour surveillance and newborn resuscitation in low-income settings.[4 21 22] Midwives and nursing students conducted most vaginal deliveries. Newborn resuscitation was mainly the responsibility of midwives.

Data collection, equipment and training

Trained non-medical research assistants observed all deliveries, documented time intervals and recorded perinatal information.[2] A newborn resuscitation monitor developed for research by Lærdal Global Health, Stavanger, Norway was mounted on the wall above all resuscitation tables (23). Each monitor was equipped with a self-inflating bag (230 mL standard or 320 mL Upright bag-mask; Laerdal Medical, Stavanger, Norway) and a dry-electrode ECG sensor to be easily placed around the newborns' trunk. Sensors for side-stream CO_2 (ISA; Masimo, Irvine, California, USA), pressure (Freescale semiconductor, Austin, Texas, USA) and flow (Acutronic Medical Systems, Hirzel, Switzerland) to record ECO_2 and ventilation parameters were placed between the mask and bag; the attachment device added a dead space of 1 mL. The monitors provided HR feedback. ECO_2 and ventilation parameters were not displayed.

The local newborn resuscitation procedure followed the Helping Babies Breathe (HBB) guidelines.[24] HBB was introduced at the study site in 2009. Midwives participated in full-day HBB courses one to two times yearly, and were educated to use clinical signs including chest rise and HR feedback to guide resuscitation. Low-dose, high-frequency skills training as described by Mduma *et al* was encouraged.[22]

Formation of the cohort

We included all live-born newborns with initial HR <120 bpm who had received BMV at birth, and had available HR, ventilation and observational data (figure 1). Our research group recently showed that normal HR is around 120 bpm in the first seconds of life.[25] Low initial HR is a known risk factor for unfavourable outcome.[21] Newborns who received BMV but had HR ≥120 bpm at onset of recording were excluded as these are likely different in pathophysiology and prognosis. Newborns randomised to receive BMV with positive end-expiratory pressure (PEEP) valve in a parallel intervention study were excluded due to potential impact of PEEP on ECO_2.

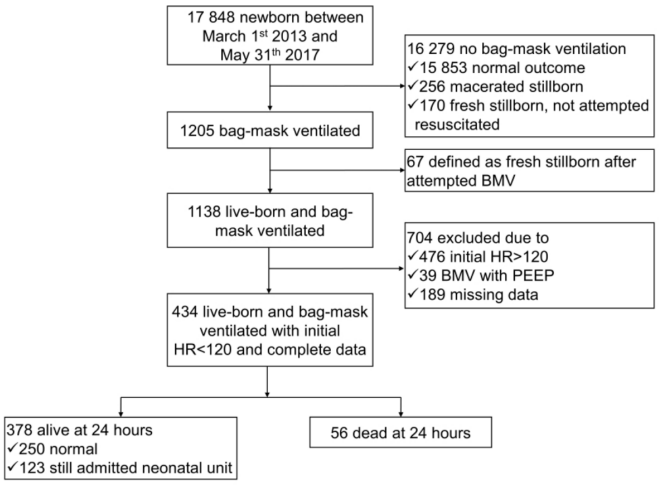

Figure 1 Overall newborn mortality at Haydom Hospital during the study period was 31 per thousand births. Among these, 28 were defined as still births, 13 fresh and 15 macerated. BMV, bag-mask ventilation; HR, heart rate; PEEP, positive end-expiratory pressure.

Outcome and covariates

The primary outcome was the maximum percentage of CO_2 in expired air per ventilation. Secondary outcome was time to ECO_2 >2% from the first BMV.

To characterise assisted ventilations ('ventilation factors'), we used repeated measures for expired V_{TE}, ventilation frequency, peak inflating pressure (PIP) and mask leak smoothed as means per five ventilations. The threshold to detect a ventilation was set to PIP >5 mbar.

As markers of clinical condition ('clinical factors'), we used the initial HR and 5 min Apgar score. Initial HR was defined as the mean of the first five HR values recorded for each newborn. The 5 min Apgar score was selected due to established association with asphyxia.[26] In a sensitivity analysis, we substituted Apgar score at 5 min with 1 min because 5 min score may be affected by treatment.

We also included BW and time as covariates. In the primary analyses, within the first 5 min of ventilation, time was recorded from the first detected ventilation. In the secondary analyses, per ventilation sequences, time was recorded from the first detected ventilation per sequence. We defined a ventilation sequence as continuous BMV with <5 s pause between two ventilations.

V_{TE} >30 mL/kg were considered unlikely to be correct measurements and were excluded. We also excluded individual observations with ventilation frequency >120/min as this is twice the upper limit of recommended ventilation frequency.

Table 1 Baseline characteristics and covariates

		All newborns (n=17 848)*	Included newborns (n=434)*	ICC†
Delivery mode	Caesarean section	3937 (23%)	215 (50%)	–
	Standard vaginal	13 331 (76%)	194 (45%)	–
	Breech	162 (0.9%)	24 (6%)	–
	Vacuum	39 (0.2%)	1 (0.2%)	–
	Other	14 (0.1%)	–	
Females		8167 (47%)	168 (39%)	–
Gestational age (weeks)		38 (37–40)	38 (37–40)	–
Gestational age <36 weeks		594 (3.3%)	29 (7%)	–
Birth weight (g)		3248 ± 535	3074 ± 593	–
Apgar 1 min		9 (9–9)	6 (5–7)	–
Apgar 5 min		10 (10–10)	10 (8–10)	–
First detected heart rate (bpm)		–	73 ± 21	–
Time from birth to first ventilation (s)		–	112 (78–158)	–
Time from first to last ventilation (s)		–	184 (80–394)	–
Time to ECO_2 >2% (s)		–	10.0 (3.1–34.9)‡	–
No of ventilation sequences		–	5 (2–8)	–
Duration of ventilation sequences (s)		–	29 ± 46§ / 18 (11 - 30)¶	0.15
Expired volume, V_{TE} (mL/kg)		–	7.9 ± 6.4§ / 6.7 (4.1–11.0)¶	0.52
Ventilation frequency (BMVs/min)		–	52 ± 24§ / 47 (38–65)¶	0.62
Mask leak (%)¶		–	44 ± 29§ / 40 (25–59)¶	0.40
Peak inflation pressure (mbar)¶		–	35 ± 11§ / 38 (25–60)¶	0.54
ECO_2 (% of expired air) ¶		–	2.9 ± 2.2§ / 2.9 (1.3–4.1)¶	0.50
Max ECO_2 in first 5 min of BMV		–	7.2 ± 2.8	–
Initial ECO_2		–	0.9 (0.3–3.3)	–

*Frequencies are given in the form of n (%), parameters with skewed distributions are given as median (25th quartile, 75th quartile), normally distributed parameters as mean±SD. For ventilation factors with repeated measurements per newborn, we report both means calculated by unconditional random intercept analysis and medians of medians.
†ICC—intercorrelation coefficient: proportion of total variance assigned to variance between patients.
‡Newborns who had ECO_2 >2% in the first ventilation (n=113) or did not reach threshold (n=23) not included.
§Mean in first 5 min of BMV, SD is given as √total variance where the total variance is the sum of variance between and within patients.
¶Median of medians in first 5 min of BMV.
BMV, bag-mask ventilation; ECO_2, expired carbon dioxide.

Statistical analyses

For cohort and data description, we report percentages, means with SD or medians with IQRs, as appropriate (table 1). For ventilation parameters, we include intercorrelation coefficients due to variation both within and between patients.

We fitted random intercept regression models to study changes in ECO_2 by variations in clinical and ventilation factors for newborns who received BMV. Associations with ECO_2 were not linear for all covariates, thus we performed log transformation for time, and included a quadratic term for V_{TE} and PIP guided by Akaike's information criteria and inspection of the residuals. To compare the effect of covariates measured on different scales, we report beta values per standardised units ((x–mean)/SD) in addition to the measured scale for each covariate and coefficients of determination (R^2 values). R^2 was calculated as the proportional reduction in prediction error variance comparing models with and without the covariate of interest.[27] For closely correlated parameters, we excluded both parameters simultaneously.

The primary analysis was performed in the first 5 min of BMV. Second, we compared the effects per ventilation sequence for newborns who had three or more sequences lasting for more than 10 s to evaluate build-up effects and the impact of pauses. We used Cox regression to study predictors for time from first BMV until ECO_2 reached 2% (≈2 kPa or 15 mm Hg at sea level). ECO_2 threshold was set at 2% as this corresponds well with changes on the colorimetric CO_2 detectors[11] and the ECO_2 level found to be most predictive for HR >60 bpm.[28] Kruskal-Wallis test was used to compare clinical and ventilation factors in three groups of infants differing by when ECO_2 >2% was achieved: never, during ventilation or spontaneously.

Data analysis was performed using MATLAB (MathWorks, Natick, Masschusetts, USA) and Stata SE V.14.2 (StataCorp, College Station, Texas, USA). We used a purposeful selection approach to build regression models; only significant covariates (p<0.05) were included in the final models.

Patient and public involvement

The study was performed in an area with high illiteracy rate, and patients and public were not directly involved in the planning of the study. Oral feedback from patients and personnel were taken into account for solving practical issues concerning data collection during the study period.

Ethical considerations

All women were informed, but consent was not considered necessary by the ethical committees.

RESULTS

During the study period, 17 484 babies were born in the hospital; 6.9% received BMV (figure 1). Among 434 included newborns, 400 had a minimum of one ventilation sequence that lasted for more than 10 s (baseline data in table 1).

Predictors of ECO_2 during first 5 min

Both clinical and ventilation factors were significantly associated with ECO_2, but ventilation explained substantially more of the variance than clinical factors (R^2 30.8% vs 10.9%); V_{TE} was the strongest single predictor (table 2). The association between V_{TE} and ECO_2 was positive and close to linear for V_{TE} <10 mL/kg, levelling off at 10–20 mL/kg and negative >20 mL/kg (figure 2A). Mask leak and V_{TE} were negatively correlated, and together explained 23% of the variance in ECO_2. Low ventilation frequency around 30/min was associated with

Table 2 Linear random intercept model for predictors of expired carbon dioxide (ECO_2) in the first 5 min of bag-mask ventilation

		Univariate model*			Multivariate model			
Covariates		**Coefficient (95% CI)**	**P value**	**R^2 (%)**	**Coefficient (95% CI)**	**P value**	**R^2 (%)**	**R^2 (%)**
ECO_2 (unconditional)		2.90 (2.75 to 3.05)						
Ventilation characteristics	*Expired tidal volume (V_{TE})* Per mL/kg increase Per standardised unit	0.37 (0.33 to 0.42) 2.37 (2.10 to 2.65)	<0.001	19.3	0.32 (0.27 to 0.37) 2.02 (1.71 to 2.33)	<0.001	23.1†	30.8
	$(V_{TE})^2$ Per 100 (mL/kg)^2 increase Per standardised unit	 −0.86 (−1.0 to 0.7) −1.29 (−1.53 to −1.06)	<0.001		 −0.78 (−0.9 to −0.6) −1.17 (−1.40 to −0.94)	<0.001		
	Mask leak Per 10% increase Per standardised unit	 −0.30 (−0.33 to −0.27 −0.85 (−0.87 to −0.84)	<0.001	16.1	 −0.056 (−0.098 to −0.014) −0.16 (−0.29 to 0.42)	0.009		
	Ventilation frequency Per 10 bpm increase Per standardised unit	 −0.17 (−0.23 to −0.11) −0.40 (−0.55 to −0.26)	<0.001	7.5	 −0.16 (−0.19 to −0.12) −0.37 (−0.45 to −0.28)	<0.001	16.1‡	
	Peak inflation pressure (PIP) Per 10 mbar increase Per standardised unit	0.41 (0.16 to 0.67) 0.46 (0.18 to 075)	0.001	1.1	0.24 (0.064 to 0.29) 0.27 (0.071 to 0.46)	0.008	−0.3	
	$(PIP)^2$ Per 10 mbar^2 increase Per standardised unit	 −0.60 (−0.87 to −0.33) −0.61 (−0.88 to −0.33)	<0.001		 −0.47 (−0.64 to −0.29) −0.47 (−0.65 to −0.29)	<0.001		
Clinical factors	*Birth weight* Per kg increase Per standardised unit	0.78 (0.51 to 1.04) 0.46 (0.30 to 0.62)	<0.001	4.4	0.81 (0.58 to 1.03) 0.48 (0.34 to 0.61)	<0.001	6.8	10.9
	Initial heart rate Per 10 bpm increase Per standardised unit	0.081 (0.012 to 0.15) 0.17 (0.024 to 0.31)	0.022	0.6	0.089 (0.034 to 0.14) 0.19 (0.070 to 0.30)	0.002	1.3	
	5 min Apgar score Per one unit increase Per standardised unit	0.054 (−0.021 to 0.13) 0.11 (−0.043 to 0.26)	0.16	0.3	0.14 (0.068 to 0.22) 0.29 (0.14 to 0.44)	<0.001	2.9	
Log2 of time in seconds Per unit increase Per standardised unit		0.33 (0.28 to 0.38) 0.64 (0.54 to 0.73)	<0.001	2.0	0.15 (0.12 to 0.19) 0.29 (0.23 to 0.36)	<0.001	0.9	0.9
Random-effects parameters					Var (_cons) 1.53 (1.31 to 1.77)§ Var (Residual) 1.53 (1.34 to 1.74) ICC 0.50			

*Intercorrelation coefficient (ICC) varied between 0.47 and 0.56 for all covariates.
†V_{TE} and mask leak were correlated (Spearman's rho −0.65). Excluding V_{TE} from the model, beta value for mask leak decreased from −0.056 (−0.098 to −0.014) to −0.28 (−0.31 to −0.24). R^2 for V_{TE} alone excluding mask leak from the model was 21.9%. R^2 for mask leak excluding V_{TE} was 17.1%.
‡Interaction term for V_{TE} and frequency was significant with beta=−0.015 (−0.020 to −0.0091), p<0.001, the model is displayed without this term for interpretability. V_{TE} and frequency were still significant in the model including the interaction term.
§R^2 for the total model: 36.6%.

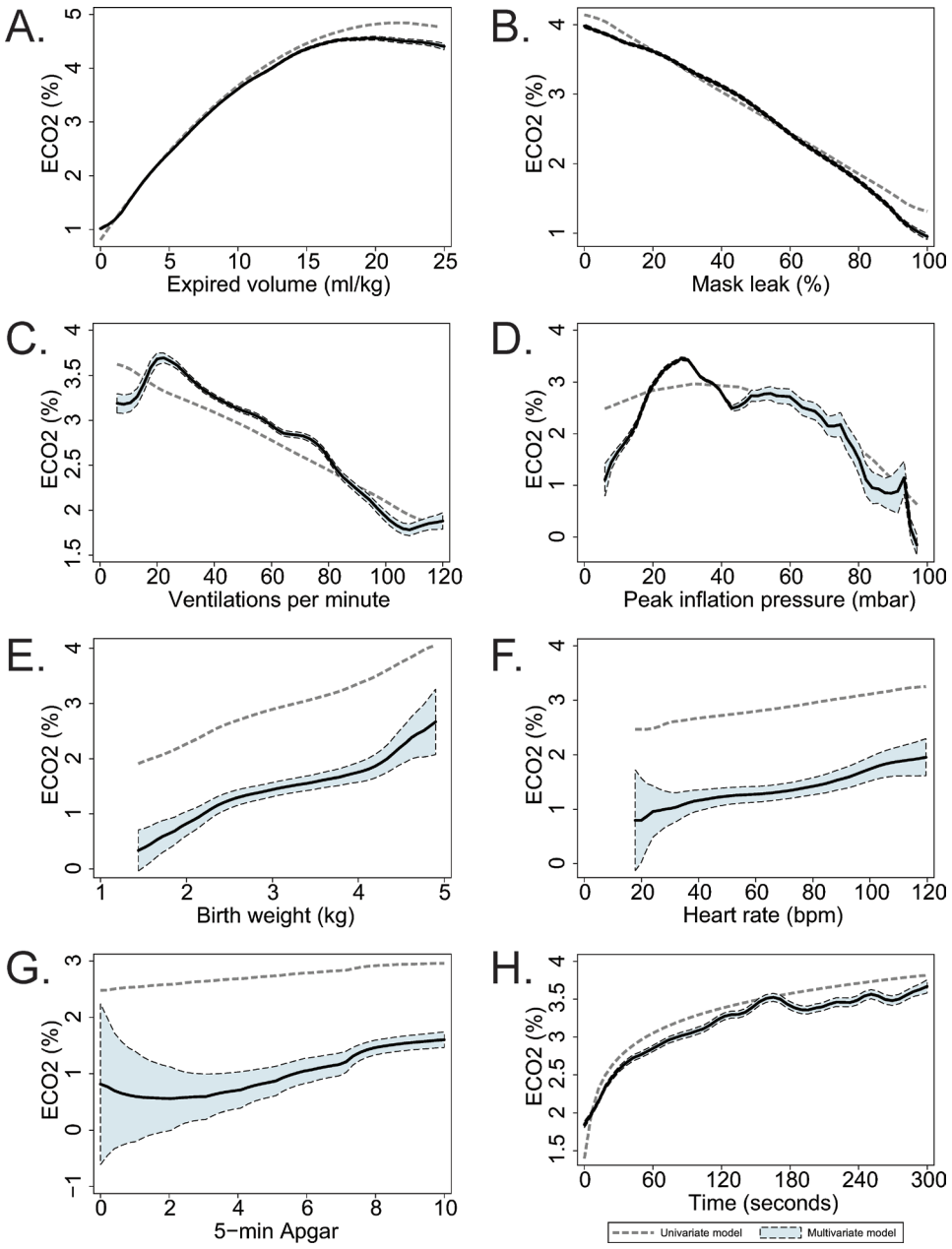

Figure 2 ECO_2 by covariates. Smoothed local polynomial plots for predicted values of expired carbon dioxide (ECO_2) per covariate in univariate (dashed, grey line) and multivariate model (solid, black line). The graphs display ECO_2 versus (A) expired tidal volume (V_{TE}, mL/kg), (B) mask leak (percentage leak), (C) ventilation frequency (ventilations per minute), (D) peak inflation pressure (PIP, mbar), (E) birth weight (kg), (F) initial heart rate (beats per minute), (G) 5 min Apgar score and (H) time (seconds). Table 2 display effect measures (beta coefficients), p values and explained variance (R^2) for the regression models.

the highest ECO_2 (figure 2C). PIP <15 or >60 mbar were associated with low ECO_2 (figure 2D). ECO_2 increased rapidly in the first minute of BMV, V_{TE} increased and mask leak decreased simultaneously (figure 3). BW and initial HR were positively associated with ECO_2 in univariate and multivariate models, 5 min Apgar score only in the multivariate model (table 2, figure 2E–G).

Predictors for ECO_2 by ventilation sequence

Analysing the first three ventilation sequences with duration >10 s (online supplementary appendix table S1 A–C) gave similar results as the primary analysis, with V_{TE} as the strongest predictor. ECO_2 increased significantly with time in the first two ventilation sequences, but not in the third (online supplementary appendix figure S1).

Predictors for time to reach threshold

The Cox model found higher V_{TE} up to 14 mL/kg to be associated with shorter time to reach ECO_2 >2% (table 3). Higher 5 min Apgar score, initial HR, BW and PIP were also associated with shorter time to reach ECO_2 >2%.

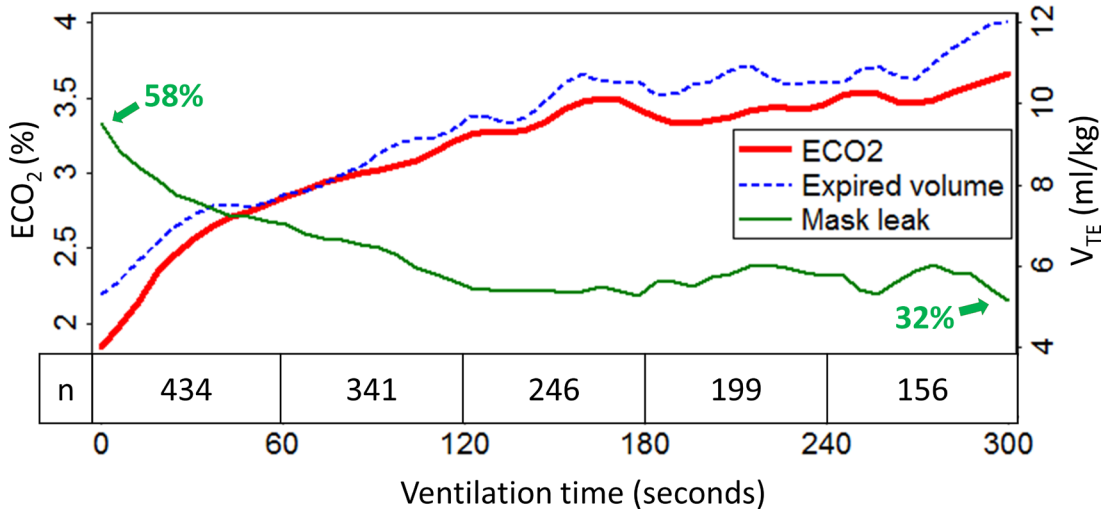

Figure 3 Change in expired carbon dioxide (ECO_2), expired volume and mask leak by time the figure illustrates trends for changes in ECO_2 (red, solid line), V_{TE} (blue, dashed line) and mask leak (green, dashed line) by time. The graphs are smoothed local polynomial plots. The integrated table displays the number of newborns (n) who received ventilations in each minute since start of ventilations.

Interactions and stratified analyses

In the primary analysis, we found a significant interaction for V_{TE} and frequency. We found no relevant differences stratified by BW ≥2500 g versus <2500 g, initial HR ≥60 versus <60 bpm, vaginal delivery versus Caesarean section or for newborns ventilated within versus after 60 s from birth (data not shown). Substituting V_{TE} and ventilation frequency with respiratory minute volume, we found a non-linear positive association between ECO_2 and minute volumes (online supplementary appendix

Table 3 Cox regression for time to ECO_2 >2% (n=321)*

	Univariate model		Multivariate model†‡	
	Hazard Ratio (95% CI)	**P value**	**Hazard Ratio (95% CI)**	**P value**
Expired tidal volume (V_{TE})				
Per 1 mL/kg increase	1.18 (1.11 to 1.24)	<0.001	1.22 (1.15 to 1.29)	<0.001
Per standardised unit	1.33 (1.18 to 1.50)		3.75 (2.56 to 5.48)	
$(V_{TE})^2$§				
Per unit increase	0.99 (0.99 to 0.99)	<0.001	0.99 (0.99 to 1.0)	<0.001
Per standardised unit	1.16 (1.02 to 1.31)		0.34 (0.22 to 0.52)	
Peak inflation pressure				
Per 10 mbar increase	1.24 (1.15 to 1.35)	<0.001	1.32 (1.21 to 1.43)	<0.001
Per standardised unit	1.28 (1.17 to 1.40)		1.36 (1.24 to 1.50)	
Birth weight				
Per kg increase	1.32 (1.09 to 1.59)	0.004	1.42 (1.17 to 1.72)	0.001
Per standardised unit	1.18 (1.05 to 1.32)		1.23 (1.10 to 1.38)	
Initial heart rate				
Per 10 bpm increase	1.08 (1.02 to 1.14)	0.004	1.08 (1.02 to 1.14)	0.006
Per standardised unit	1.18 (1.05 to 1.32)		1.17 (1.05 to 1.30)	
Apgar at 5 min				
Per unit increase	1.10 (1.04 to 1.16)	0.001	1.17 (1.11 to 1.24)	<0.001
Per standardised unit	1.23 (1.09 to 1.38)		1.42 (1.25 to 1.61)	

*Among n=434 included newborns, 113 were censured before analysis due to ECO_2 >2% in the first ventilation, 321 were included in the Cox regression, 23 never reached ECO_2 >2%.
†Hazard Ratios were not proportional for V_{TE} alone, including a quadratic term gave acceptable fit in the multivariate model.
‡Mask leak was significant (p<0.001) in univariate model, but not in multivariate model (p=0.26) including V_{TE} due to correlation with volume. Taking V_{TE} out of the model, mask leak was significant with p<0.001, Hazard Ratio 0.89 (0.86 to 0.93) per 10% increase.
§Ventilation frequency was not significant with p=0.63 in the univariate and p=0.18 in the multivariate Cox model and was omitted from the final models.

Table 4 Comparison of groups by time to threshold ECO_2 >2%

	Category of time to ECO_2 >2%			Kruskal-Wallis test *
	A: ECO_2 >2% in first ventilation	B: ECO_2 >2% during ventilation	C: ECO_2 >2% never achieved	P value
n	113	298	23	–
Expired tidal volume, V_{TE} (mL/kg)	7.3 (4.3–11.3)	4.2 (1.9–7.4)	2.9 (1.0–5.0)	<0.001*
Mask leak (%)	41 (25–60)	55 (36–43)	78 (44–93)	<0.001†
Ventilation frequency (per minute)	45 (33–61)	48 (38–69)	64 (46–73)	0.009‡
Peak inflation pressure (mbar)	35 (31–39)	36 (31–39)	33 (25–38)	0.16
Minute volume (mL/kg per minute)	325 (171–553)	201 (82–421)	154 (51–406)	<0.001§
Birth weight (kg)	3.2 (2.9–3.5)	3.1 (2.7–3.4)	2.9 (2.6–3.2)	<0.001¶
First detected heart rate (bpm)	70 (59–94)	67 (56–85)	77 (59–83)	0.15
Apgar 1 min	7 (6–7)	6 (5–7)	5 (5–7)	<0.001**
Apgar 5 min	10 (8–10)	10 (8–10)	9 (7–10)	0.19
Time from first to last ventilation (s)	126 (63–258)	217 (95–458)	66 (22–130)	<0.001††

All values are medians (IQR). For ventilation factors, we used median per group of medians per newborn within the first 30 s of ventilation. Kruskal-Wallis test was performed to rank medians. The column shows p values for comparison of all three groups, p values for significant differences between groups compared in pairs are given as footnotes.
*V_{TE}: A≠B (p<0.001), A≠C (p<0.001), B≠C (p=0.07).
†Mask leak: A≠B (p<0.001), A≠C (p<0.001), B≠C (p=0.04).
‡Ventilation frequency: A≠B (p=0.02), A≠C (p=0.008), B≠C (p=0.07).
§Minute volume: A≠C (p=0.009), B≠C (p<0.001).
¶Birth weight: A≠B (p<0.001), A≠C (p=0.010).
**Apgar at 1 min: A≠B (p<0.001), A≠C (p=0.017).
††Time from first to last ventilation: A≠B (p=0.023), A≠C (p<0.001), B≠C (p>0.001).

table S2). Substituting 5 min Apgar scores with 1 min scores did not affect the main conclusions.

Other analyses

Table 4 groups included newborns in three: (A) ECO_2 >2% at onset of BMV, (B) reached ECO_2 >2% during BMV and (C) never reached ECO_2 >2%. Group A had significantly higher BW, Apgar scores and V_{TE} and lower mask leak and ventilation rate in the first 30 s of ventilations compared with groups B and C. We found no significant differences in the clinical parameters between group B and C. However, infants in group C were ventilated with higher frequencies, had more mask leak and had lower V_{TE} in the first 30 s of BMV.

DISCUSSION

In this large observational study, ventilation factors were stronger predictors for ECO_2 than clinical markers of asphyxia during initial resuscitation of term and near-term newborns. V_{TE} >10 mL/kg, low mask leak and a ventilation frequency around 30/min were associated with the highest ECO_2.

Simultaneous collection of ventilation parameters and observation of clinical factors in a large sample of newborns allowed for analyses considering both clinical differences and quality of delivered ventilations. The main findings were replicated in alternative statistical models. The major burden of death and morbidity due to neonatal asphyxia occurs in low-income countries.[29] Even if the midwives' ventilation skills may not be representative for all places, the physiological factors affecting ventilation parameters and ECO_2 must be expected to be similar for newborns all over the world. High baseline morbidity is more likely to strengthen than hide associations with clinical factors. We do not find obvious reasons limiting the validity of the main findings in a global context.

As in any observational study, our results may be affected by unmeasured or residual confounding. It is likely that subtle interactions occurred between clinical and ventilation factors due to variations in lung compliance and muscle tone. The first detected HR defined as 'initial HR' was collected with variable delay after birth depending on when the HR sensor was applied. Apgar scores are subjective measures, and interobserver variability large.[26 30] Measures of umbilical artery pH, base excess or lactate are more objective to assess degree of asphyxia, but were not available at the study site.

We propose that ventilation characteristics associated with higher and a faster increase in ECO_2 during initial BMV are favourable to quickly establish effective gas exchange. The observed close association between V_{TE} and ECO_2 supports studies pointing to ECO_2 as an indicator of lung aeration immediately after birth.[5 6] An increase in ECO_2 with increasing minute volumes, different from later in life, further strengthens the theory that ECO_2 is diffusion limited during initial ventilation of fluid-filled newborn lungs.[31] As we observed an increase in ECO_2 for V_{TE} 10–20 mL/kg, and shorter time to reach ECO_2 >2% up to 14 mL/kg, we speculate that higher V_{TE} than

the commonly recommended 4–8 mL/kg may promote a faster lung aeration. Two other studies from our group found a positive relationship between delivered V_{TE} and HR, with the most rapid increase in HR during BMV at volumes around 10 mL/kg.[4 17] Larger V_{TE} may be needed during BMV than in intubated patients to compensate for upper airway distension.[32]

We found that ventilation frequency was negatively associated with ECO_2, suggesting less effective lung aeration at high frequencies. Highest observed ECO_2 at ventilation frequencies around 30/min points to inflation rates in the lower range of recommended values as potentially more favourable, as suggested by the European resuscitation guidelines.[19 20]

Several authors have proposed that capnography may serve as feedback to identify airway obstruction during newborn resuscitation.[10 13 33] Our findings partly support this. Low ECO_2 associated with high PIP may be due to obstructed airway or low lung compliance. Mask leak and PIP effects were substantially reduced in our models when adjusting for V_{TE}, likely because they mainly worked through V_{TE} modifications. We do not see obvious ways to discriminate between airway obstruction and liquid-filled lungs as explanation for low ECO_2 before higher levels have been observed.[34] Stronger positive linear association between PIP and ECO_2 in the first ventilation sequence compared with later sequences supports a need for higher opening pressure during initial inflations.[35]

We observed a fast ECO_2 increase in the first minute of ventilation. This is line with previous studies indicating a gradual lung aeration.[7–9] Efforts to improve ventilation, like clearing the airway and reducing mask leak, probably contributed to ECO_2 increase over time. Reduced ECO_2 after ventilation pauses suggests re-entry of lung liquid and supports a recommendation for continuous, effective ventilation to non-breathing newborns.[18]

The process of lung aeration has been found to be slower during BMV than in spontaneously breathing newborns.[8 9 36 37] Newborns with gasping or spontaneous breaths before initiation of BMV have already started the lung-aeration process. This may explain higher initial ECO_2 in newborns with higher Apgar scores. Moreover, larger newborns may have higher respiratory drive and better reserves to handle complications during labour despite low initial HR and low Apgar scores, explaining the positive association between ECO_2 and BW.

Significant but weak negative associations found between Apgar scores, initial HR and ECO_2 underline that severely compromised circulation may cause persistently low ECO_2.[16 28] Waste of valuable time trying to improve correctly performed ventilations based on ECO_2 feedback may be a pitfall. To measure V_{TE} in combination with ECO_2 may reduce this risk.[36 38]

Our findings indicate that somewhat higher V_{TE} than currently recommended and a low ventilation frequency may be favourable during bag-mask ventilation of term and near-term infants at birth. However, this is an observational study and long-term outcomes have not been studied. Near-term newborns have more mature and less vulnerable lungs than premature infants, and asphyxia is often the cause when they do not start breathing spontaneously.[39] Still, the optimal V_{TE} needed to balance fast establishment of adequate ventilation to avoid brain damage against the risk for lung injury remains unclear.[6 40] Our findings alone are not sufficiently strong to change guideline recommendations, but may provide background information for future randomised studies of V_{TE}, ventilation frequency and the use of ECO_2 feedback during newborn resuscitation.

CONCLUSIONS

Ventilation factors are important predictors for ECO_2 during the first minutes of bag-mask ventilation in newborn resuscitation. V_{TE} of 10–14 mL/kg and ventilation frequency around 30/min are associated with the highest ECO_2 and the shortest time to reach ECO_2 >2%. Low ECO_2 may be useful to detect inefficient ventilation. Low BW, HR and Apgar scores are also associated with low ECO_2, and this must be accounted for in the interpretation.

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Contributors KH, KS, HLE and JE had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. HK, KS, JE and CK designed the study protocol. JE, JL, SJ, HK, JE and MT practically implemented, supervised and carried out the study and the data collection on site. JE gave technical support, extracted and processed the data. RH, KS, RH and JE performed the statistical analyses. KH drafted the initial manuscript. All authors have reviewed and approved the final manuscript as submitted.

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Competing interests JE is an employee of Laerdal Medical. JL is married to an employee at Laerdal Global Health.

Patient consent for publication Not required.

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Correction: *Predictors for expired CO2 in neonatal bag-mask ventilation at birth: observational study*

Holte K, Ersdal HL, Eilevstjønn J, *et al*. Predictors for expired CO2 in neonatal bag-mask ventilation at birth: observational study. *BMJ Paediatrics Open* 2019;3:e000544. doi: 10.1136/bmjpo-2019-000544

This article has been corrected since it was published. The surname of the co-author Samwel Jatosh is corrected. There are no changes in the scientific content of the article.

BMJ Paediatrics Open 2019;**3**:e000544corr1. doi:10.1136/bmjpo-2019-000544corr1

Appendix

Predictors for expired CO_2 in neonatal bag-mask ventilation: observational study

Table S1

Linear random intercept models for predictors of expired carbon dioxide (ECO_2) per ventilation sequence in newborns who received more than three ventilation sequences lasting for more than 10 seconds (n=227)

A: First ventilation sequence

		Univariate model [a]			Multivariate model			
Predictors		**Coef (95%CI)**	**P-value**	**R^2 (%)**	**Coef (95%CI)**	**P-value**	**R^2 (%)**	**R^2 (%)**
ECO2 (unconditional)		2.15 (1.92, 2.38)						
Markers for BMV quality	**V_{TE}** Per ml/kg increase Per standardized unit	0.41 (0.31, 0.51) 2.65 (2.01, 3.3)	<0.001	27.1	0.40 (0.30, 0.50) 2.60 (1.97, 3.24)	<0.001	23.6 [b]	28.1
	$(V_{TE})^2$ Per unit increase Per standardized unit	-0.0096 (-0.013, -0.006) -1.48 (-2.06, -0.90)	<0.001		-0.0098 (-0.013, -0.0062) -1.51 (-2.06, -0.95)	<0.001		
	Mask leak Per 10 units [%] increase Per standardized unit	-0.28 (-0.35, -0.21) -0.81 (-1.02, -0.60)	<0.001	16.8	-0.024 (-0.086, 0.037) -0.070 (-0.25, 0.11)	0.4 [b]		
	Ventilation frequency Per 10 bpm increase Per standardized unit	-0.11 (-0.19, -0.03) -0.23 (-0.39, -0.065)	0.006	4.2	-0.12 (-0.19, -0.051) -0.25 (-0.40, -0.11)	0.001 [c]	5.2	
	PIP Per 10 mbar increase Per standardized unit	0.062 (-0.34, 0.46) 0.065 (-0.36, 0.49)	0.8	0.3	-0.36 (-0.64, -0.071) -0.38 (-068, -0.075)	0.01	-0.4	
	$(PIP)^2$ Per unit increase Per standardized unit	-0.019 (-0.055, 0.017) -0.18 (-0.52, 0.16)	0.3		-0.065 (-0.016, -0.071) 0.062 (-0.16, 0.28)	0.6		
Clinical factors	**Birth weight** Per kg increase Per standardized unit	0.83 (0.44, 1.23) 0.48 (0.25, 0.70)	<0.001	5.0	0.81 (0.50, 1.12) 0.46 (0.29, 0.64)	<0.001	6.9	11.6
	Initial HR Per 10 bpm increase Per standardized unit	0.20 (0.09, 0.31) 0.42 (0.19, 0.65)	<0.001	3.8	0.15 (0.056, 0.23) 0.30 (0.12, 049)	0.001	3.2	
	5 min Apgar Per 1 unit increase Per standardized unit	0.012 (-0.084, 0.11) 0.028 (-0.19, 0.25)	0.802	0.0	0.10 (0.015, 0.19) 0.24 (0.034, 0.44)	0.02	1.9	
Time Per doubling Per standardized unit		0.23 (0.14, 0.32) 0.36 (0.22, 0.50)	<0.001	3.8	0.13 (0.046, 0.20) 0.19 (0.072, 0.32)	0.002	3.1	
Random effect parameters					**Var(_cons) 1.88 (1.50, 2.35) [d]** **Var (Residual) 1.00 (0.80, 1.25)** **ICC =0.65**			

[a] ICC in the univariate models varied from 0.64 to 0.68.

[b] Mask leak and volume (V_{TE}) were correlated. Excluding V_{TE} from the model, mask leak came out significant with P<0.001, beta -0.28 (-0.35, -0.21) and R^2 18.0%.

[c] An interaction term for frequency and V_{TE} was significant with P<0.001, beta –0.027(-0.040, -0.013). V_{TE} was still a strong positive predictor for ECO2, whereas frequency and mask leak lost significance.

[d] Explained variance in the total model: 37.3%.

B: Second ventilation sequence

		Univariate model [a]			Multivariate model			
Predictors		**Coef (95%CI)**	**P-value**	**R^2 (%)**	**Coef (95%CI)**	**P-value**	**R^2 (%)**	**R^2 (%)**
ECO2 (unconditional)		2.90 (2.65, 3.17)						
Markers for BMV quality	**V_{TE}** Per ml/kg increase Per standardized unit	0.34 (0.27, 0.40) 2.19 (1.75, 2.63)	<0.001	30.1	0.29 (0.21, 0.36) 1.88 (1.35, 2.39)	<0.001	32.0	36.3
	$(V_{TE})^2$ Per unit increase Per standardized unit	-0.0084 (-0.011, 0.006) -1,29 (-1.66, -0.91)	<0.001		-0.080 (-0.011, -0.054) -1.22 (-1.62, -0.82)	<0.001		
	Mask leak Per 10 units increase Per standardized unit	-0.26 (-0.32, -0.21) -0.76 (-0.90, -0.61)	<0.001	19.0	-0.080 (-0.14, -0.020) -0.23 (-0.40, -0.058)	0.009 [b]		
	Ventilation frequency Per 10 bpm increase Per standardized unit	-0.10 (-0.23, 0.024) -0.22 (-0.49, 0.050)	0.1	4.5	-0.18 (-0.31, -0.050) -0.38 (-0.65, -0.11)	0.006 [c]	7.6	
	PIP Per 10 mbar increase Per standardized unit	0.72 (0.33, 1.12) 0.76 (0.35, 1.18)	<0.001	1.6	0.27 (-0.024, 0.57) 0.29 (-0.027, 0.58)	0.07	1.4	
	$(PIP)^2$ Per unit increase Per standardized unit^2	-0.78 (-0.12, -0.031) -0.74 (-1.19, -0.29)	0.001		-0.048 (-0.080, -0.015) -0.46 (-0.77, -0.14)	0.004		
Clinical factors	**Birth weight** Per kg increase Per standardized unit	0.99 (0.59, 1.40) 0.57 (0.34, 0.80)	<0.001	5.9	0.78 (0.46, 1.09) 0.44 (0.26, 0.63)	<0.001	6.0	10.8
	Initial HR Per 10 bpm increase Per standardized unit	0.13 (-0.003, 0.26) 0.27 (-0.0007, 0.54)	0.05	1.4	0.12 (0.028, 0.21) 0.25 (0.058, 0.44)	0.01	1.9	
	5 min Apgar Per 1 unit increase Per standardized unit	0.054 (-0.071, 0.18) 0.12 (-0.16, 0.41)	0.4	0.3	0.14 (0.040, 0.25) 0.33 (0.092, 0.56)	0.007	3.4	
Time Per doubling Per standardized unit		0.23 (0.091, 0.36) 0.35 (0.14, 0.56)	0.001	2.6	0.12 (-0.008, 0.26) 0.19 (-0.012, 0.40)	0.07	0.3	
Random effects parameters					**Var(_cons) 2.03 (1.57, 2.62) [d]** **Var (Residual) 1.04 (0.64, 1.70)** **ICC =0.66**			

[a] ICC in the univariate models varied from 0.71 to 0.75.

[b] Excluding volume (V_{TE}) from the model, mask leak got increasing significance: Beta = -0.25 (-0.32, -0.19), P<0.001, R^2 21.0%. Excluding mask leak from the model, R^2 for V_{TE} alone was 31.5%.

[c] Interaction term for frequency and V_{TE} was not significant, beta -0.017(-0.035, 0.014), P<0.07.

[d] Explained variance R^2 in the total model: 43.4%.

C: Third ventilation sequence

		Univariate model [a]			Multivariate model			
Predictors		**Coef (95%CI)**	**P-value**	**R^2 (%)**	**Coef (95%CI)**	**P-value**	**R^2 (%)**	**R^2 (%)**
ECO2 (unconditional)		3.14 (2.89, 3.39)						
Markers for BMV quality	**V_{TE}** Per unit increase Per standardized unit	0.31 (0.22, 0.40) 2.02 (1.42, 2.61)	<0.001	21.4	0.28 (0.19, 0.37) 1.82 (1.25, 2.39)	<0.001	16.2 [b]	25.6
	$(V_{TE})^2$ Per unit increase Per standardized unit	-0.0072 (-0.010, 0.0044) -1.10 (-1.51, -0.68)	<0.001		-0.0067 (-0.009, -0.004) -1.03 (-1.43, -0.63)	<0.001		
	Mask leak Per 10 units increase Per standardized unit	-0.24 (-0.31, -0.18) -0.70 (-0.88, -0.51)	<0.001	10.6	-0.064 (-0.12, -0.005) -0.18 (-0.35, -0.014)	0.03 [b]		
	Ventilation frequency Per 10 bpm increase Per standardized unit	-0.17 (-0.36, 0.015) -0.36 (-0.76, 0.031)	0.07	9.0	-0.16 (-0.30, -0.013) -0.33 (-0.63, -0.026)	0.03 [c]	9.9	
	PIP Per 10 mbar increase Per standardized unit	-0.20 (-1.10, 0.69) -0.21 (-1.16, 0.73)	0.7	-0.9	-0.37 (-0.96, 0.22) -0.39 (-1.01, 0.24)	0.2	-2.6	
	$(PIP)^2$ Per unit increase Per standardized unit	0.21 (-0.060, 0.10) 0.20 (-0.57, 0.98)	0.6		-0.011 (-0.039, 0.062) 0.11 (-0.37, 0.59)	0.7		
Clinical factors	**Birth weight** Per kg increase Per standardized unit	0.82 (0.38, 1.25) 0.47 (0.22, 0.72)	<0.001	4.7	0.66 (0.31, 1.01) 0.38 (0.18, 0.58)	<0.001	4.5	9.0
	Initial HR Per 10 bpm increase Per standardized unit	0.20 (0.088, 0.32) 0.42 (0.18, 0.66)	0.001	3.8	0.14 (0.040, 0.24) 0.29 (0.082, 0.49)	0.006	2.7	
	5 min Apgar Per 1 unit increase Per standardized unit	0.051 (-0.062, 0.16) 0.12 (-0.14, 0.38)	0.4	0.3	0.11 (0.002, 0.21) 0.25 (0.047, 0.49)	0.05	2.1	
Time Per doubling Per standardized unit		0.11 (0.029, 0.19) 0.18 (0.047, 0.31)	0.008	1.7	0.028 (-0.047, 0.10) 0.045 (-0.075, 0.17)	0.5	0.7	
Random effects parameters					**Var(_cons) 2.32 (1.87, 2.87) [d]** **Var (Residual) 0.78 (0.63, 0.96)** **ICC =0.75**			

[a] ICC in the univariate models varied from 0.71 to 0.75.

[b] Excluding volume (V_{TE}) from the model, mask leak got increasing significance: Beta = -0.25 (-0.32, -0.19), P<0.001, R^2 8.2%. Excluding mask leak from the model, R^2 for V_{TE} alone was 16.7%.

[c] Interaction term for frequency and V_{TE} was not significant, beta -0.0067(-0.014, 0.00081), P=0.08.

[d] Explained variance R^2 in the total model: 33.5%.

Table S2

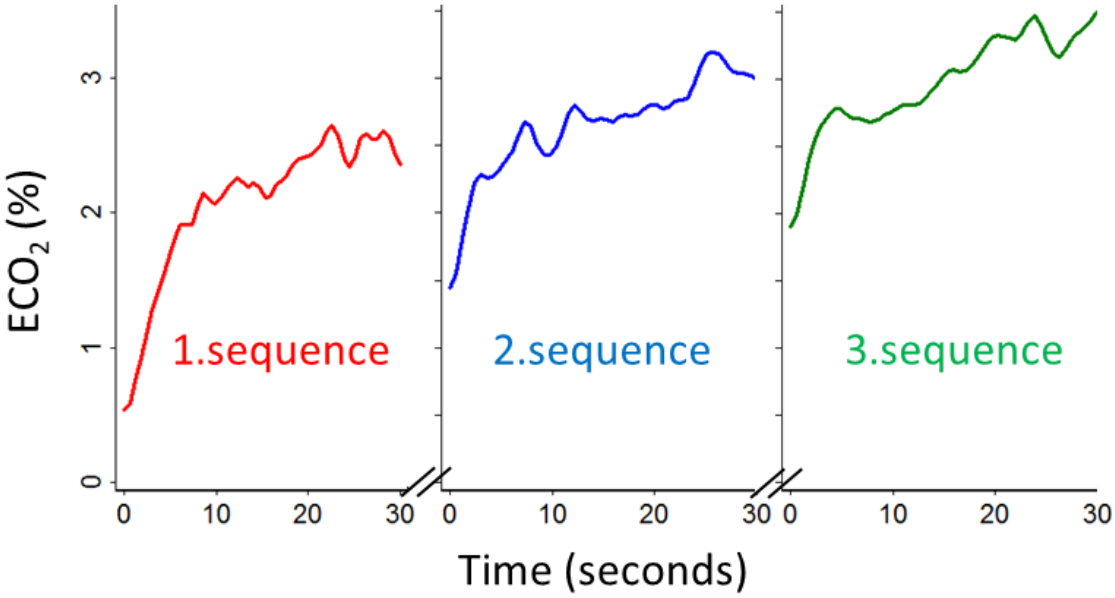
Linear random intercept models for predictors of expired carbon dioxide (ECO_2) in the first 5 minutes substituting volume and frequency with minute volume

		Univariate model			Multivariate model		
Covariates		**Coef (95%CI)**	**P-value**	**R^2 (%)**	**Coef (95%CI)**	**P-value**	**R^2 (%)**
ECO2 (unconditional)		2.90 (2.75, 3.05)					
Ventilation factors	**Minute volume** Per 100 ml/kg min^{-1} increase	0.56 (0.48, 0.64)	<0.001	7.5	0.36 (0.27, 0.44)	<0.001	12.4
	(Minute volume)^2 Per (10 ml/kg min^{-1})^2 increase	-0.03 (-0.3, -0.2)	<0.001		-0.18 (-0.02, -0.01)	<0.001	
	Mask leak Per 10% increase	-0.30 (-0.33, -0.27)	<0.001	16.1	-0.13 (-0.16, -0.099)	<0.001	
	PIP Per 10 mbar increase	0.41 (0.16, 0.67)	0.001	1.1	0.016 (0.048, 0.36)	0.1	
	PIP^2 Per 10 $mbar^2$ increase	-0.60 (-0.87, -0.33)	<0.001		-0.34 (-0.53, -0.15)	<0.001	
Clinical factors	**Birth weight** Per kg increase	0.78 (0.51, 1.04)	<0.001	4.4	0.80 (0.54, 1.05)	<0.001	
	Initial HR Per 10 bpm increase	0.081 (0.012, 0.15)	0.022	0.6	0.086 (0.019, 0.15)	0.01	
	5 min Apgar Per 1 unit increase	0.054 (-0.021, 0.13)	0.16	0.3	0.14 (0.045, 0.20)	0.002	
Log2 of time in seconds Per unit increase		0.33 (0.28, 0.38)	<0.001	2.0	0.22 (0.17, 0.26)	<0.001	2.1
Random effects parameters					**Var (_cons) 2.10 (1.83, 2.42)** [a] **Var (Residual) 1.75 (1.53, 2.01)** **ICC 0.55**		

[a] R^2 for the total model 20.0%

Figure S1

Median expired carbon dioxide (ECO_2) in first three ventilation sequences



The figure displays ECO_2 as smoothed median observed values (per second) for all included newborns in the first 30 seconds per ventilation sequence.

Expired Carbon Dioxide during Newborn Resuscitation as Predictor of Outcome

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Abbreviations:

AUC – Area Under the Receiver Operating Curves
BMV - Bag-mask ventilation
BW – Birth weight
bpm - beats per minute
ECO_2 – Expired carbon dioxide
GA - Gestational age
HR - Heart rate
Mbar – millibar
ROC – Receiver Operating Characteristics
V_{TE} - Expired tidal volume

Abstract

Aim
To explore and compare expired CO_2 (ECO_2) and heart rate (HR), during newborn resuscitation with bag-mask ventilation, as predictors of 24-hour outcome.

Methods
Observational study from March 2013 to June 2017 in a rural Tanzanian hospital. Side-stream measures of ECO_2, ventilation parameters, HR, clinical information, and 24-hour outcome were recorded in live born bag-mask ventilated newborns with initial HR <120 bpm. We analysed the data using logistic regression models and compared areas under the receiver operating curves (AUC) for ECO_2 and HR within three selected time intervals after onset of ventilation (0-30 seconds, 30.1-60 seconds and 60.1-300 seconds).

Results
Among 434 included newborns (median birth weight 3100 grams), 378 were alive at 24 hours, 56 had died. Both ECO_2 and HR were independently significant predictors of 24-hour outcome, with no differences in AUCs. In the first 60 seconds of ventilation, ECO_2 added extra predictive information compared to HR alone. After 60 seconds, ECO_2 lost significance when adjusted for HR. In 70% of newborns with initial ECO_2 <2% and HR <100 bpm, ECO_2 reached ≥2% before HR ≥100 bpm. Survival at 24 hours was reduced by 17% per minute before ECO_2 reached ≥2% and 44% per minute before HR reached ≥100 bpm.

Conclusions
Higher levels and a faster rise in ECO_2 and HR during newborn resuscitation were independently associated with improved survival compared to persisting low values. ECO_2 increased before HR and may serve as an earlier predictor of survival.

Introduction

Adequate ventilation is the key to successful resuscitation in newborns who fail to initiate spontaneous breathing at birth. An increase in heart rate (HR) is currently considered the most important indicator for a positive response to ventilations. HR response is, however, an indirect measure dependent on sufficient oxygen delivery to the heart, and gives no direct feedback on lung aeration and airway patency. The 2015 international consensus for newborn resuscitation mentioned expired carbon dioxide (ECO_2) as a potentially more sensitive marker of effective ventilation, and stated that more research is needed to determine whether ECO_2 monitoring is useful to assess response to resuscitation.[1]

At birth a successful transition from placental to pulmonary gas exchange is critical for survival.[2] ECO_2 may serve as a marker for lung aeration and pulmonary circulation.[3,4] ECO_2 also depends on ventilation technique, and is used by resuscitation teams to aid recognizing airway obstruction, mask leak and correct endotracheal tube placement.[5-9] In cardiopulmonary resuscitation after the newborn period, persisting low ECO_2 is associated with decreased survival.[10-12] Results from clinical studies in mainly preterm newborns suggest that ECO_2 increases before HR during positive pressure ventilation in the delivery room.[3,13,14] Linde et al found that median ECO_2 in the first minute of bag-mask ventilation (BMV) at birth was lower in newborns who died before 24 hours of age compared to survivors.[15]

The aims of this study were to explore ECO_2 as a predictor of 24-hour outcome (survival vs death) during newborn resuscitation with BMV, and to compare the predictive information of ECO_2 and HR.

Methods

Study design and setting

This descriptive observational study is part of Safer Births, a research project on labour surveillance and newborn resuscitation in low-income settings.[16] We used data collected between March 1st 2013 and June 1st 2017 at Haydom Lutheran Hospital, a rural Tanzanian referral hospital with 3600 - 4600 deliveries annually.[17]

The local procedure for newborn resuscitation followed Helping Babies Breathe (HBB) emphasizing stimulation and early initiation of BMV, excluding chest compressions, intubation and medication.[18] Newborn resuscitation was mainly the responsibility of midwives. Cord clamping was done prior to BMV. After resuscitation the midwives decided, based on the clinical condition, whether to keep the newborn with the mother or transfer to a neonatal ward offering basic care including antibiotics, phototherapy, and intravenous fluids, but no respiratory support except supplemental oxygen by nasal cannula.[19]

Data collection

A newborn resuscitation monitor (Laerdal Global Health, Stavanger, Norway) was mounted on the wall above all resuscitation tables.[20] Each monitor was equipped with a self-inflating bag (230 ml standard or 320 ml Upright bag-mask, Laerdal Medical, Stavanger, Norway) and a dry-electrode ECG sensor to be easily placed around the newborns' trunk. Sensors for side-stream measures of ECO_2 (ISA^{TM}, Masimo, Irvine, California, USA), pressure (Freescale semiconductor, Austin, Texas, USA) and flow (Acutronic Medical Systems, Hirzel, Switzerland) were placed between the mask and bag. The monitors started data recording automatically when used, and provided HR feedback during resuscitation. ECO_2 and ventilation parameters were not displayed. Pulse oximetry was not available. Trained non-

medical research assistants observed all deliveries documenting perinatal information, time intervals, and 24-hour outcomes.

We included all live-born newborns with initial HR <120 beats per minute (bpm) and available data for both ECO_2 and HR (n=434) (Fig.1). Stillborns, defined locally as Apgar score 0 at both 1 and 5 minutes or gestational age (GA) <28 weeks, were excluded. We also excluded newborns ventilated with positive end-expiratory pressure as part of a concurrent randomized trial as this could potentially affect ECO_2 and HR.[21] Data from the same cohort of newborns were used in a recently published article on predictors of ECO_2 during newborn resuscitation.[22]

Regression models

To study the associations between 24-hour outcome (survival vs. death) and the covariates ECO_2, HR, and expired tidal volume (V_{TE}), we performed logistic regression analyses. In the main models, ECO_2 and HR were studied independently (unadjusted). In secondary models, ECO_2 and HR were mutually adjusted, and then adjusted for V_{TE}. ECO_2 was recorded as maximum percent of expired air per ventilation. All observations of ECO_2, regardless of leak and V_{TE}, were included. HR was smoothed per approximately 12 beats per algorithm in the monitor.

Exploring graphs made to display ECO_2 and HR by time in the first 300 seconds of ventilation (Supplemental Fig.1), we selected three time intervals (0-30 seconds, 30.1-60 seconds, and 60.1-300 seconds) for further analyses. Due to large variations in especially ECO_2 (between ventilations), we decided to study both the single maximum value and the median of all recorded ECO_2- and HR-values per newborn within each time interval. We also

studied time from first delivered ventilation until ECO_2 reached ≥2% and HR ≥100 bpm in secondary models. To determine time to ECO_2 ≥2%, we used ECO_2 smoothed as means per 5 ventilations. For V_{TE}, the median value per newborn within each time interval was used.

Non-linear associations between ECO_2, HR and 24-hour outcome were assessed by categorical logistic regression models. Due to potential differences in pathophysiology between preterm or small for GA newborns compared to term newborns, stratified analyses for birth weight (BW) ≥2500g vs. <2500g were performed.

Further analyses

Receiver operating characteristics (ROC) curves graphically display sensitivity as a function of 1-specificity for all possible cut off values of the test parameters in diagnostic tests with binary outcomes.[23] The area under the ROC curves (AUC) gives a measure for the total predictive information of the test parameters. To estimate the classification accuracy of ECO_2 and HR as predictors of 24-hour survival, we made ROC curves and calculated AUC for predicted sensitivity and specificity of the covariates, based on the results of the main (unadjusted) logistic regression models. We used Pearson Chi Square tests to compare the AUCs for maximum ECO_2 and HR within each time interval. We further plotted sensitivity and specificity for selected cut-off values for maximum ECO_2 (≥1, 2 and 4%) and HR (≥60, 100 and 120 bpm) in the ROCs. We also calculated AUCs for the secondary (adjusted) models to estimate the total predictive information of all included covariates.

The ECO_2 and HR thresholds of 2% and 100 bpm, respectively, were studied in more detail. Among newborns with initial ECO_2 <2% and HR <100 bpm, we compared time intervals from first ventilation until ECO_2 ≥2% and HR ≥100 bpm. We performed post hoc analyses

using Wilcoxon rank sum tests to assess for differences in initial HR, Apgar scores, BW and ventilation factors (V_{TE} and mask leak) depending on which threshold was reached first.

Data processing and analyses were performed using Matlab (MathWorks, Natick, MA, USA) and Stata SE version 16 (StataCorp, Texas, USA). Significance level was set to $p<0.05$.

Ethical considerations

Ethical approval was granted by the National Institute for Medical Research in Tanzania (Ref. NIMR/HQ/R.8a/Vol.IX/1434) and the Regional Committee for Medical and Health Research Ethics for Western Norway (Ref.2013/110). All women were informed. Consent was not considered necessary by the ethical committees.

Results

Among 434 live born newborns who received BMV, with first registered HR <120 bpm and complete data, 378 survived to 24 hours, 56 (12.9%) died (Fig. 1). Survivors had significantly higher BW and Apgar scores than deaths and were ventilated for a shorter time (Table 1).

ECO_2 and HR as predictors for survival

Both ECO_2 and HR increased during BMV, with higher levels in survivors compared to deaths (Fig. 2 and Supplemental Fig.1). Odds ratios for 24-hour survival increased significantly with higher levels of ECO_2 and HR (Table 2). In the first minute of BMV, maximum ECO_2 and HR were both significant predictors for survival in adjusted models, indicating independent effects. After the first minute, ECO_2 lost significance when adjusted for HR. Adjusting for V_{TE} non-significantly increased the odds ratios for survival by ECO_2.

When studied independently, we found no significant differences in AUCs for maximum ECO_2 compared to HR (Fig. 3). Though not significant, maximum ECO_2 gave slightly larger AUCs within the first minute of BMV. After the first minute, AUC for HR was largest. AUCs were similar using medians compared to maximums per time interval for both ECO_2 and HR (Table 2).

Sensitivity and specificity for selected cut-offs of maximum ECO_2 and HR within time intervals are plotted in ROC curves in Fig. 3. Reaching ECO_2 ≥2% within the first 30 seconds of ventilation had a higher sensitivity to predict 24-hour survival than HR ≥100 bpm (80% versus 68%). After one minute of ventilation, ECO_2 ≥2% had slightly lower sensitivity than HR ≥100 bpm (94% versus 99%).

In categorical models, we found no non-linear associations to support decreased survival with high levels of ECO_2 or HR (Supplemental table 1). The predictive information of ECO_2 and HR on survival were weaker in newborns with BW < compared to ≥ 2500 g (Supplemental table 2).

Time to thresholds

The time to reach ECO_2 ≥2% and HR ≥100 bpm, in analyses including only newborns with initial measures below the thresholds, was significantly lower in survivors compared to deaths (Table 3). Odds ratio (95% CI) for survival per minute increase in time to reach ECO_2 ≥2% was 0.83 (0.71, 0.97) compared to 0.56 (0.40, 0.78) per minute before HR reached ≥100 bpm. Thus, 24-hour survival was reduced by approximately 17% per minute before ECO_2 reached ≥2% and 44% per minute before HR reached ≥100 bpm.

A majority of newborns (159/226, 70%) who reached both thresholds, crossed ECO_2 ≥2% before HR ≥100 bpm. This was evenly distributed between the groups (131/188 (70%) survivors compared to 28/38 (74%) deaths, p=0.62). Newborns who reached HR ≥100 bpm first had lower median V_{TE} (3.9 (1.0-8.2) vs. 5.6 (2.9-10.1) ml/kg, p=0.007) and a higher leak (64 (35-83) vs. 45 (22-71) %, p=0.005) in ventilations prior to reaching the threshold compared to newborns who reached ECO_2 ≥2% first. Time to reach HR ≥100 bpm was independent of which threshold was reached first (31 (21-61) seconds), but time to reach ECO_2 ≥2% was significantly longer in newborns who crossed HR ≥100 bpm first (12 (5-29) vs. 67 (39-120) seconds, p<0.001). We found no differences in initial HR, Apgar score or BW depending on which threshold was reached first.

Discussion

Association between HR and outcome in newborn resuscitation is well established, and a cornerstone for recommendations to ventilate if HR is <100 bpm.[15,19,24-27] New in this study is that ECO_2 measured during BMV at birth can also serve as a predictor of survival. We found ECO_2 to be an earlier marker of 24-hour survival than HR. After the first minute of ventilation, ECO_2 added no extra predictive information compared to HR.

The main finding of higher levels of ECO_2 as a predictor of survival is similar to results from cardiopulmonary resuscitation after the newborn period.[11,12] However, newborns in need of positive pressure ventilation at birth, are rarely in cardiac arrest. In a recent study of apnoeic newborns, the first recorded HR was distributed in two peaks around 60 and 165 bpm.[25] Thus, an increase in ECO_2 during newborn resuscitation, is usually not a sign of return of spontaneous circulation, but may be seen as a marker for established pulmonary gas exchange.

Measured values of ECO_2 during mask ventilation, will generally be lower than in intubated newborns due to dilution in a larger dead space, and occurrence of leak and obstructed airway. No exclusions can be done when interpreting measured values during ongoing resuscitation, and the ventilation technique is potentially relevant for survival. We therefore decided to retain all observations. This may explain the large variation in ECO_2 between ventilations, and a lower median ECO_2 in our results than in studies where exclusions of ventilations with low V_{TE} or high leak were done. [3,4,28,29]

As ECO_2 during BMV is highly dependent on ventilation parameters, especially V_{TE},[6,22] inadequate ventilation cannot be ruled out as a contributing explanation for low ECO_2 in non-surviving newborns. However, we propose that the reason for lower ECO_2 in deaths compared to survivors was mainly a more severely compromised clinical condition at birth. Prior studies from the same study site have estimated that around 60% of 24-hour newborn deaths were due to intrapartum related events (birth asphyxia and meconium aspiration syndrome).[30,31] Despite a presumptive larger impact of ventilation technique on medians compared to maximums, we found maximum ECO_2 within the selected time interval to predict survival as good as medians. If newborn death was often associated with inadequate V_{TE}, we would expect adjustment for V_{TE} to reduce OR and AUC in models with ECO_2. However, adjusting for V_{TE} in our analyses non-significantly increased the predictive information, especially of median ECO_2. This suggests against inadequate ventilation as a major cause of death, but rather points to low ECO_2 with simultaneously high V_{TE} as a sign of a more compromised clinical condition.

Three prior smaller studies of mainly preterm newborns in high resourced settings have shown a significant increase in ECO_2 preceding HR response during mask ventilation in newborn resuscitation. [3,13,14] Different from these studies, our study was performed in a larger sample of mainly term newborns in rural Tanzania. In concordance with the previous studies, we found that among newborns who reached both predefined thresholds, 70% crossed ECO_2 ≥2% before HR ≥100 bpm. This underpins ECO_2 as an earlier marker for treatment response than HR. We also found a group who reached HR ≥100 bpm before ECO_2 ≥2%. A lower V_{TE} and higher leak in this group, suggest suboptimal ventilations as explanation for the slower rise in ECO_2. Because there were no differences in time to HR ≥100 bpm for those who reached HR ≥100 bpm first compared to those who reached ECO_2 ≥2% first, we speculate that these newborns were likely less severely asphyxiated, despite the low initial HR, and may have had some spontaneous breathing and intact reflexes. The delay from birth until BMV was started may have contributed to increased differences in ECO_2 and HR between mild and severely compromised newborns.

Slight differences in predictive value of ECO_2 and HR in newborns with BW <2500 g compared to ≥2500 g, may be due to a higher risk of death by other causes than birth asphyxia in newborns who were preterm or small for GA.[30]

To our knowledge, this is the first study to compare ECO_2 and HR measured in the delivery room as predictors of 24-hour survival in newborns who receive BMV at birth. The unique research infrastructure comprising both continuous prospective observer-monitored and automatically recorded biomedical signal-data of a large cohort of newborns is a major strength. Data were collected in a rural low-income setting with high morbidity, long transport and potential delay for complicated deliveries to be assisted, representative for where most

newborn deaths occur.[32] The local resuscitation procedure followed HBB.[18] Advanced neonatal care and respiratory support after initial resuscitation, including continuous positive airway pressure therapy, were not available. This likely affected 24-hour survival, and thus the results may not be generalizable to all settings. Variation in clinical condition between included newborns and experience between providers will naturally occur in all studies performed in real life situations. This make the results more representative for newborns in need for respiratory support at birth, but is also a limitation as some newborns may have had some spontaneous breathing and some may have received suboptimal care.

Large breath-to-breath variation makes ECO_2 measured during BMV potentially difficult to interpret in clinical situations. Finding maximum ECO_2 to give as good predictive information as median values, we suggest using the highest observed values within time intervals if ECO_2 should be utilised as prognostic information during newborn resuscitation.

Plotting selected cut-off values for maximum ECO_2 and HR in ROC curves, we found that choosing lower cut-offs would give a more sensitive, but less specific predictive test for survival, than higher cut-off values. ECO_2 $\geq$2% is approximately equivalent to a partial pressure of 15 mmHg or 2 kPa, which is the limit for colour change in colorimetric ECO_2-sensors.[14] This may be a reasonable choice to indicate successful lung aeration and favourable prognosis during BMV of asphyxiated newborns.

The dual nature of ECO_2 as both a marker for severity of the clinical condition and of ventilation quality,[22] makes ECO_2-monitoring potentially useful during resuscitation for prognostic information and to help improve ventilations. However, the duality also implies pitfalls for the interpretation. Providers must be aware that low ECO_2 may have several

causes, including high leak, airway obstruction, unaerated lungs or compromised pulmonary circulation.[3,4,6,22] The results of this study indicate that persisting low ECO_2 may, like persisting low HR, be used to support decisions to discontinue resuscitation. ECO_2 ≥2% or HR ≥100 should encourage further efforts, even in seemingly non-viable newborns. However, we found low specificities of ECO_2 or HR used as tests to predict survival, and strongly advice against depending on this alone. The information must be combined with thorough considerations taking the quality of given ventilations, clinical responses, duration of resuscitation and availability of advanced neonatal care into account.

Importantly, HR was the only displayed parameter in this study, and thus the midwives could not adjust ventilation technique as a response to changes in ECO_2. A feedback on ECO_2 may help providers improve ventilation technique, which may further improve prognosis and the predictive information by ECO_2. We do not think that ECO_2 should replace HR for prognostic information during newborn resuscitation. However, being an earlier and more direct marker of effective ventilation, ECO_2 may add useful information. In low resourced settings, colorimetric end-tidal CO_2-detectors may be more easily available than HR monitoring.[14] Further clinical trials with ECO_2-feedback to the provider, are needed to address the practical value before ECO_2-monitoring during BMV in newborn resuscitation could be recommended for routine clinical use..

Conclusions

ECO_2 during BMV in the delivery room can predict 24-hour survival. ECO_2 increased before HR in most cases. ECO_2 may serve as an early marker for severity of clinical condition, ventilation quality, treatment response and prognosis during newborn resuscitation.

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Conflicts of interest
Joar Eilevstjønn is an employee at Laerdal Medical. The other authors have no potential conflicts of interest to disclose.

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Figures

Expired Carbon Dioxide during Newborn Resuscitation as Predictor of Outcome

Fig.1 – Flow chart

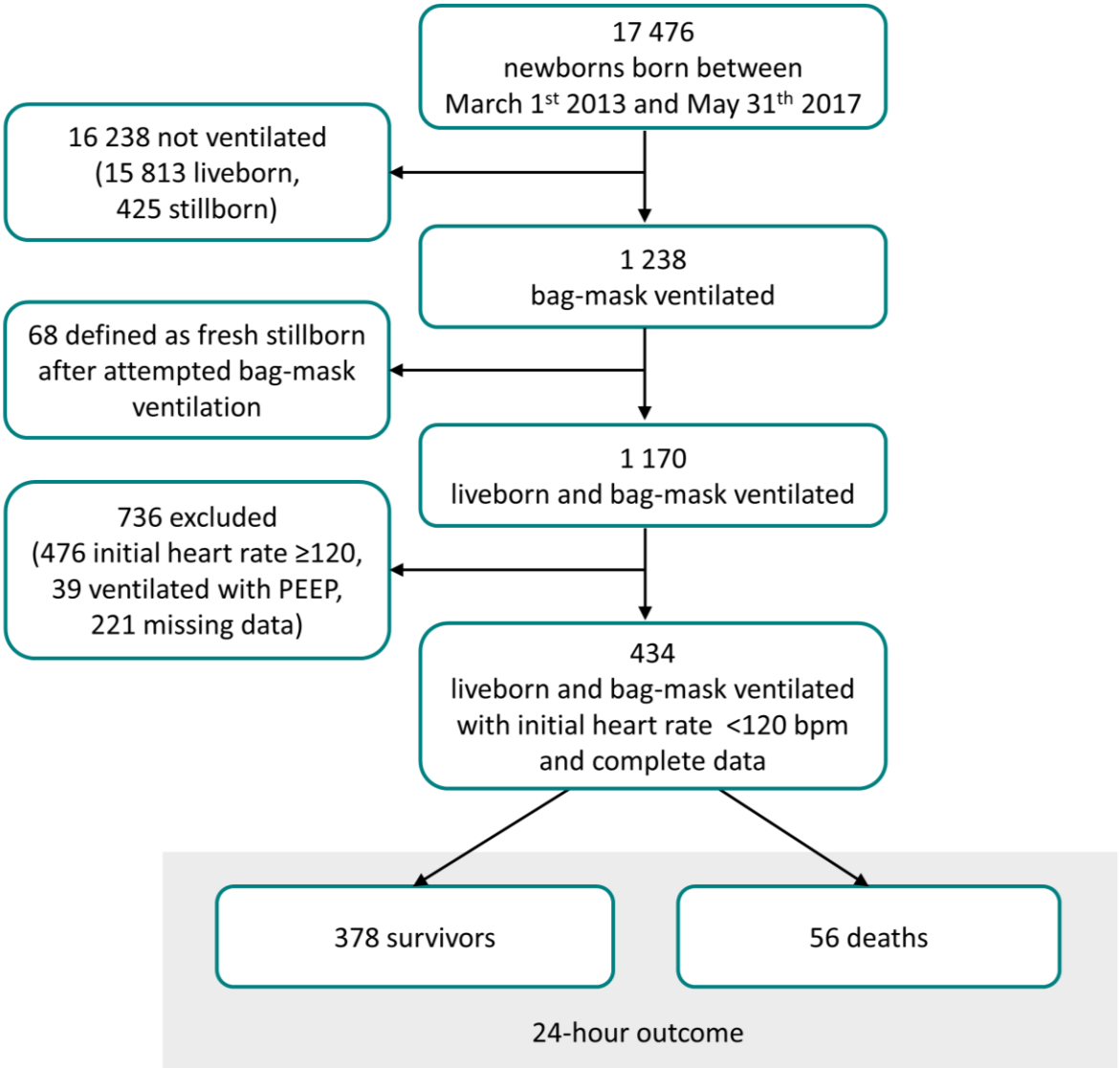
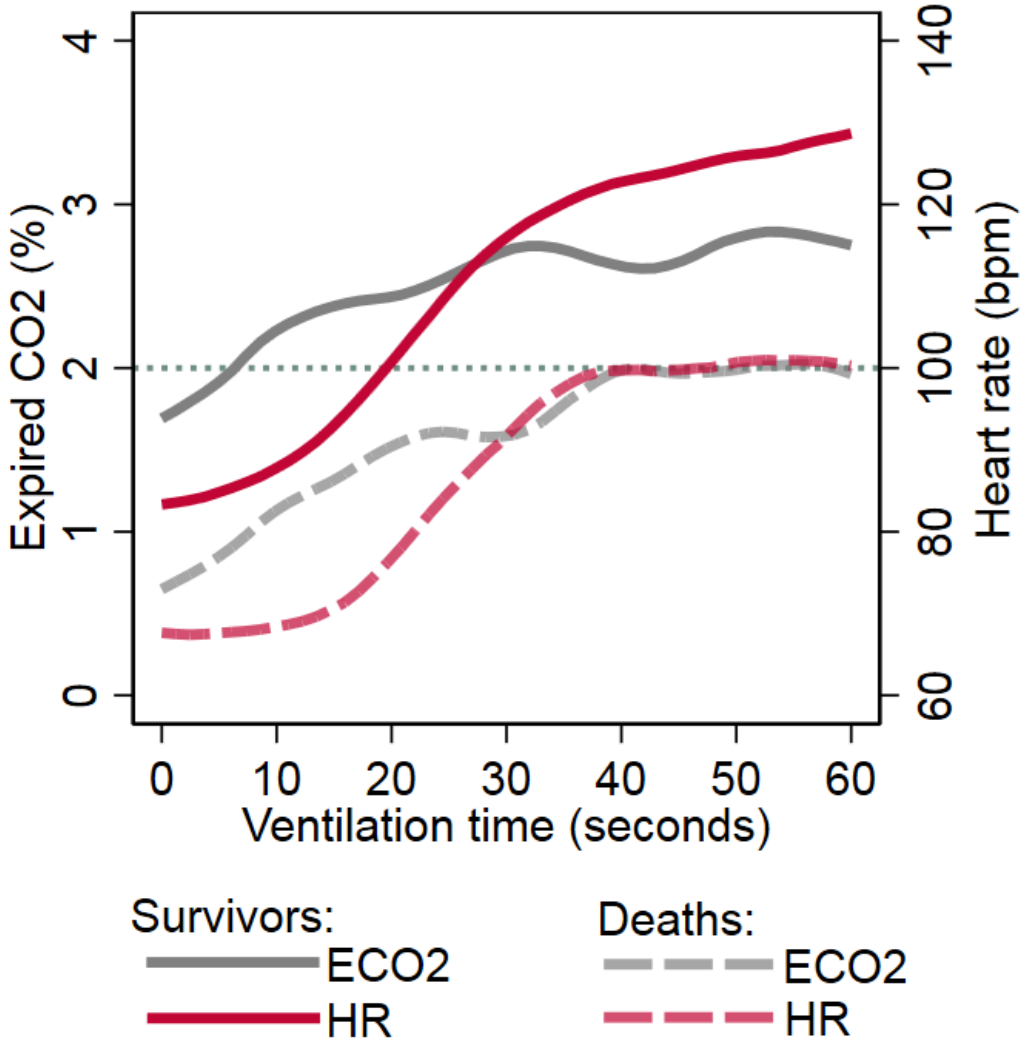


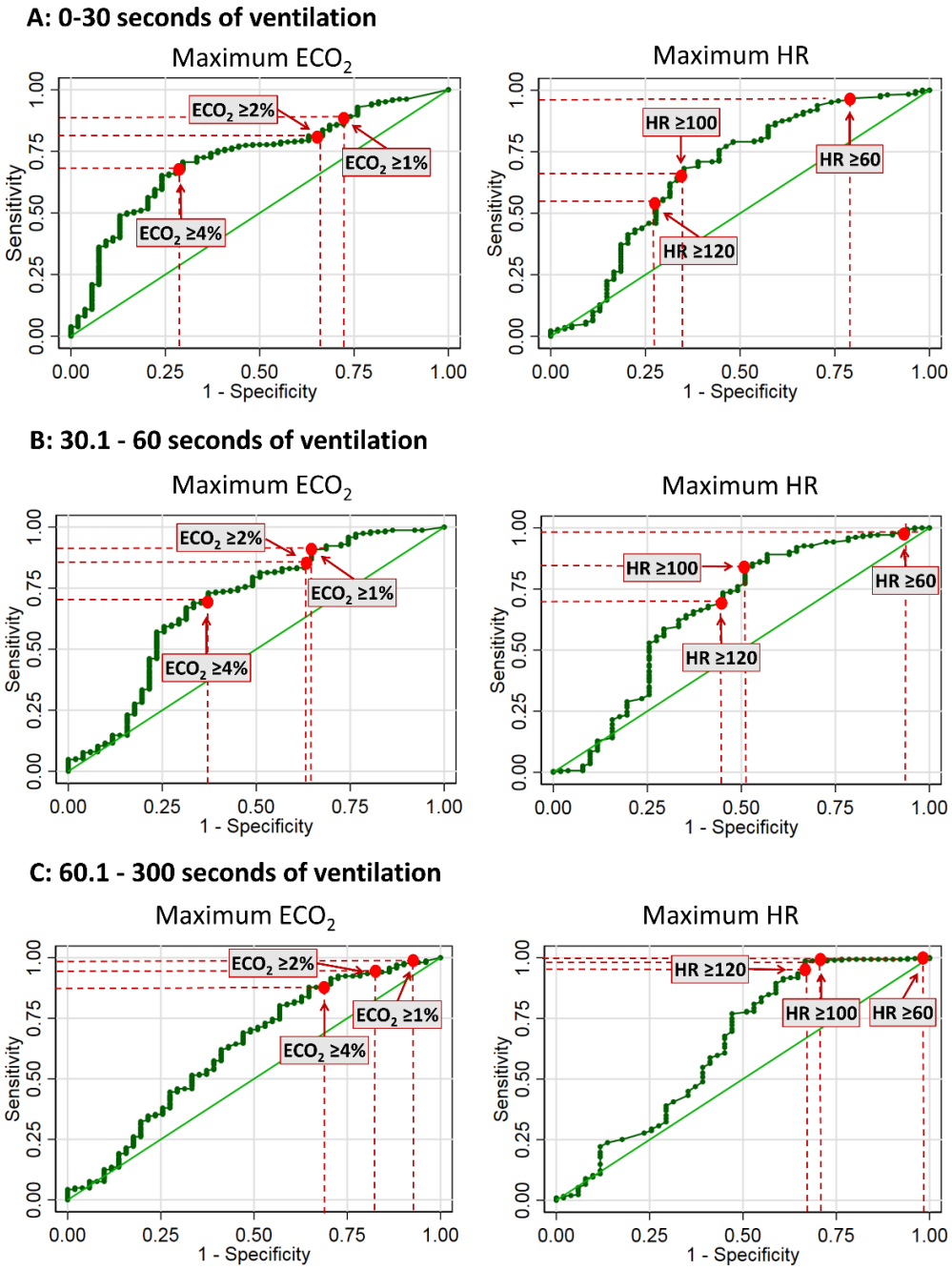
Fig. 2 - ECO_2 and HR by time in survivors compared to deaths in the first 60 seconds of bag-mask ventilation



ECO_2 increased before HR in a majority of newborns, survivors had higher levels of ECO_2 and HR than deaths. The graphs are smoothed local polynomial plots of all measured values for ECO_2 and HR in all included newborns.

ECO_2=expired CO_2, HR=heart rate

Fig. 3 –Receiver operating characteristics curves for maximum ECO_2 and HR within time intervals as predictors for 24-hours survival



The graphs display ROC curves for maximum ECO_2 and HR within the three selected time intervals after start of ventilation (A: 0-30 seconds, B: 30.1-60 seconds, and C: 60.1-300 seconds) as predictors for 24-hours survival. Sensitivity and specificity for selected cut-off values of maximum ECO_2 (left panel; ECO_2 ≥1, 2, and 4%) and HR (right panel; HR ≥60, 100, and 120 bpm) are plotted.

Comparison of AUC for ECO_2 and HR (Pearsons Chi^2-test):
A: AUC for maximum ECO_2 = 0.72 (0.65, 0.79), AUC for maximum HR = 0.67 (0.58, 0.76), p=0.21
B: AUC for maximum ECO_2 = 0.69 (0.60, 0.78, AUC for maximum HR = 0.66 (0.56, 0.76), p=0.56
C: AUC for maximum ECO_2 = 0.62 (0.53, 0.71), AUC for maximum HR = 0.64 (0.54, 0.64), p=0.74

ECO_2 = expired CO_2 in percent of expired air, HR = heart rate in beats per minute, ROC= Receiver Operating Characteristics, AUC=area under the ROC curves

Tables

Expired Carbon Dioxide during Newborn Resuscitation as Predictor of Outcome

Table 1. Comparison of demographic and delivery room data between survivors and deaths at 24 hours

	Survivors		Deaths		
	n		**n**		**p-value**
Birth weight (grams)	378	3100 (2780, 3450)	56	3000 (2500, 3200)	**0.01**
Birth weight <2500g, n=60 (14%)	46	12%	14	25%	**0.01**
Gestational age (weeks)	356	38 (37, 40)	47	38 (36, 39)	0.46
Gestational age < 37 weeks, n=97 (22%)	85	21%	12	22%	0.86
Female, n=169 (39%)	146	41%	23	39%	0.73
Caesarean Section, n=215 (50%)	182	59%	33	48%	0.13
Time from birth to cord clamping	376	22 (12, 57)	55	18 (13, 49)	0.37
Apgar at 1 minute	378	7 (5, 7)	56	4 (3, 5)	**<0.001**
Apgar at 5 minutes	378	10 (8, 10)	56	7 (4, 10)	**<0.001**
Time from birth to first BMV (seconds)	375	125 (84, 160)	54	111 (77, 158)	0.49
Time from first to last BMV (seconds)	378	162 (71, 317)	56	624 (227, 1358)	**<0.001**

Data are displayed as medians (IQR) or numbers (%). P-values were calculated by Wilcoxons rank sum test or Pearsons Chi^2 test as appropriate.
HR=heart rate, BMV=bag-mask ventilation.

Table 2. Logistic regression models and area under receiver operating characteristics curves (AUC) for 24-hours survival by maximum (upper panel) and median (lower panel) expired CO_2 and heart rate per newborn for the three selected time intervals

			Main models		Secondary models			
			Unadjusted		Mutual adjustment ECO_2 / HR		Adjusted for ECO_2 / HR and V_{TE} [a]	
Maximum ECO_2 and HR		**n**	**OR (95% CI)**	**AUC [b]**	**OR (95% CI)**	**AUC [c]**	**OR (95% CI)**	**AUC [c]**
0 – 30 seconds of BMV		422						
ECO_2	Per 1 pp increase		1.31 (1.17, 1.46) [d]	0.72	1.24 (1.10, 1.39) [d]	0.73	1.27 (1.12, 1.44) [d]	0.74
HR	Per 10 bpm increase		1.18 (1.09, 1.28) [d]	0.67	1.10 (1.00, 1.20) [f]		1.10 (1.00, 1.20) [f]	
30.1 – 60 seconds of BMV		363						
ECO_2	Per 1 pp increase		1.26 (1.13, 1.40) [d]	0.69	1.17 (1.04, 1.32) [e]	0.69	1.18 (1.02, 1.22) [f]	0.69
HR	Per 10 bpm increase		1.18 (1.09, 1.28) [d]	0.66	1.11 (1.02, 1.22) [f]		1.12 (1.02, 1.22) [e]	
60.1 - 300 seconds of BMV		354						
ECO_2	Per 1 pp increase		1.18 (1.07, 1.32) [e]	0.62	1.06 (0.95, 1.19)	0.64	1.07 (0.95, 1.20)	0.68
HR	Per 10 bpm increase		1.28 (1.17, 1.40) [d]	0.64	1.25 (1.13, 1.38) [d]		1.27 (1.14, 1.41) [d]	
Median ECO_2 and HR								
0 – 30 seconds of BMV		422						

ECO_2	Per 1 pp increase		1.43 (1.17, 1.74) [d]	0.65	1.31 (1.08, 1.60) [e]	0.71	1.46 (1.16, 1.83) [d]	0.74
HR	Per 10 bpm increase		1.28 (1.13, 1.45) [d]	0.68	1.23 (1.09, 1.40) [d]		1.22 (1.07, 1.38) [e]	
30.1 – 60 seconds of BMV		363						
ECO_2	Per 1 pp increase		1.27 (1.08, 1.49) [e]	0.65	1.15 (0.97, 1.37)	0.67	1.21 (0.99, 1.47)	0.67
HR	Per 10 bpm increase		1.16 (1.07, 1.25) [d]	0.65	1.11 (1.02, 1.22) [f]		1.12 (1.02, 1.22) [f]	
60.1 - 300 seconds of BMV		354						
ECO_2	Per 1 pp increase		1.20 (1.02, 1.40) [f]	0.61	1.00 (0.84, 1.21)	0.63	1.07 (0.88, 1.29)	0.67
HR	Per 10 bpm increase		1.20 (1.11, 1.29) [d]	0.63	1.19 (1.09, 1.31) [d]		1.20 (1.09, 1.32) [d]	

The main models present unadjusted OR of 24-hour survival for both ECO_2 and HR independently. The secondary models present OR of 24-hour survival for 1) ECO_2 and HR when mutually adjusted and 2) ECO_2 and HR when adjusted for each other and for the median V_{TE} within each time interval. The AUC values displayed, were calculated based on the results of the corresponding logistic regression models. Newborns (n) with available data for both ECO_2 and HR within each time interval were included.

[a] Median V_{TE} turned significant with negative impact on survival ≤30 seconds and between 60.1-300 seconds of ventilation in models with median ECO_2 and between 60.1-300 seconds in models with HR. Median V_{TE} was not associated with survival in unadjusted models.
[b] Receiver operating characteristics curves and AUC with 95% confidence intervals for maximum ECO_2 and HR in the unadjusted models, and statistical tests to assess for differences, are displayed in fig. 3.
[c] AUC reported for adjusted models describes the combined predictive information of all the included parameters in the model.
[d] $p<0.001$, [e] $p<0.01$, [f] $p<0.05$

ECO_2=expired CO_2, pp=percent point, HR=heart rate, OR=Odds Ratio, pp=percent point, bpm=beats per minute, V_{TE}=expired volume, BMV=bag-mask ventilation, AUC=area under the receiver operator curve.

Table 3. Comparison of time to expired CO_2 ≥2% and heart rate ≥100 bpm between survivors and deaths at 24 hours

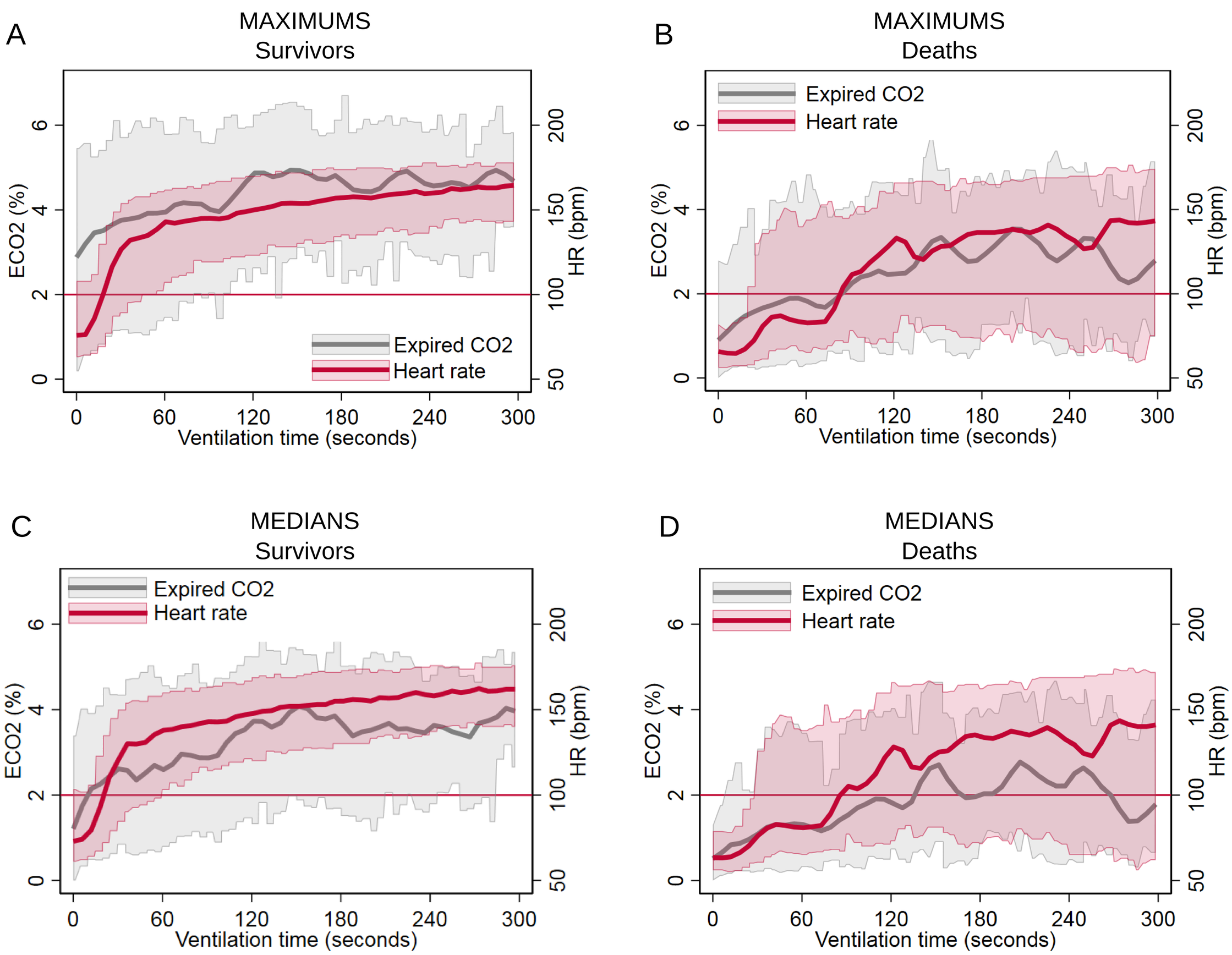
	Survivors	Deaths	p-value
Expired CO_2 (ECO_2)			
Time from first BMV until ECO_2 ≥2% (seconds)[a]	16 (6, 47)	37 (11, 93)	0.06[d]
Time from birth until ECO_2 ≥2% (seconds)[b]	137 (95, 197)	149 (119, 280)	0.12[d]
Number of newborns with ECO_2 ≥2% in first BMV	109 (29%)	4 (7%)	0.001[e]
Number of newborns who did not reach ECO_2 ≥2%while monitored [c]	15 (4%)	8 (14%)	0.001[c]
Heart rate (HR)			
Time from first BMV until HR ≥100 bpm [a]	27 (19, 50)	47 (24, 127)	<0.001[d]
Time from birth until HR ≥100 bpm [b]	151 (110, 209)	185 (125, 274)	0.02[d]
Number of newborns with HR ≥100 bpm at start of BMV	108 (29%)	4 (7%)	0.001[e]
Number of newborns who did not reached HR ≥100 bpm while monitored [c]	4 (1%)	8 (14%)	<0.001[e]

[a] Newborns with ECO_2 <2% (254 survivors and 44 deaths) or HR <100 bpm (266 survivors and 44 deaths) at or after start of BMV were included.
[b] The times given are based on available data. ECO_2-data was not available before initiation of BMV, HR-data depended on placement of the HR-sensor around the newborn's trunk. ECO_2>2% and/or HR>100 bpm may have occurred between birth and initiation of BMV in some newborns.
[c] The time interval with monitoring varied between newborns and could be shorter than 5 minutes in newborns with fast clinical improvement, and longer in newborns in need for prolonged ventilation.
P-values were calculated by [d]Wilcoxons rank sum test or [e]Pearsons Chi^2-test.
ECO_2=Expired CO2, BMV=bag-mask ventilation, HR=heart rate

Expired Carbon Dioxide during Newborn Resuscitation as Predictor of Outcome

Supplemental material

Supplemental Fig. 1 - Maximum and median expired CO_2 and heart rate during the first 5 minutes of ventilation by 24-hour outcome; survivors and deaths



The figures display graphs of median (25-75 percentiles) of the maximum (A+B) and median (C+D) values of ECO_2 and HR per newborn per 5 seconds intervals from start BMV to 300 seconds of BMV for newborns who A+C) survived to 24 hours (n=378), and B+D) died before 24 hours of age (n=56). Number of newborns who survived and died with available data for both ECO_2 and HR within each minute after start of BMV were in 1st min: 376 and 54, 2nd min: 294 and 48, 3rd min: 205 and 44, 4th min 164 and 40, and 5th min: 115 and 37, respectively.

ECO_2=expired CO_2, HR=heart rate, BMV=bag-mask ventilation

Supplemental table 1 - Logistic regression models for 24-hours survival by categories of maximum ECO_2 and HR per newborn for the three selected time intervals: 0-30 seconds, 30.1-60 seconds, and 60.1-300 seconds

Categories of maximum values		n	OR (95% CI)	p-value	AUC
0 – 30 seconds of BMV		422			
ECO_2	< 2 %	94	0.36 (0.16, 0.84)	0.02	0.72
	2 - 3.99 %	63	0.24 (0.10, 0.59)	0.002	
	4 - 5.99 %	101	1 (ref)	-	
	6 - 7.99 %	86	2.01 (0.60, 6.76)	0.26	
	≥ 8 %	78	2.45 (0.64, 9.36)	0.19	
HR	< 60 bpm	25	0.10 (0.03, 0.27)	< 0.001	0.69
	60 - 99 bpm	127	0.33 (0.15, 0.74)	0.007	
	100 - 140 bpm	127	1 (ref)	-	
	>140 bpm	143	1.01 (0.40, 2.58)	0.98	
30.1-60 seconds of BMV		363			
ECO_2	<2 %	71	0.25 (0.10, 0.61)	0.002	0.68
	2-3.99 %	51	0.27 (0.10, 0.69)	0.007	
	4-5.99 %	96	1 (ref)	-	
	6-7.99 %	71	2.06 (0.53, 8.06)	0.30	
	≥ 8 %	74	0.75 (0.27, 2.10)	0.58	
HR	< 60 bpm	11	0.23 (0.06, 0.92)	0.04	0.68
	60 - 99 bpm	68	0.30 (0.14, 0.66)	0.003	
	100 - 139 bpm	102	1 (ref)	-	
	> 140 bpm	182	1.60 (0.71, 3.61)	0.26	
60.1-300 seconds of BMV		354			
ECO_2	< 2 %	26	0.36 (0.13, 1.02)	0.06	0.62
	2 - 3.99 %	27	0.38 (0.13, 1.07)	0.07	
	4 - 5.99 %	80	1 (ref)	-	
	6 - 7.99 %	105	1.13 (0.48, 2.67)	0.78	
	≥ 8%	116	1.52 (0.63, 3.70)	0.36	
HR	< 60 bpm	4	0.06 (0.05, 0.63)	0.02	0.66
	60 - 99 bpm	15	0.04 (0.01, 0.19)	< 0.001	
	100 - 139 bpm	42	1 (ref)	-	
	> 140 bpm	293	1.46 (0.57, 3.75)	0.43	

The models present unadjusted OR of 24-hour survival for both ECO_2 and HR independently. Newborns (n) with available data for both ECO_2 and HR within each time interval were included.

ECO_2=Expired CO2, BMV=bag-mask ventilation, HR=heart rate, OR=Odds Ratio

Supplemental table 2 - Logistic regression models for 24-hours survival by maximum (upper panel) and median (lower panel) ECO_2 and heart rate per newborn for the time intervals: 0-30 seconds, 30.1-60 seconds, and 60.1-300 seconds, stratified for birth weight ≥2500g versus <2500g

		Newborns with birth weight ≥2500 g			Newborns with birth weight <2500 g		
Maximum ECO_2 and HR per time intervals							
0 – 30 seconds of BMV		**n**	**OR (95% CI)**	**AUC**	**n**	**OR (95% CI)**	**AUC**
ECO_2	Per 1 pp increase	363	1.32 (1.17, 1.49)	0.73	59	1.20 (0.95, 1.52)	0.68
HR	Per 10 bpm increase		1.20 (1.09, 1.31)	0.68		1.08 (0.90, 1.30)	0.58
30.1 – 60 seconds of BMV							
ECO_2	Per 1 pp increase	311	1.26 (1.12, 1.44)	0.69	52	1.13 (0.90, 1.41)	0.65
HR	Per 10 bpm increase		1.19 (1.08, 1.30)	0.66		1.10 (0.92, 1.32)	0.60
60.1 - 300 seconds of BMV							
ECO_2	Per 1 pp increase	303	1.30 (1.17, 1.43)	0.67	51	1.00 (0.81, 1.25)	0.46
HR	Per 10 bpm increase		1.28 (1.17, 1.40)	0.64		1.13 (0.87, 1.46)	0.51
Median ECO_2 and HR per time intervals							
0 – 30 seconds of BMV		**n**	**OR (95% CI)**	**AUC**	**n**	**OR (95% CI)**	**AUC**
ECO_2	Per 1 pp increase	363	1.39 (1.12, 1.72)	0.64	59	1.43 (0.86, 2.37)	0.63
HR	Per 10 bpm increase		1.30 (1.12, 1.49)	0.69		1.19 (0.90, 1.58)	0.59
30.1 – 60 seconds of BMV							
ECO_2	Per 1 pp increase	311	1.22 (1.02, 1.45)	0.62	52	1.34 (0.91, 1.98)	0.68
HR	Per 10 bpm increase		1.17 (1.07, 1.29)	0.66		1.07 (0.90, 1.28)	0.57
60.1 - 300 seconds of BMV							
ECO_2	Per 1 pp increase	303	1.23 (1.02, 1.40)	0.62	51	0.93 (0.66, 1.32)	0.49
HR	Per 10 bpm increase		1.24 (1.13, 1.35)	0.64		0.99 (0.82, 1.19)	0.49

The models present unadjusted OR of 24-hour survival for both ECO_2 and HR independently. Newborns (n) with available data for both ECO_2 and HR within each time interval were included.

ECO_2=expired CO_2, pp=percent point, HR=heart rate, bpm=beats per minute, BMV=bag-mask ventilation, OR=Odds Ratio, AUC=area under the receiver operator characteristics curve.

Paper III:

Holte K, Ersdal HL, Eilevstjønn J, Gomo Ø, Klingenberg C, Thallinger M, Linde J, Stigum H, Yeconia A, Kidanto H, Størdal K
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