A prospective observational study on newborn resuscitation in a high-resource setting

Peder Aleksander Bjorland

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2022

UNIVERSITY OF BERGEN

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Date of defense: 28.10.2022

Year: 2022

Title: A prospective observational study on newborn resuscitation in a high-resource setting

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Print: Skipnes Kommunikasjon / University of Bergen

“O, that I could but call these dead to life!”

William Shakespeare’s King Henry VI

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Scientific environment and funding

The present work was carried out at Stavanger University Hospital from 2016 to 2022. The project started with an observational study over a twelve month period in 2016-17, a collaborative between the Department of Obstetrics and Department of Paediatrics at Stavanger University Hospital (*Paper I* and *II*). *Paper III* and *IV* used data from the Safer Births Bundle from 2019 to 2021, a collaborative initiative between Stavanger University Hospital, the University of Stavanger and the Laerdal Foundation. The doctoral candidate received grants from the Laerdal Foundation in 2018 and 2020 (Bjørn Lind Grant no 30026 and 30031), and became a PhD candidate at the University of Bergen in 2019. Main Supervisor has been Siren Rettedal, Professor II at the University of Stavanger. Co-supervisors has been Knut Øymar, Professor at the University of Bergen, and Hege Ersdal, Professor at the University of Stavanger.

Acknowledgements

Professor Siren Rettedal, my main supervisor and colleague. You welcomed me to the neonatal department and into the field of research more than five years ago. Your enormous engagement and belief in what you are doing is nothing less than impressive, and has been a great inspiration to me. Where I see limitations, you find opportunities. Without your support, this project would never have been. Through peaks and troughs, you have always found the time for me, and I sincerely thank you for all your backing and motivation.

Professor Knut Øymar, my co-supervisor. Thorough, solid and reliable, your reputation precedes you. I was always amazed by how quickly and methodically you uncovered the logic flaws and inconsistencies in my manuscripts. You encourage me to think scientifically, and your guidance has been decisive in my evolution as a researcher. I thank you for you all your wise advice, and for your patience as you politely reminded me of this advice.

Professor Hege Ersdal, my co-supervisor. So down to earth, despite all that you have accomplished for the benefit of perinatal survival in low resource settings. Your insight in the field of newborn resuscitation has greatly improved the credibility of our project. You are a role model, and I thank you for sharing your knowledge.

Joanna Haynes, my fellow PhD student and co-writer of *Paper IV*. It has been so nice to have you as my sister in arms, your insight in and understanding of the ventilation data has saved me many times. Thank you so much for proofreading all my manuscripts. I have certainly been clever to befriend a fellow researcher with English as her native tongue.

Joar Eilevstjønn, genius and senior scientist at Laerdal Medical. Co-writer of *Paper III*. Thank you for hours and hours of technical and analytical support for *Paper III* and *IV*. Your long experience in dealing with heart rate- and respiratory signal data has been of great help; I would be truly lost without it.

Anastasia Ushakova, statistician at the Section of Biostatistics at Stavanger University Hospital. Co-writer of *Paper IV*. I am grateful for all your statistical advice throughout

the whole project and for our many sit-downs where you patiently tried to enlighten me.

Professor Peter G Davis, co-writer of *Paper III*. I was honoured, and a bit star-struck, when you accepted to work with us. Thank you for your friendly advice and valuable contribution to our work.

James Miller from Viste&Sømme, and Arnfinn Arnesen, in-house technician at Stavanger University Hospital. Thank you for the help in setting up and maintaining the camera equipment for the data collection. You have shown great interest in this project and the service you have provided has been far beyond what we could ever have expected.

All the midwives and nurse assistants from the birth department. Your support and interest in this project has been overwhelming. A special thanks to Elsa Lindtjørn, who helped me crosscheck the incident report forms from nearly 5000 births.

Former and current fellow researchers in the Safer Births Bundle. I am proud to have been part of this team, and hope to have a place at the table in some of the exciting projects to come.

All my colleagues at the neonatal intensive care unit. You stand tall and look out for the smallest ones, while we researchers are out to pursue our own goals. I look forward to finally spending more time with you in the NICU again.

The director of the Research Department and his colleagues at the research department. Thank you for your kind service and assistance. The former and current director of the Obstetrics and Gynaecology and Paediatric Division, and the former and current head of the Department of the Paediatric and Adolescent Medicine. I appreciate your encouragement and efforts to facilitate research in our department.

Laerdal Foundation. I am grateful for your generous grant, and for believing in this project.

Finally, my profound gratitude to all of my family and friends. My dear old mother, always caring for my well-being; I promise I will get more sleep, eat more regularly, and dress warmly, now that I have fulfilled this project. My dearest daughters, brave

Siren (7) and caring Ane (5), you make me so proud. My magnificent wife, Line. I am forever grateful for all your support, your patience, you advice, and for your effort to organize our family in my absence. I owe it all to you.

Abbreviations

ANZCOR	Australian and New Zeeland Committee on Resuscitation
CoSTR	Consensus on Science and Treatment Recommendations
Bpm	Beats per minute
ECG	Electrocardiogram
ERC	European Resuscitation Council
FRC	Functional Residual Capacity
GA	Gestational Age
GEE	General Estimating Equations
ILCOR	International Liaison Committee On Resuscitation
LOESS	Locally Estimated Scatterplot Smoothing
MAP	Mean Arterial Pressure
NRR	Norsk Rescusitasjonsråd (Norwegian Resuscitation Council)
PEEP	Positive End-Expiratory Pressure
PIP	Peak Inflating Pressure
PO	Pulse Oximetry
PPV	Positive Pressure Ventilation

Sammendrag

Bakgrunn: Omkring åtte prosent av verdens nyfødte har behov for pustehjelp for å klare overgangen fra intra- til ekstrauterint liv. Nøyaktig forekomst er usikker og varierer antagelig mellom ulike settinger, men resuscitering av nyfødte er likevel en av de vanligste akuttbehandlinger i sykehus rundt om i verden. Internasjonale retningslinjer for nyfødtresuscitering skal sikre lik og optimal behandling av syke nyfødte. Imidlertid er kunnskapsgrunnlaget for internasjonale retningslinjer mangelfullt, og baserer seg i stor grad på prekliniske studier uten sikker forankring i den kliniske hverdagen. Pustestøtte ansees som det viktigste tiltaket, og retningslinjer presiserer at overtrykksventilering bør starte innen ett minutt fra fødsel hos barn som ikke puster selv. Lav hjertefrekvens kan indikere behov for pustestøtte, og ved eventuelle tiltak vil rask bedring i hjertefrekvens indikere at behandlingen er effektiv. Retningslinjer anbefaler derfor tidlig vurdering av barnets hjertefrekvens, og at hjertefrekvens overvåkes under resuscitering ved hjelp av pulsoksymetri (PO) eller elektrokardiografi (EKG). Likevel finnes det lite kunnskap om hva som faktisk er normal hjertefrekvens de første minuttene etter fødsel, og man vet ikke hvilken metode som mest effektivt overvåker barnets hjertefrekvens under resuscitering. T-stykke ventilator er blitt et vanlig apparat for å gi luftveisstøtte til nyfødte. Forskning på bruk av disse apparatene under resuscitering i hovedsak utprøvd på premature nyfødte. Resultater fra forskning på nyfødtresuscitering danner et viktig grunnlag for videre utvikling av evidensbaserte anbefalinger.

Mål: Mål for dette prosjektet var å i) studere forekomst av, karakteristika ved, og utfall av nyfødtresuscitering på kort sikt i en høyressurs setting, ii) studere etterlevelsen av retningslinjer for nyfødtresuscitering og undersøke hvor effektivt PO og EKG er til å overvåke hjertefrekvens under resuscitering, iii) beskrive normal hjertefrekvens hos friske nyfødte etter vaginal forløsning og sen avnavling, og iv) beskrive hvilke trykk og volum som leveres ved overtrykksventilering av ikke-pustende nyfødte til termin, når man bruker en T-stykke ventilator.

Metode: Denne sammenstillingen bygger på fire prospektive observasjonsstudier. Alle studiene er utført ved Stavanger Universitetssjukehus. *Studie I* benyttet seg av

rapporteringsskjema og videofilming over 12 måneder for å registrere og analysere tiltak ved nyfødtresuscitering. Vi registrerte forekomst av overtrykksventilering, kontinuerlig positivt luftveistrykk (CPAP), intubasjon, hjertekompresjoner og intravenøs administrasjon av adrenalin. Utfall etter resuscitering ble hentet fra elektroniske pasientjournaler. I *studie II* brukte vi videofilmer fra resuscitering av ikke-pustende barn ≥ 34 gestasjonsuker sammen med PO og/eller EKG-signal fra pasientmonitor. Vi målte tid fra fødsel til vurdering av hjerterytme og tid til oppstart av overtrykksventilering. Videre målte vi tid til pålitelig signal fra PO og EKG. I *studie III* målte vi hjertefrekvens de første fem minuttene etter fødsel hos friske, vaginalforløste terminbarn med sen avnavling, ved hjelp av en nyutviklet hjertefrekvensmåler med tørrelektrode-EKG (NeoBeat). Vi brukte 'locally estimated scatterplot smoothing' for å beregne og tegne percentiler. I *studie IV* brukte vi en ventilasjonsmonitor for å måle og analysere venilasjonsparametre under overtrykksventilering av terminbarn etter fødsel med T-stykke ventilator som var innstilt etter internasjonale anbefalinger (30/5 cmH2O). Vi analyserte de første 100 innblåsingene i hver resuscitering, og delte dem inn i tidlig (1.-20. innblåsing) og sen (21.-100. innblåsing) fase. Vi brukte 'general estimating equations' for å analysere assosiasjoner mellom tidalvolum og topptrykk, innblåsingstid og ventilasjonsfrekvens.

Resultat: I *studie I* inkluderte vi 4693 nyfødte. Av disse ble 291 (6.2%) behandlet med pustehjelp eller annen støtte umiddelbart etter fødsel. Antall nyfødte som ble behandlet med overtrykksventilering, CPAP, intubasjon, brystkompresjoner og intravenøs administrasjon av adrenalin var henholdsvis 170 (3.6%), 121 (2.6%), 19 (0.4%), ti (0.2%), og tre (0.1%). Median (IQR) varighet av overtrykksventilasjon var 106 (54-221) sekunder. 63% av de resusciterte nyfødte ≥34 gestasjonsuker ble igjen hos foreldre etter resusciteringen. I *studie II* analyserte vi resusciteringer av 104 nyfødte som ikke pustet etter fødsel. I bare 35% av tilfellene ble hjertefrekvens vurdert (ved palpasjon eller auskultasjon) og overtrykksventilering startet innen 60 sekunder etter fødsel. Tiden fra fødsel til vurdering av hjertefrekvens og oppstart av overtrykksventilering var henholdsvis 70 (47-118) og 78 (42-118) sekunder. Tiden fra fødsel til pålitelig registrering av hjertefrekvens fra PO og EKG var henholdsvis

348 (217-524) og 174 (105-227) sekunder (p<0.001). Tiden fra PO måler eller EKG elektroder ble festet på barnet og til pålitelig registrering av hjertefrekvens var henholdsvis 199 (77-352) og 16 (11-22) sekunder (p<0.001). I *studie III* målte vi hjertefrekvens etter fødsel hos 898 friske nyfødte terminbarn. Hjertefrekvensen økte raskt fra 123 (98-147) slag per minutt ved 5 sekunders alder til 175 (157-189) slag per minutt ved 61 sekunders alder. I *studie IV* analyserte vi venilasjonsparametre under resuscitering av 129 nyfødte terminbarn. Topptrykket var 30 (28-31) mbar i tidlig fase og 30 (27-31) mbar i sen fase. Tidalvolum var 4.5 (1.6-7.8) ml/kg i tidlig fase og 5.7 (2.2-9.8) ml/kg i sen fase. Innblåsingstid på mer enn 0.41 sekunder i tidlig fase og 0.50 sekunder i sen fase var assosiert med de høyeste tidalvolumene. Ventilasjonsfrekvens på mer enn 32 innblåsinger per minutt i tidlig fase og 41 innblåsinger i per minutt i sen fase var assosiert med reduserte tidalvolum.

Konklusjon: Nyfødtresuscitering forekom hyppig i denne høyressurs-settingen. De fleste nyfødte responderte raskt på luftveisstøtte. Etterlevelsen av gjeldende retningslinjer var dårlig. Under resuscitering av nyfødte ble pålitelig overvåkning av hjertefrekvens etablert raskere med EKG enn med PO. Vi har presentert percentiler for normal hjertefrekvens etter fødsel hos friske vaginalforløste terminbarn etter sen avnavling. Når man ventilerte nyfødte terminbarn ved hjelp av en T-stykke ventilator ble det levert stabile topptrykk, men det var vesentlig variasjon i tidalvolum. Innblåsingstid på omtrent 0.5 sekunder og ventilasjonsfrekvens på 30-40 innblåsinger i minuttet var assosiert med det høyeste tidalvolumet.

Abstract

Background: An estimated eight percent of newborns globally need respiratory support at birth to make the transition from intra- to extra uterine life. Although these estimates are uncertain, and presumably vary between settings, newborn resuscitation remains one of the most commonly occurring emergencies in the hospital. Resuscitation guidelines should ensure optimal treatment of compromised newborns; however, there is a general lack of evidence to support the different treatment recommendations. Existing knowledge is in large part derived from pre-clinical studies, and the transferability to real-world resuscitations is uncertain. Guidelines highlight support of breathing as the single most important task during newborn resuscitation, and positive pressure ventilation (PPV) should be initiated within the first minute of life in apnoeic newborns. Furthermore, guidelines acknowledge the newborn heart rate as an important factor to guide resuscitative interventions, and recommend continuous heart rate monitoring during resuscitation by either pulse oximetry (PO) or electrocardiography (ECG). However, there is limited data on the normal heart rate in healthy newborns, and the optimal method for monitoring heart rate during newborn resuscitation remains unknown. The flow driven T-piece resuscitator is a widely used device for respiratory support at birth. However, research into its ventilation performance during resuscitation is limited to premature newborns. Studies on newborn resuscitations provide important feedback to support the process of evolving evidence based resuscitation guidelines.

Aim: The aim of this thesis was to i) study the incidence, characteristics and short-term outcomes in newborn resuscitation in a high-resource setting, ii) study compliance with resuscitation algorithms and efficacy of PO versus ECG as heart rate monitoring during resuscitation, iii) describe the normal heart rate in vaginally delivered healthy term newborns after delayed cord clamping, and iv) describe delivered pressures and tidal volumes during positive pressure ventilation of apnoeic term newborns with a T-piece resuscitator.

Method: This thesis consists of four prospective observational studies. All studies were conducted at Stavanger University Hospital in Norway. *Study I* used incident report

forms and video recordings to register and analyse resuscitative interventions during a period of 12 months. We recorded the incidence of PPV, continuous positive airway pressure (CPAP), intubation, chest compressions and intravenous administration of adrenaline. From electronic patient records we extracted short-term outcomes after resuscitation. In *study II*, we combined video recordings of resuscitations with PO and ECG signals from the patient monitor, to analyse guideline compliance and efficacy of heart rate monitoring in newborns ≥34 weeks of gestation receiving PPV after birth. We recorded the time from birth to initiation of PPV and time from birth to initial heart rate assessment by palpation or stethoscope. We compared time to accurate heart rate monitoring between PO and 3-lead ECG. For *study III*, we used a novel dry electrode ECG heart rate meter (NeoBeat, Laerdal Medical, Stavanger, Norway) to record physiological newborn heart rate in healthy vaginally born newborns after delayed cord clamping the first five minutes after birth. Heart rate centiles were drawn using a local regression model. In *study IV* we combined video recordings of resuscitations and a respiratory function monitor to record and analyse ventilation parameters during PPV of apnoeic term newborns after birth, using a T-piece resuscitator at standard internationally recommended settings of 30/5 cmH2O. We analysed the first 100 inflations from each resuscitation, and divided them into an early (inflation 1-20) and a late (inflation 21-100) phase. We applied general estimating equations to analyse the association between delivered tidal volumes, and peak inflating pressure, inflation time, and inflation rate.

Results: *Study I* included 4693 newborns. Of those, 291 (6.2%) received interventions after birth. The incidence of PPV, CPAP (only), intubation, chest compressions, and intravenous administration of adrenaline were 170 (3.6%), 121 (2.6%), 19 (0.4%), ten (0.2%), and three (0.1%), respectively. Median (IQR) duration of PPV was 106 (54-221) seconds. 63% of newborns ≥34 weeks of gestation were returned to parental care immediately after resuscitation. For *study II*, we analysed video- and heart rate recordings of 104 resuscitations. Initial heart rate assessment (stethoscope or palpation) and initiation of PPV were achieved within 60 seconds for 35% of the resuscitated newborns. The time from birth to initial heart rate assessment and initiation of PPV was 70 (47-118) and 78 (42-118) seconds, respectively. Time from birth to provision

of a reliable heart rate signal was 348 (217-524) seconds for PO, and 174 (105-227) seconds for ECG ($p<0.001$). Time from sensor application to a reliable heart rate signal was 199 (77-352) seconds for PO, and 16 (11-22) seconds for ECG ($p<0.001$). In *study III*, we recorded heart rates from five seconds to five minutes in 898 healthy, vaginally delivered term newborns. Following birth, the heart rate increased rapidly from 123 (98-147) beats per minute at five seconds after birth to 175 (157-189) beats per minute at 61 seconds after birth. In *study IV* we analysed ventilation parameters from the resuscitation of 129 term newborns. PIP was 30 (28-31) mbar in the early phase and 30 (27-31) mbar in the late phase. Tidal volume was 4.5 (1.6-7.8) ml/kg in the early phase and 5.7 (2.2-9.8) ml/kg in the late phase. Inflation times exceeding 0.41 seconds in the early phase and 0.50 seconds in the late phase were associated with the highest delivered tidal volumes. Inflation rates exceeding 32 per minute during the early phase and 41 per minute in the late phase were associated with a decrease in tidal volumes.

Conclusion: The need of resuscitative interventions after birth was frequent in this high-resource setting, and most newborns responded quickly to airway support. The adherence to guidelines was poor. ECG provided a reliable heart rate signal significantly faster than PO during newborn resuscitation. We presented normal heart rate centiles in vaginally delivered term newborns after delayed cord clamping. When ventilating apnoeic newborns at birth with a T-piece resuscitator, there was a consistent delivery of PIP, however, tidal volumes varied substantially. Inflation time of approximately 0.5 seconds and rates of approximately 30-40 per minute were associated with the highest delivered tidal volumes.

List of Publications

1. Bjorland PA, Øymar K, Ersdal HL, Rettedal S. **Incidence of newborn resuscitative interventions at birth and short-term outcomes: a regional population-based study**. BMJ Paediatrics Open 2019.

   DOI:10.1136/bmjpo-2019-000592

2. Bjorland PA, Ersdal HL, Øymar K, Rettedal S. **Compliance with Guidelines and Efficacy of Heart Rate Monitoring during Newborn Resuscitation: A Prospective Video Study**. Neonatology 2020;117:175-181.

   DOI: 10.1159/000506772

3. Bjorland PA, Ersdal HL, Eilevstjønn J, Øymar K, Davis PG, Rettedal S. **Changes in heart rate from 5 s to 5 min after birth in vaginally delivered term newborns with delayed cord clamping**. Arch Dis Child Fetal Neonatal Ed 2020. DOI: 10.1136/archdischild-2020-320179

4. Bjorland PA, Ersdal HL, Haynes J, Ushakova A, Øymar K, Rettedal S. **Tidal volumes and pressures delivered by the NeoPuff T-piece resuscitator during resuscitation of term newborns**. Resuscitation 2022.

   DOI: 10.1016/j.resuscitatoin.2021.12.006

All papers are open access.

1. Introduction

1.1 Preface / Background

The day of birth is considered the most dangerous in a human's life. It is the day when the risk of death and disability is greatest[1]. At birth, the transition from intrauterine to extra uterine life involves a series of physiological changes in the newborn[2]. Failing this transition might result in birth asphyxia, i.e. the lack of oxygen in the newborn brain, with a potential risk of severe neurological impairment, or death. Globally, intrapartum related events account for more than 600,000 deaths each year, making it amongst the leading causes of neonatal morbidity and mortality[3].

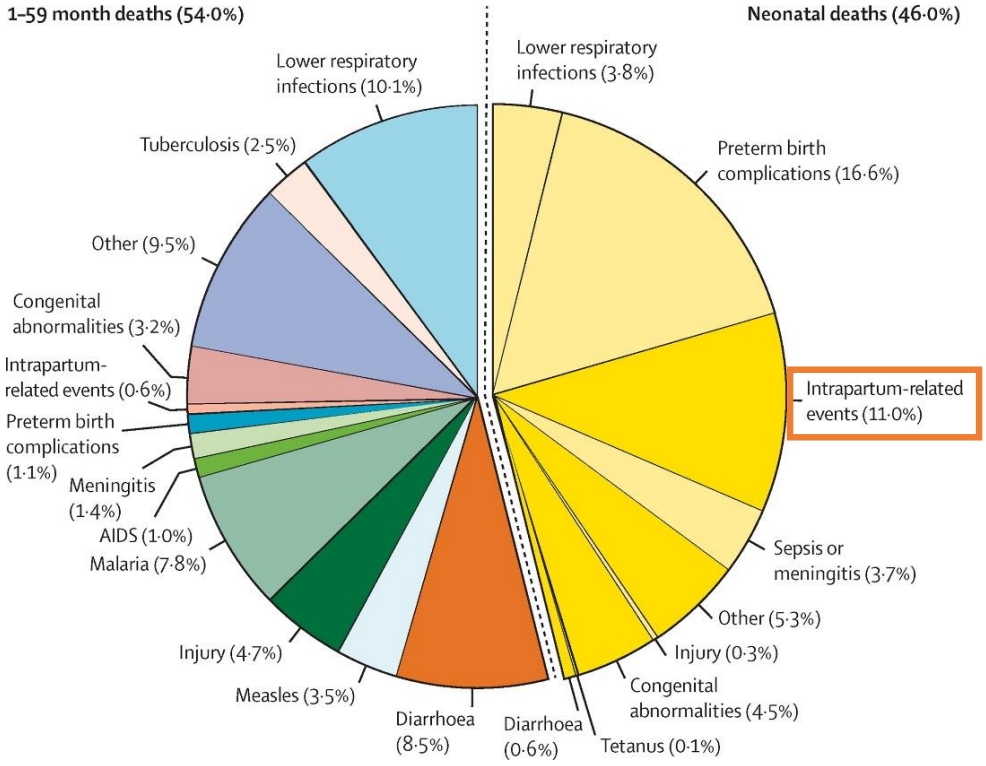


Figure 1 Global causes of the 5.3 million under-5-deaths in 2019. Deaths of neonates (aged 0–27 days) are on the right-hand side. Adapted from J Perin et al.[3]. Published by Elsevier Ltd (Open Access)

A high number of neonatal deaths may be prevented through effective resuscitation[4]. This depends upon immediate performance of several interventions simultaneously, and time is of the essence. Thus, resuscitation guidelines are designed to aid prioritizing measures and to define specific time intervals for the most crucial steps. While guidelines have originally been largely based on expert opinion, there has been an increase in research on newborn transition and resuscitation over the last decades, and guidelines are regularly updated to reflect current knowledge. However, many issues remain unsolved, and the overall aim of this project has been to contribute to the ongoing development of evidence-based resuscitation guidelines.

In the following chapters, I will discuss the burden of neonatal asphyxia before describing the physiological transition of the newborn at birth and the pathological pathways of asphyxia. I will present current guidelines on newborn resuscitation, highlighting central steps in the algorithm and summarize the knowledge from which these recommendations are based. Finally, I will describe standard equipment for treating and monitoring newborns during resuscitation.

Since the beginning of this project, new guidelines and recommendations have been published. In the general introduction, I refer to the recommendations and guidelines from 2015. The current guidelines published in 2020 are addressed in the discussion section. More recent publications unrelated to resuscitation guidelines have been included in the general introduction.

1.2 The burden of neonatal mortality

In 2019, more than 2.4 million newborns died in the neonatal period (before 28 days of life), corresponding to near 6700 newborns every day[3]. Intrapartum-related complications such as birth asphyxia accounts for near one-quarter of the neonatal mortality[3]. The inconvenient truth is that these deaths are in large part preventable.

The reduction of child mortality has been one of the defined United Nations Millennium Development Goals since year 2000, and the progress has been remarkable; The global under 5-mortality has dropped from 93 per 1000 live births in 1990 to 38 per 1000 live births in 2019[5]. However, neonatal mortality has declined at

a slower pace than that of children aged from one month to five years. Thus, the share of neonatal deaths among all under-five deaths is increasing.

The burden of asphyxia-related mortality is geographically unevenly distributed. The United Nations Inter-agency Group for Child Mortality Estimation (UN IGME) states, "*A child born in sub-Saharan Africa is 10 times more likely to die in the first month of life than a child born in a high-income country"*. The improved quality of antenatal care, skilled care at birth, and an advanced postnatal care for the newborn baby, has reduced the neonatal mortality in Europe to three per 1000 live births in 2019[6]. In Norway, the neonatal mortality rate in 2020 was 1.3 per 1000 births, which is amongst the lowest in the world[7]. Still, the socioeconomic burden of birth asphyxia for society and the families affected is immense, and its prevention should remain a focus in all settings around the world.

1.3 Transition from intrauterine to extrauterine life

1.3.1 Foetal circulation

Before birth, the foetal lungs are filled with liquid and the lung circulation functions as a parallel system, meaning that most of the blood bypasses the foetal lung[8,9]. Instead, the placenta acts as the foetus` lungs, clearing the blood of carbon dioxide (CO_2) and replacing it with oxygen[10].

The blood leaving the placenta has an oxygen saturation level of 75-85%[11]. The oxygenated blood flows to the foetus through the umbilical cord into the foetal venous system, most of it bypassing the liver through the *ductus venosus* that leads the blood directly into the inferior vena cava and the right atrium of the heart. There, high resistance in the lung vessels ensures a supra-systemic pulmonary blood pressure, so that the blood preferentially flows directly into the systemic circulation and to the aorta through the *foramen ovale* between the atria and through the *ductus arteriosus* between the pulmonary artery and the aorta[12]. This way, the major part of the freshly oxygenated blood is canalized directly from the placenta to the aorta, to prioritize oxygenation of the foetal brain[13]. Finally, blood flows from the aorta to the iliac arteries to the

umbilical arteries and then to back to the placenta, for re-oxygenation. At birth, the newborn`s respiration and circulation system must undergo two critical changes: The liquid filled lungs must be aerated, and the bloodstream must be canalized through the lung vessels[14].

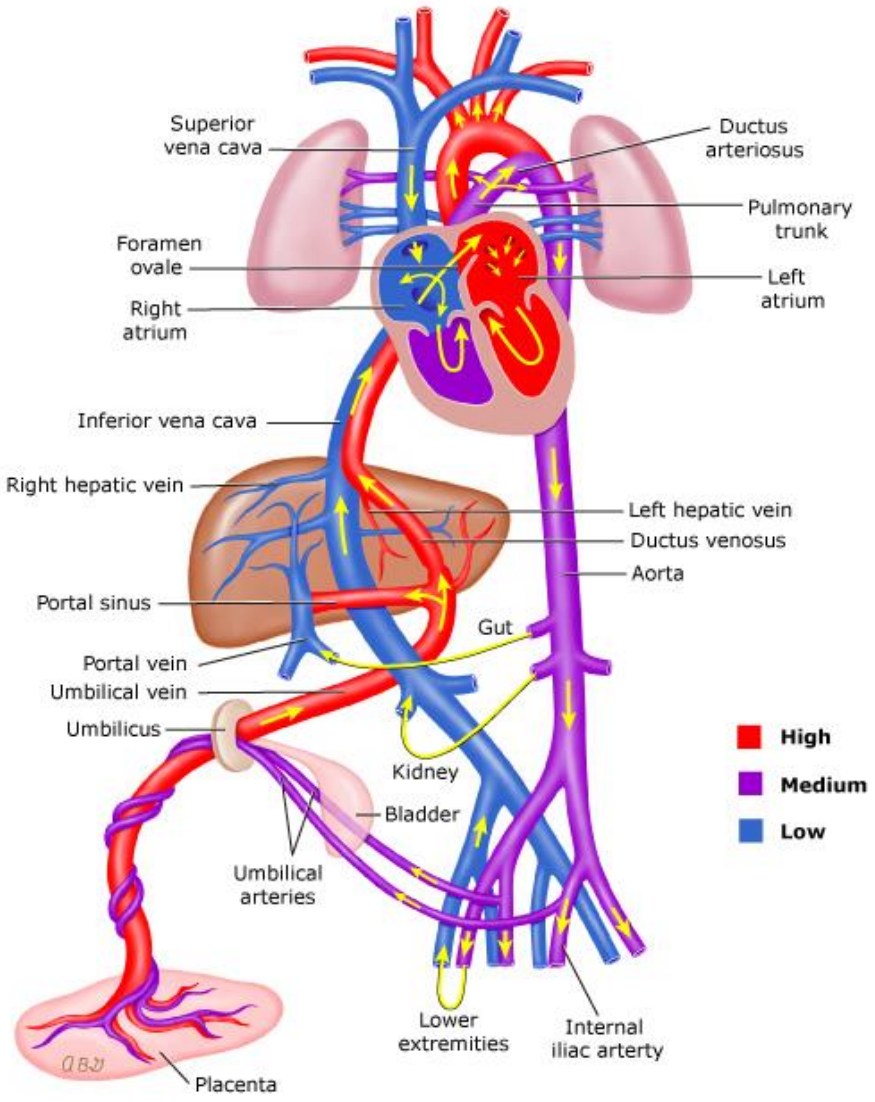


Figure 2 Illustration of the foetal circulation. Reproduced with permission from: Fernandes CJ. Physiologic transition from intrauterine to extra uterine life. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on 27.04.2022.) Copyright © 2020 UpToDate, Inc. For more information visit www.uptodate.com.

1.3.2 The aereation of the liquid filled lungs

The aeration of liquid filled lungs is a result of several processes[15]. During birth, uterine contractions mechanically squeeze some of the liquid from the lungs through the nose and mouth of the newborn[16,17]. Then, when the newborn initiates breathing after birth, it generates a negative intrathoracic pressure though expanding the chest wall. As a result, a pressure gradient arises between the interstitial tissue and the alveolar lumen, transferring the remaining liquid from the alveoli into the surrounding interstitial tissue space. The same pressure gradient propagates to the upper airways, allowing air to flow into the alveoli. This mechanism has been nicely demonstrated through X-ray imaging of lung recruitment in spontaneously breathing newborn rabbits, showing a stepwise increase in functional respiratory capacity (FRC) with each breath, and a near complete liquid clearance within the first five breaths after birth[18,19]. In addition to the mechanical mechanisms described above, there is an increase in adrenaline and vasopressin levels during labour, which increases Na uptake across the alveolar wall through epithelial Na channels[20-22]. This builds up an osmotic gradient, which aids the liquid clearance from the alveoli. Although the relative importance of these different mechanisms is debated, the overall effect is certain: the lunges are now aerated.

Subsequently, the liquid accumulated within the lungs interstitial tissue compartment must be cleared away through blood- and lymphatic vessels. During this phase, which normally lasts from minutes to hours, there is a constant re-entering and re-absorption of liquid between the alveoli and the interstitial tissue compartment[18,19]. Depending on the amount of liquid in the newborn lungs at birth, the newborn may need to compensate by an increased work of breathing, resulting in tachypnea, nasal flaring, chest retractions, or grunting. This state of respiratory distress may last until the transition phase is fully completed.

1.3.3 Transition to newborn circulation

At onset of breathing, the expansion of the lung and lung vessels, and the oxygen-mediated relaxation of the pulmonary arterioles, leads to a marked decline in the pulmonary vascular resistance[23]. As a result, the pulmonary blood pressure decreases, inverting the pulmonary- and systemic pressure gradient[9,14]. The blood will now

preferentially flow from the right heart through the lungs. The clamping of the umbilical cord further increases the systemic blood pressure by reducing the peripheral capillary bed. The reversed blood flow allows the patent foramen ovale to functionally close. The ductus arteriosus will eventually close as a response to the natural rise in blood oxygen.

1.3.4 Delayed cord clamping

Insight in the transition from foetal to newborn circulation allows an important understanding into the benefit of delayed cord clamping (i.e. delaying cord clamping for at least one minute from birth). Delayed cord clamping allows the newborn to initiate breathing, and thus increase its pulmonary blood flow prior to cord clamping. When the cord is then finally clamped, the left heart will be less dependent on the venous return from the placenta, ensuring a more stable systemic (and cerebral) circulation and oxygenation[24-28]. It is for this reason that delayed cord clamping is now recommended as standard of care.

1.3.5 The first cry

It is thus clear that the key to successful transition is the aeriation of the lungs through onset of breathing. In utero, the foetus has breathing moments[29], however these are discontinuous and only involve small volumes. The factors inducing continuous and deep respiration at birth are not well understood. Sensory stimulation and drop in temperature during labour and delivery probably plays an important role[30,31]. In addition, a transient hypercapnia stimulates central chemoreceptors[32]. Recent experiments also suggest that placental perfusion inhibits the foetal central respiratory system and that this effect may be mediated by a respiratory inhibitor produced in the placenta[31,33]. Thus, withdrawal of a respiratory inhibitor from the circulation may play an important role in maintaining breathing in the newborn after sensory stimulation wanes and hypercapnia resolves.

1.3.6 Apgar score

In 1952, the anaesthesiologist Virginia Apgar proposed a standardized method of evaluating newborns after birth[34]. Even today, the method remains the accepted method of assessment. It scores the newborn according to five criteria: Skin colour, Pulse, Grimace Response or Reflex Irritability in Response to Stimulation, Muscle Tone, and Respiratory effort.

Table 1 – The Apgar scoring system

Score	0 points	1 point	2 points
Appearance (Skin colour)	Blue; Pale	Pink body; Blue extremities	Pink
Pulse (Heart rate)	Absent	<100	>100
Grimace response (Reflex irritability)	Floppy	Minimal response to Stimulation	Prompt response to stimulation
Activity (Muscle Tone)	Floppy	Flexed arms and legs	Active
Respiration	Apnoeic	Slow, irregular breathing	Strong cry

The Apgar scores are assessed at one, five and ten minutes of age. It allows for rapid evaluation and can be used without additional equipment. Although lower Apgar scores are associated with adverse outcome[35-37], it is imprecise due to a high grade of subjectivity and high inter-observer variability[38-40]. A retrospective review found that 47% of newborns with Apgar of zero at ten minutes survived, of which 24% without abnormalities on magnetic resonance imaging (MRI) of the brain[41]. The Apgar score should therefore not be used alone as an outcome measure.

1.4 Perinatal asphyxia

Perinatal asphyxia is a condition where interrupted blood flow and/or gas-exchange in the newborn before, during or immediately after birth leads to severe and/or persistent hypoxemia, hypercapnia and acidemia.

During birth, the contractions briefly interrupt the venous blood flow though the umbilical cord and induce deceleration of the heart rate[42,43]. The resulting hypoxia, hypercapnia and acidosis is normally brief, quickly resolved after onset of breathing, and is generally tolerated by the foetus[44-48].

Asphyxia occurs when this hypoxemia, hypercapnia and acidemia are severe and/or prolonged due to birth complications, or in case of an insufficient respiratory effort of the newborn. If adequate ventilation is not rapidly established, a cycle of worsening hypoxia and acidemia may ensue, leading to brain injury, multiorgan injury and eventually death.

1.4.1 Primary and secondary apnea

The immediate physiological response to perinatal hypoxia in a newborn is believed to follow a defined sequence as described by Geoffrey Dawes in 1968[49], and shown in figure 3.

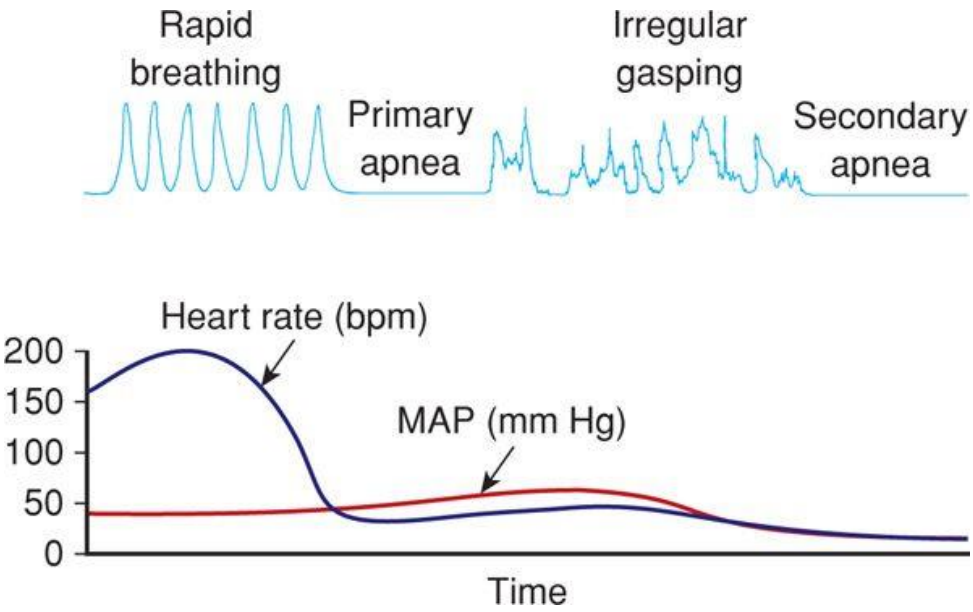


Figure 3. Illustration of the physiological changes associated with primary and secondary apnoea in the newborn. Bpm = beats per minute; MAP = mean arterial pressure. Adapted from G Dawes 1968[49]

Initially, the hypoxia causes a temporary increased breathing effort, followed by a decrease in the heart rate, before the newborn enters a state of primary apnoea. In this state, newborns will normally respond to tactile stimulation and/or brief respiratory support. However, if hypoxia persists, the newborn will develop irregular deep gasping respiration, followed by a further decline in heart rate, a loss of neuromuscular tone, and a fall in blood pressure. Eventually a state of secondary apnoea occurs, which, if untreated, eventually leads to death. Newborns in the state of secondary apnoea will no longer respond to stimulation alone and are in urgent need of respiratory and/or circulatory support.

As primary and secondary apnoea can be hard to distinguish clinically in a newborn child, apnoeic newborns that do not rapidly respond to stimulation should receive respiratory support without further delay.

1.4.2 Severe birth asphyxia

Severe birth asphyxia may result in brain damage with permanent neurodevelopmental sequela (hypoxic ischemic encephalopathy) or death. The traditional diagnostic criteria for severe birth asphyxia include an Apgar score <7 at five minutes of age, an umbilical artery pH <7.00, and a base deficit ≥12 mmol/l [50-52]. The severity of the brain damage is traditionally associated with the severity of acidosis[53,54]. However, it is unclear whether it is the cell poisoning due to secondary acidosis, or a reduced availability of cell energy caused by hypoxia, that causes the brain damage. Indeed, only a small percentage of newborns admitted to the neonatal intensive care units with severe acidosis had moderate to severe encephalopathy[48,55,56]. Furthermore, even with severe acidosis, there is a high chance of survival without sequelae[45-48,57].

There are two causes of acidosis: Hypercapnia (i.e. respiratory acidosis) or the lactic acidosis due to tissue hypoxia (i.e. metabolic acidosis). Normally, both causes are simultaneously present during birth asphyxia. However, it seems that the metabolic acidosis involves a greater risk to the newborn than respiratory acidosis. The risk of death or brain injury will increase as metabolic acidosis increases; moderate or severe complications occur in 10% of newborns with an umbilical artery base deficit of 12-16 mmol/l, and 40% with a base deficit of >16 mmol/l[54]. The respiratory acidosis

however implies a lower risk for brain injury, and moderate hypercapnia may even have protective effects[58].

Ultimately, both hypoxia and acidosis need to be swiftly resolved, and immediate support of the compromised newborn after birth is crucial. The risk of death and/or prolonged admission, in a low-resource setting, increased 16% for every 30-second delay in initiating facemask ventilation[4]. Thus, newborns who do not initiate breathing on their own should receive PPV without delay.

1.5 Newborn resuscitation

1.5.1 Historical background

"And when Elisha came into the house, behold, the child was dead, and laid upon his bed… he went up, and lay upon the child, and put his mouth upon his mouth … and the flesh of the child waxed warm… and the child opened his eyes."

(Kings 4:34-35, approximately 800 BC)

Written sources of resuscitation can be found as far back as in the Old Testament. Still, it would take until the 20th century before the idea of cardiopulmonary resuscitation would be generally recognized by the wider medical community. Throughout history, aiding stillborn newborns with mouth-to-mouth resuscitation has presumably been passed on as a *secret of midwives*, considered by physicians of their time as inelegant and undignified, and beneath their station. Several other techniques of stimulating breathing of the newborn child have been practiced (figure 4), until the physicians Peter Safar and James Elam convinced the world of the effectiveness of mouth-to-mouth resuscitation in the late 1950s[59]. The first efforts at testing this technique were performed on dogs; soon the technique was suggested to assist breathing in children[60].

Figure 4 Dr Bernhard Schultze demonstrates neonatal resuscitation in 1871[61].

1.5.2 Towards evidence based resuscitation guidelines

During the second half of the 20th century, resuscitation councils have emerged around the world, establishing resuscitation guidelines. The first neonatal resuscitation program was established in 1987 in New Orleans, US. As there was generally little scientific data on newborn resuscitation and translational medicine, guidelines were largely based on expert opinion, or adapted from adult resuscitation. This has however changed over the last decades. In 1992, the International Liaison Committee on Resuscitation (ILCOR) was formed as a collaboration of representatives from resuscitation councils around the world. Aiming to promote international implementation of evidence-based resuscitation, they regularly review scientific literature on different aspects of resuscitation, and publish Consensus on Science Treatment Recommendations (CoSTR). The CoSTR are used as a basis for developing specific resuscitation guidelines appropriate for implementation in respective

countries. Furthermore, it is designed to provide a summary of "gaps in knowledge" in the different aspects of resuscitation, set to stimulate investigators to pursue targeted studies in order to help close the gaps.

1.5.3 Current guidelines in newborn resuscitation

The different regional and national resuscitation algorithms around the world are with few exceptions identical on the central elements. They stress the aeration of the lungs and ensuring gas exchange to reverse hypoxia and acidosis.

The Norwegian Resuscitation Council (*Norsk ResuscitasjonsRåd*, NRR)[62] bases their newborn resuscitation algorithm on the ILCOR[63] recommendations as well as guidelines from the European Resuscitation Council (ERC)[64], the Australian and New Zeeland Committee on Resuscitation (ANZCOR)[65], and the American Heart Association (AHA)[66]. The 2015 Norwegian guideline for neonatal resuscitation (figure 5) is summarized as follows: newborns not breathing sufficiently after birth, and not responding to drying and tactile stimulation, are to be brought to a resuscitation bay without further delay. Within 60 seconds after birth, trained healthcare workers should assess the heart rate and initiate positive pressure ventilation (PPV) if the newborn is apnoeic or if the heartrate is below 100 beats per minute (bpm). Suction of the airways prior to ventilation is not advised, as it may delay the onset of PPV. If heart rate remains below 100 bpm after one minute of PPV, healthcare workers should ensure delivering of adequate PPV, either through securing free airways (i.e. reposition, suction or endotracheal intubation), or increasing inflation pressures. If the bradycardia is severe, i.e. heart-rate remains below 60 bpm, full cardiopulmonary resuscitation must be initiated, including chest compressions, intravenous adrenaline, and/or fluid volume expansion.

1.5.4 Guideline adherence

Resuscitation guidelines prioritize interventions and define specific time intervals for the crucial steps of newborn resuscitation. While these guidelines may seem implementable in theory, several studies describe deviations from guidelines during

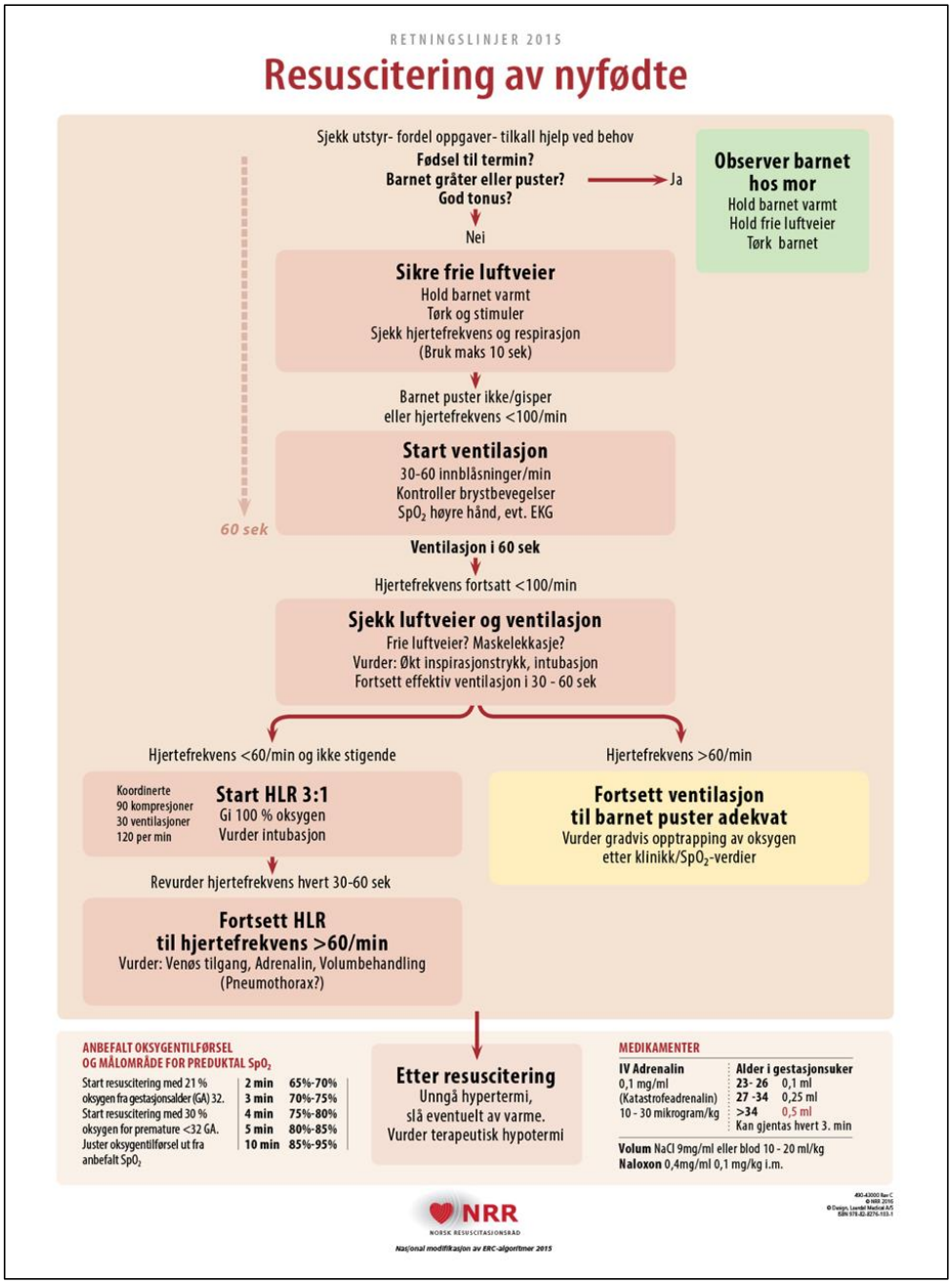


Figure 5 Guidelines on newborn resuscitation published by the Norwegian resuscitation council 2015. Printed with permission from Norsk Resuscitasjonsråd (NRR) Copyright © 2015, [62]

real-life newborn resuscitation in different settings around the world[67-74]. It is important to understand the real-life performance of resuscitation interventions and to study if and how clinical management deviates from current guidelines. A commonly reported challenge is to comply with the time frames recommended by guidelines, even in settings were teams stand prepared[68,70,74]. Such knowledge serves as important feedback to optimize future resuscitation guidelines, and may inform development of more targeted training strategies and programs. Combined with a general lack of information and evidence-based literature within this field, this highlights the need for further research to better understand delivered care and effects on newborns.

1.5.5 Incidence of newborn resuscitation

It is estimated that about three to eight percent of all newborns require basic resuscitation after birth, and about one percent requires full cardiopulmonary resuscitation[67,69,75-80]. However, the incidences of resuscitation interventions such as provision of PPV, continuous positive airway pressure (CPAP), intubation, chest compressions and/or administration of intravenous fluids or drugs are likely to vary substantially between different settings and countries. Current estimates are largely based on numbers from low-resource settings, with limited quality of antenatal care and perinatal monitoring. A study from Oslo University Hospital found that as much as 5.3% of all newborns received respiratory support after birth (PPV and/or CPAP), indicating that this is a frequent concern even in high resource settings[67]. However, Oslo University Hospital is a referral hospital for complicated deliveries, such as known congenital malformations, and the need for postnatal support may be overestimated.

1.5.6 Newborns at increased risk of requiring resuscitation

Several ante- and intrapartum risk factors are identified as predictors for the need of resuscitation after birth[75,81,82]. Known birth related risk factors are shoulder dystocia, instrumental delivery (i.e. forceps or vacuum delivery), breech presentation, meconium-stained amniotic fluid, emergency caesarean sections, and foetal heart rate abnormalities. In addition, prematurity and very low birth weight pose an increased

risk of need of support after birth, independent of other birth-related risk factors. In deliveries with a known increased risk of problems, an experienced team should be called upon and stand ready to assist the newborn[64]. However, most newborn resuscitations occur unexpectedly, and resuscitation teams will have little or no time to prepare[83].

1.6 The newborn heart rate

1.6.1 The normal heart rate after birth

During labour, the normal foetal baseline heart rate is 110-160 bpm. Brief decelerations of the foetal heart rate to 100-120 bpm are common, and attributed to vagal activation in association with uterine contractions[42,43]. The same drop in heart rate occurs as the newborn descends through the birth canal, followed by a rapid increase during the first minutes of life. There is limited evidence related to the normal change in newborn heart rate during the first minutes after birth. The widely referenced heart rate centiles published by Dawson et.al studied normal heart rate transition in 488 newborns, finding a medium heart rate of < 100 bpm in healthy newborns at one minute after birth[84]. These findings have confused healthcare personnel, since they suggest that many healthy spontaneously breathing newborns meet criteria for intervention[63]. However, the study from Dawson et al. was conducted using PO, which may have resulted in an underestimation of the heart rate[85]. In addition, the newborns included in the study all underwent early cord clamping. Delayed cord clamping is considered beneficial for cardiovascular transition and newborn outcomes (Chapter 1.3.4). The immediate effect of delayed cord clamping on heart rate is not clear, and randomized controlled studies on ventilated preterm lambs show conflicting results[24,25]. Clinical studies on newborns confirm that delayed cord-clamping results in a lower heart rate during the first minutes after birth[86,87]. As delayed cord clamping is increasingly implemented as standard of care worldwide, there is a need for re-evaluation of the pattern of normal heart rate changes during the first minutes of life.

1.6.2 Heart rate as an indicator of the newborn`s condition

Heart rate is probably the most important clinical indicator when evaluating the status of a newborn, and current guidelines stress the need for rapid and reliable measurement of heart rate in newborns requiring resuscitation. A normal heart rate may suggest that the newborn has not suffered severe hypoxia, and that it may respond to tactile stimulation. A depressed heart rate may be a sign of asphyxia and should prompt the initiation of respiratory support without delay. Severe bradycardia, defined in guidelines a heart rate below 60 bpm, may suggest a state of secondary apnoea, and full cardiopulmonary resuscitation is warranted. A rise in the newborns heart rate during treatment suggests that the newborn is responding, whereas persistent bradycardia should prime the team to act on severe asphyxia[88]. Overestimating the heart rate may result in delayed interventions while underestimations may result in the initiation of resuscitation when not required. Thus, a continuous and reliable feedback on the newborns heartrate during resuscitation is vital and of high priority.

1.6.3 Methods for heart rate assessment at birth

There are several methods of assessing and monitoring heart rate immediately after birth (figure 6). The most common are: palpation of pulse, auscultation by a stethoscope, and instrumental monitoring through pulse oximetry (PO) or electrocardiography (ECG)[89]. Doppler ultrasound has been demonstrated as a rapid and accurate alternative of assessing heart rate[90]. However, it requires an experienced clinician to operate it optimally[91]. More novel methods such as photo plethysmography or video plethysmography are not yet implemented in clinical settings, and are not discussed further.

The pulses are normally found by palpating the base of the umbilical cord, the brachial or femoral pulses or by palpating the precordium directly. Palpation is quick but unreliable, and auscultation by a stethoscope is the preferred method for manually assessing the heart rate. However, studies have suggested that clinical assessment of heart rate is inaccurate, and may lead to underestimation[92-94]. Furthermore, these methods are impractical for continuous heart rate monitoring, as they require repeated

assessments possibly interrupting the resuscitation[95]. Hence, guidelines recommend continuous instrumental heart rate monitoring during newborn resuscitation[63,64].

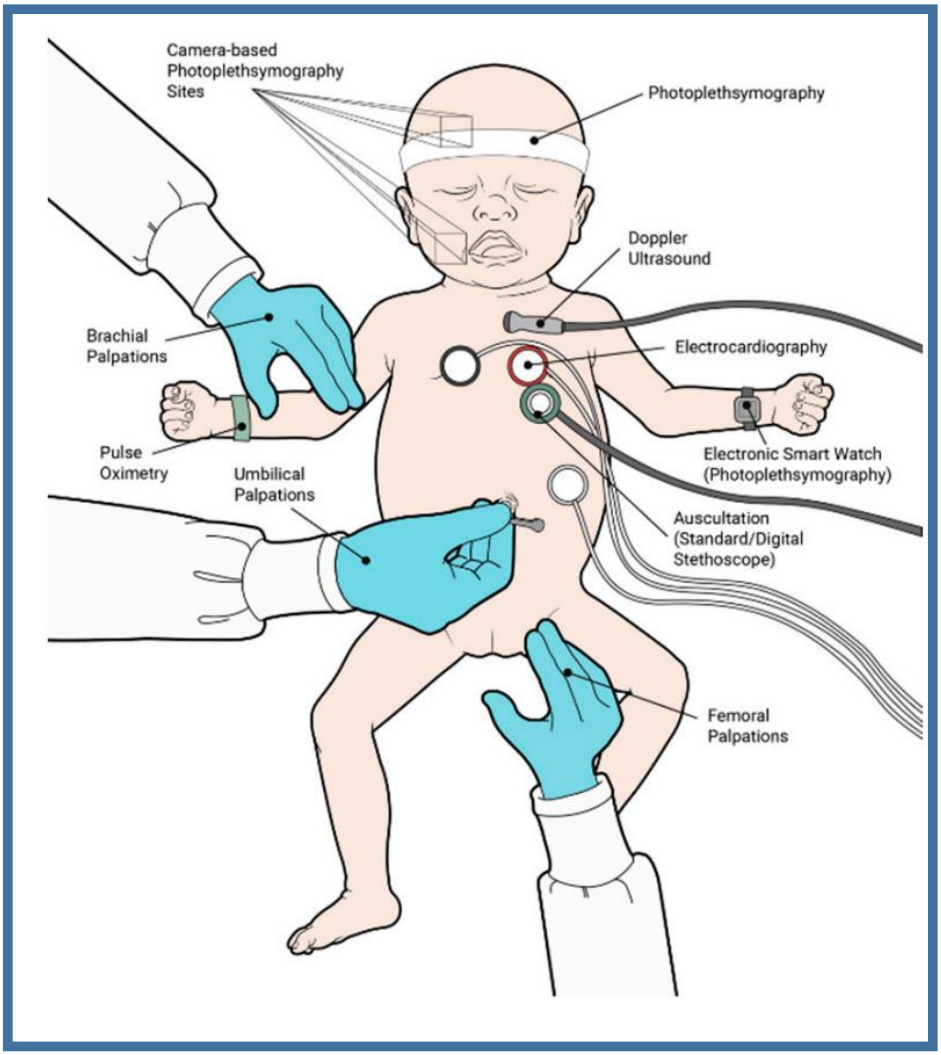


Figure 6 Illustration of different current techniques of assessing and/or monitoring newborn heart rate in the delivery room; Electrocardiography, pulse-oximetry, auscultation with a stethoscope, and palpation from brachial, femoral and umbilical arteries. The illustration also present some novel technologies including Doppler ultrasound and different forms of photo plethysmography. Adapted from Johnsen et.al 2020[96]. Published by MDPI (Open Access).

1.6.4 Pulse oximetry

PO can provide continuous heart rate monitoring by passing red and infrared light through a translucent body part (usually the hand or foot of the newborn) and to a photodetector. Oxygenated haemoglobin absorbs the infrared light and lets the red light pass through to the sensor, whereas deoxygenated blood absorbs the red light and lets the infrared light pass. Thus, the light detected by the sensor corresponds with the oxygenation level of the blood[97]. Importantly, the sensor also detects the heart rate through the changing absorbance due to the pulsing arterial blood volume. The sensor is relatively easy to apply, and its ability to simultaneously measure and display heart rate and blood oxygenation has made it the preferred method for monitoring heart rate in newborns after birth. However, studies report a considerable delay in obtaining reliable heart rate monitoring in freshly born newborns[98-101]. As PO relies on peripheral circulation, it is reasonable to assume that this delay may be even more significant in compromised newborns.

1.6.5 Electrocardiography

ECG measures the electric pacing from the heart, and is the gold standard of heart rate monitoring in general. Several studies have shown that the use of ECG is an effective method of monitoring newborn heart rate in the delivery room, and that it is superior to PO, in terms of reliability and time to detect heart rate signals[98,100,102,103].

However, most studies on time intervals for detection of heart rate using PO and ECG during resuscitation were conducted in high-risk deliveries where multiple collaborators were standing by for immediate application of heart rate monitoring after birth, demonstrating what is practically achievable in research settings with current devices. As newborn resuscitation often happens under different circumstances, the optimal instrument for heart rate assessment and the time to establish reliable heart rate monitoring during different real-life situations, remains unclear.

There are some limitations to ECG; PO is still required for displaying blood oxygenation, and there have been case reports of pulseless electric activity occurring in the delivery room[104,105]. Pulseless electric activity is a situation where the heart is

not able to maintain a (pulsating) blood flow despite internal electric pacing, due to e.g. asphyxia or lack of blood volume. Falsely interpreting the ECG signals as a pulse-giving heart rate may delay resuscitation. Furthermore, the ECG electrodes are more loosely attach to the newborn, thus may more easily fall off during handling of the newborn. ILCOR calls for improved technology for rapid application of ECG.

1.7 Respiratory support

The key to successful resuscitation is the early and effective provision of respiratory support. Most compromised newborns will respond to PPV alone, and only a small percentage will need circulatory support such as chest compressions or intravenous administration of adrenaline. The 2015 update from ILCOR acknowledges this by prolonging the duration of respiratory support before considering chest compressions[63]. Providing PPV in apnoeic newborns may still prove a challenging task, as it must ensure both the establishment of FRC as well as well as an adequate gas exchange[15]. It is important to understand these aspects to support the lung adaptation during resuscitation.

1.7.1 Establishing functional respiratory capacity (FRC)

During the first inflations, air will flow into lungs, displacing liquid from the airways down to the alveoli and further into the interstitial lung tissue. Experiments on spontaneously breathing rabbits have demonstrated near complete airway liquid clearance within 3-5 breaths[18]. During PPV of apnoeic newborns, studies suggest that FRC is established within the first 20 inflations[106]. Most of the inflated air will remain in the alveoli, starting to build up FRC[106]. In this early phase, the provision of sufficient inflation pressure is probably more important than reaching a target volume[107].

The liquid from the airways and alveoli is now stored in the interstitial lung tissue, from where is cleared through lymphatic- and blood vessels. However, this clearance may take several hours[108]. In the meantime, there is a constant re-entry of liquid into the alveoli during expiration due to the reduction of intra alveolar pressure[19]. Each inflation

must then counteract this, and this constant cycle of clearance and re-entry of liquid in the alveoli is what defines this phase of ventilation while upholding the FRC.

1.7.2 Pulmonary gas exchange

When the FRC is established, further ventilation aims to ensure adequate oxygenation and CO2-clearence, achieving respiratory homeostasis. This resembles the mechanics of traditional assisted ventilation that takes place in the neonatal intensive care unit. Gas exchange depends primarily on inflation rates and tidal volumes, and tidal volumes depend on peak inflating pressures (PIP) and inflation times. Of course, the gas exchange is also dependent on adequate pulmonary circulation, as described in the section on circulatory transition after birth (Chapter 1.3.3).

1.7.3 Tidal volumes

Tidal volume is the volume entering the lungs during each inflation. It is traditionally measured during expiration, as a fraction of the inflated air will be lost due to mask leak[109]. Spontaneously breathing term newborns are reported to breathe with tidal volumes between 5-8 ml/kg in the first minutes after birth[110-112]. This is also suggested as target volumes when providing PPV during resuscitation. However, larger tidal volumes may be required during the first breaths, as some of the inspired air remains in the lungs to establish and uphold FRC[106]. Recent studies have suggested both a more rapid rise in heart rate and higher CO2 clearance with tidal volumes around 10 ml/kg[113,114]. On the other hand, tidal volumes between 8 and 15 ml/kg have been shown to induce lung damage in animal studies[115,116]. What's more, high tidal volumes have also been associated with brain damage in preterm newborns[117]. Thus, optimal tidal volumes during PPV in the delivery room remain unknown.

1.7.4 Peak inflating pressure (PIP)

PIP is the highest pressure provided during the inflation (figure 12). In order to ensure lung recruitment, the PIP must overcome both the hydrostatic pressure of liquid filled alveoli, and the recoil pressure of the lung tissue[107]. When ventilating term newborns, AHA recommends an initial PIP of 20-25 cmH_2O[66], whereas the ERC[64] and

ANZCOR[65] recommend an initial PIP of 30 cmH_2O. However, airway resistance, lung compliance, the newborn's tone and respiratory effort will vary substantially during the first minutes of PPV. Indeed guidelines acknowledge that higher inflation pressures may sometimes be needed. A recent study, conducted with a self-inflating bag without positive end-expiratory pressure (PEEP), found that tidal volumes of 9-10 ml/kg ensured the most rapid increase in heart rate in non-breathing newborns and was achieved by a PIP of 32 cmH_2O, exceeding the current recommendations[114]. The addition of PEEP during neonatal ventilation may facilitate establishment of FRC with lower inflation pressures, however, there are no studies confirming this.

1.7.5 Inflation time and rate

There is no clear evidence to determine optimal inflation times and rates during newborn resuscitation. However, inflation time must be sufficiently long to ensure an adequate tidal volume, and also to move the fluid from the alveoli into the interstitial lung tissue. Similarly, inflation rates must stay sufficiently low to ensure adequate inflation times. Guidelines differ: ERC and AHA recommend inflation times <1 second, ANZCOR recommend 0.3 – 0.5 seconds. ERC suggests inflation rates of 30 per minute, whereas AHA and ANZCOR recommend 40-60 per minute[64-66].

Sustained inflations

It has been suggested that sustained inflations (inflation time >5 seconds) may be an effective alternative to intermittent PPV for facilitating lung recruitment. Although sustained inflations have appeared beneficial in preclinical studies[118-120], no evidence of benefit has been found in clinical trials on newborns[121-123]. A large RCT including preterm newborns found an association between sustained inflations and an increased risk of death in the first 48 hours of life[124]. ILCOR suggest against sustained inflations due to lack of convincing evidence to support it. ECR has suggested an alternative approach by recommending five "opening" ventilations for 2-3 seconds[64].

1.7.6 Positive end-expiratory pressure (PEEP)

PEEP is the retention of a small intra-alveolar pressure at the end of expiration (Fig 12). Adding PEEP during PPV counteracts lung recoil and prevents the lung tissue from collapsing, causing atelectasis. It also alters the pressure gradient preventing the liquid from re-entering the alveoli. Its effect has been proven beneficial for the establishment of FRC in animal studies[125,126]. The effect in term-newborns is however uncertain. The 2015 ILCOR guidelines concluded that no recommendation of PEEP during resuscitation could be given because of insufficient data[63].

1.7.7 Respiratory monitoring

The quality of provided ventilation is essentially indirectly determined by a response in heart rate. There are however more direct ways to evaluate provided ventilation. Guidelines suggest observing chest rise as feedback for successful inflations. However, chest rise is a poor predictor of delivered tidal volumes[127]. Some ventilation devices are equipped with a pressure display (e.g. the T-piece resuscitators), however, the appropriate PIP will vary and is poorly correlated to tidal volumes[128]. The 2015 CoSTR has suggested expired CO_2 as a potentially more sensitive marker of effective ventilation than heart rate[63]. Expired CO_2 is however also dependent on metabolism and pulmonary circulation, adding complexity to its interpretation[113]. Respiratory function monitoring provides a simultaneous display of pressure, tidal volume, ventilation frequency and possibly expired CO_2. Studies have suggested that it may improve the quality of PPV in the delivery room[129-133].

1.7.8 Devices for providing respiratory support

There are three commonly used devices for providing PPV in newborns: the flow-inflating bag, the self-inflating bag, and the flow-dependent T-piece resuscitator[134-136]. Both the flow inflating and the self-inflating bag are referred to as bag-and-mask ventilators, sharing similar function and ventilator techniques. Resuscitation with a T-piece resuscitator compared with a self-inflating bag has been shown to be beneficial, e.g. in terms of reducing the duration of PPV and risk of bronchopulmonary dysplasia in premature newborns[137-140]. There are however no studies that show a benefit of the

T-piece resuscitator in term newborns. Thus, ILCOR states that there is insufficient data to suggest one device over another for resuscitating term newborns[63].

The self-inflating bag

The self-inflating bag is the most frequently used device globally[141]. Its greatest advantage is that it is relatively inexpensive and does not require a pressurized-gas source to operate. The delivered PIP depends on the operators squeeze, necessitating some experience to maintain a consistent inflation pressure. For many this is looked upon as a disadvantage. For others, this permits an easier and more rapid accommodation of changes in airway resistance during resuscitation. Most self-inflating bags have a pop-up valve that relieves pressure exceeding a set threshold, usually 35 cmH_20. However, it is possible to seal this valve when a higher PIP is desired.

Figure 7 A self-inflating bag used in our hospital (Laerdal Silicone Resuscitator™, Laerdal Medical, Stavanger Norway). Photo: P. Bjorland

The T-piece resuscitator

T-piece resuscitators such as the flow-dependent NeoPuff™ (Fisher&Paykel Healthcare, Auckland, New Zealand) have increased in popularity as a first-line device due to ease of use and the ability to provide a steady PIP and PEEP. The t-piece resuscitator is relatively costly compared to the self-inflating bag. This, in addition to its dependence on external gas sources makes it unavailable in most low-resource settings.

The T-piece resuscitator relies on pressurized gas. The gas flow to the device is set to 8-10 litres/minute[64]. The inflation pressure is then regulated by the flow of air delivered from the device to the newborn through a patient supply line. The T-shaped coupling at the patient-end of the supply line has a PEEP adjustment cap, acting as a valve, and the PEEP is regulated by turning the cap clock or anti-clock wise. By occluding the PEEP-cap with a finger, PIP is applied to the newborn.

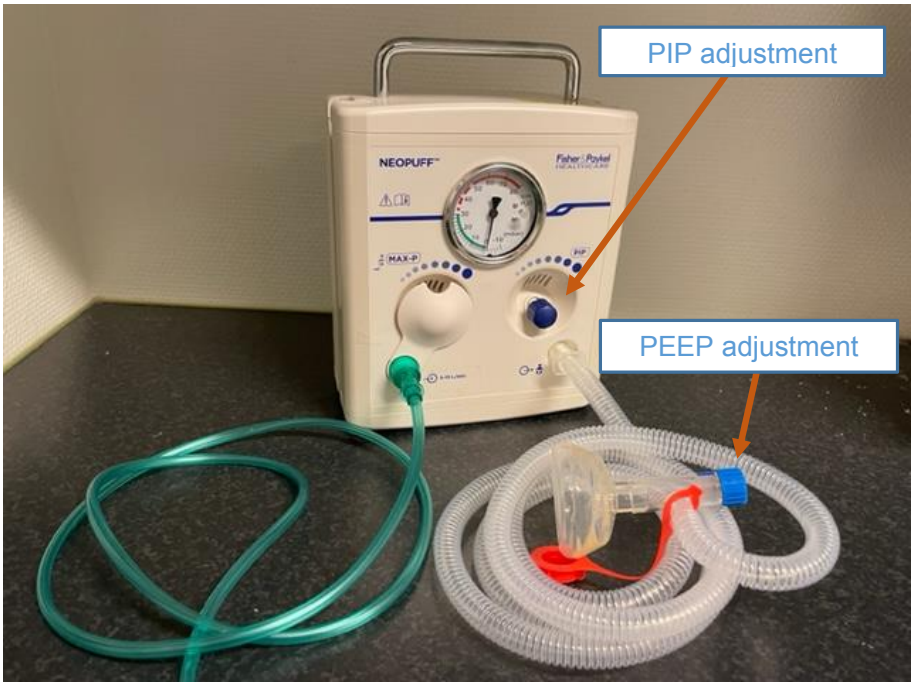


Figure 8 A T-piece resuscitator used in our hospital (NeoPuff from Fisher & Paykel). PIP: Peak Inflating Pressure. PEEP: Positive End-Expiratory Pressure. Photo: P.Bjorland

When resuscitating term newborns with a T-piece resuscitator, guidelines recommend a standard setting of 30 cmH_2O for PIP and 5 cmH_2O for PEEP[63,64]. The set PIP (and PEEP) can be adjusted during the resuscitation, but some hands-off time is necessary to do so. Although T-piece resuscitators deliver a consistent PIP, airway resistance, lung compliance, and the newborn's tone and respiratory effort will vary substantially during the first minutes of PPV. Thus, a single set PIP is unlikely to result in appropriate tidal volumes in all neonates. Furthermore, the inflation time and rate are also likely to affect the delivered tidal volume. However, the optimal inflation time and rate have not been determined.

1.8 Postface/summary

The global burden of perinatal asphyxia is substantial, and largely preventable. The respiratory and circulatory adaptions undergone at birth are complex. As much as three to eight percent of all newborns require support to make this transition, however this may vary between different countries and settings. Resuscitation guidelines prioritize tasks and define time frames for intervention, although complying with those time frames are not always feasible. Heart rate assessment plays an essential role during resuscitation, yet knowledge on normal heart rate at birth is limited. Furthermore, the optimal method of heart rate monitoring during resuscitation is debated. Respiratory support is often provided by T-piece resuscitators, however its ventilatory effects in term-born newborns have not been described. ILCOR is committed to "periodically developing and publishing a consensus on resuscitation science". They also provide a summary of "gaps in knowledge", addressing fields of interest for future studies. These prospective observational studies aim to narrow some of the identified gaps.

2. Aim of the thesis

The overall aim of this thesis has been to provide new knowledge in central aspects of newborn resuscitation, in a real-world setting.

The specific aims were:

2.1 Study I – the incidence of newborn resuscitation

In an unselected population in a high resource setting

- To study the incidence and characteristics of newborn resuscitative interventions during the first minutes of life
- To assess the short-term outcomes after resuscitation.

2.2 Study II – compliance with the resuscitation algorithm and reliability of heart rate monitoring

In apnoeic or inadequately breathing late-preterm and term newborns

- To describe if time from birth to initial assessment of heart rate and initiation of PPV comply with current guidelines
- To compare the efficacy of PO versus ECG in providing a reliable heart rate signal during real-life newborn resuscitation.

2.3 Study III – Normal Heart rate

- To describe the normal heart rate during the first minutes after birth in uncompromised term newborns delivered vaginally and undergoing delayed cord clamping

2.4 Study IV - To study positive pressure ventilation

In non-breathing term newborns ventilated with a t-piece resuscitator at internationally recommended pressure settings of 30/5 cmH_2O.

- To describe PIP and PEEP, tidal volumes, mask leak and lung compliance
- To study the association between PIP, inflation time, inflation rate and achieved tidal volumes

3. Methodology

3.1 Setting

This study was conducted at Stavanger University Hospital located in Stavanger, Norway. Stavanger University Hospital serves a population of 330,000 and is the only hospital in the region with delivery and newborn services. In 2016, the hospital had approximately 4700 deliveries; witch slowly declined over the next five years to approximately 4300 deliveries in 2021.

The neonatal department consists of a level three neonatal intensive care unit, providing care for newborns GA≥23. Newborns with antenatally diagnosed severe cerebrospinal-, cardiac- or gastrointestinal malformations requiring surgery immediately after birth are delivered elsewhere. This accounts for less than ten pregnancies each year.

The department of obstetrics includes a midwife-run low-risk delivery unit, a general labour ward, and an operating theatre for elective and emergency caesarean sections. The midwife-run delivery unit is responsible for approximately one third of all vaginal deliveries. The overall caesarean section rate is approximately 16%.

Each of the three delivery sites has a centrally placed resuscitation room with a main resuscitation bay with monitoring and resuscitation equipment. The distance from the delivery rooms to the resuscitation room varies between three and 20 meters (mean 12 meters). For caesarean sections, the resuscitation room is adjacent to the operating theatre. A backup resuscitation bay can be used in case of, for example, twin deliveries. In cases of extreme preterm deliveries (GA<28), a fully equipped mobile incubator (GE Giraffe Incubator) is brought from the neonatal intensive care unit for convenient transportation back to the neonatal intensive care unit after stabilization.

3.1.1 Resuscitation team, training, and guidelines

A resuscitation team is called upon for high-risk deliveries (i.e. shoulder dystocia, pathologic foetal heart rates and emergency caesarean sections), consisting of a paediatric resident and/or a consulting neonatologist and the midwife or nurse-assistant

responsible for the delivery. A neonatal nurse, an anaesthesiologist and/or an anaesthetic nurse can be called upon if needed. All staff involved in newborn resuscitation undergo regular simulation-based training with fortnightly in-situ simulation sessions for those on duty, and a yearly whole-day simulation training session.

National resuscitation guidelines are based on the guidelines from ILCOR, ERC, AHA and ANZCOR. Apnoeic or inadequately breathing newborns not responding to drying and stimulation have the umbilical cord clamped and cut, and are without delay brought to the resuscitation bay. Assessing the initial heart rate (by stethoscope or palpation) and initiating PPV should be accomplished within 60 seconds after birth. Continuous heart rate monitoring should be established, either by PO placed around the newborn´s right wrist or hand and/or gel-electrode ECG applied to the newborn´s chest in newborns requiring PPV. The order of heart rate sensor application, PO and/or ECG, is left to the discretion of the resuscitation teams.

3.2 Equipment and data sources

3.2.1 Standard Equipment during resuscitation

Each resuscitation bay (Dräger Babytherm®, Drägerwerk AG & Co, Lübeck, Germany) is equipped with a radiant heater, suction device, oxygen blender, self-inflating bag without PEEP (Laerdal Silicone Resuscitator™, Laerdal Medical, Stavanger Norway), T-piece resuscitator (NeoPuff) and instruments for endotracheal intubation and intravenous access. Our patient monitors (Carescape B450, General Electrics, Boston, MA) use the Masimo LNCS Neo wrap-around sensor (Masimo, Irvine, CA, US) for PO monitoring and the Neonatal ECG electrodes (CareFusion San Diego, CA, US) for ECG monitoring.

The airflow of compressed gas to the NeoPuff is routinely set at 8 litres per minute. PIP is set at 30 cmH_20 and PEEP at 5 cmH_2O, in accordance with resuscitation guidelines. Settings are checked by midwives once every 8-hour shift, and are to be crosschecked by the resuscitation team on arrival at the resuscitation bay.

3.2.2 Data sources

The following sources for data collection were implemented for this study:

Video recordings of resuscitation (*Paper I, II*, and *IV*)
Recordings of ECG and PO signals from the patient monitors (*Paper I and II*)
The Liveborn tablet application (*Paper III* and *IV*)
The NeoBeat heart rate meter (*Paper III*)
Respiratory data from the Laerdal Newborn Resuscitation Monitor (*Paper IV*)

In addition we extracted patient data from the electronic patient journals for all papers.

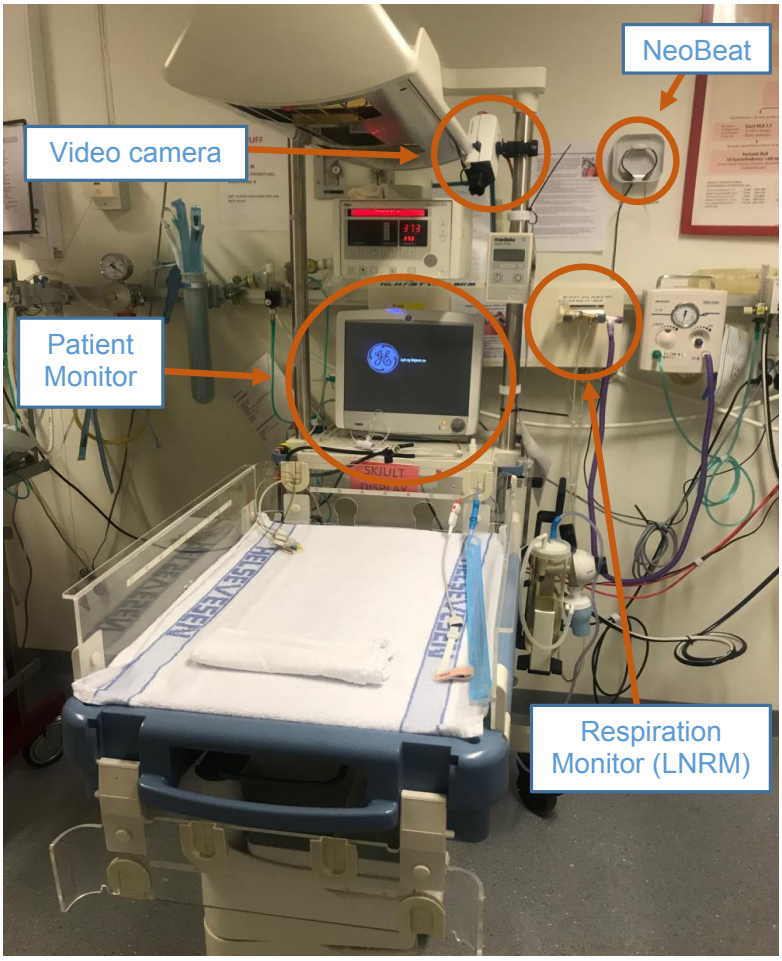


Figure 9 Photo of the resuscitation bay with the equipment used for data collection. LNRM: Laerdal Newborn Resuscitation Monitor. Photo: P. Bjorland

Video recordings of resuscitations

Carbine et.al introduced video recording as a reliable tool for investigating neonatal resuscitation in 2000[72], and it has since then been commonly used in observational studies on the subject[67-71]. Video recording allows for detailed assessment of incidences, performance, and real-life feasibility of resuscitation guidelines. For this project, a high definition video- and voice recording camera was mounted above the main resuscitation bay at each delivery site. The cameras had a motion sensor, and would automatically record whenever detecting movement within the defined field of view. To prevent recordings going astray, the cameras did not have internal storage. Instead, a cabled network was installed, from each delivery site and to a centrally placed server with restricted access, where all videos were recorded.

The secondary resuscitation bays are seldom used, and due to economic and technical limitations, they were not equipped with cameras. One additional camera was mounted on a stand that could easily be attached to the NICU`s mobile incubator. In order to record resuscitation of premature newborns, staff would have to attach the stand to the mobile incubator and plug the camera in to a network point for data transfer.

Figure 10 Screenshot of a video-recorded resuscitation (demonstration with a manikin). Photo: P. Bjorland

The patient monitors (Carescape B450) have a video-out port meant for slave monitors. We used this port to extract the signals displayed on the patient monitor and recorded them as a separate video stream. These recordings were transformed through the cabled network and stored synchronically with the recordings from the video camera. This way, both the newborn and the patient monitor was clearly visible during analysis.

For viewing and analysing the recordings, we used the video management software: XProtect® Smart Client (Milestone, Copenhagen, Denmark). For patient and personnel privacy purposes, all video recordings were automatically erased three weeks after capture, in agreement with the approval from the hospital data protection officer.

The Liveborn app and the NeoBeat heart rate meter

The Liveborn app and the NeoBeat heart rate meter are both designed and developed by Laerdal Global health (Stavanger, Norway). The Liveborn app is a research tool used for live observations of newborn care immediately after birth. The app generates a timeline from birth where specific tasks are marked, i.e. stimulation, suction, cord clamping, assessment of heart rate, and ventilation.

NeoBeat is a novel neonatal heart rate meter. Instead of gel-electrodes used in traditional 3-lead ECG, NeoBeat uses dry electrodes, which makes skin drying prior to application unnecessary. The dry-electrodes are incorporated in an abdomen-shaped circlet, which can be easily applied around the newborns abdomen. Studies have shown that dry-electrode ECG is equally reliable and accurate on newborns as compared to a conventional 3-lead ECG[142,143]. NeoBeat displays the measured heart rate to the caregivers, but can also transfer heart rate measurements via Bluetooth to the Liveborn app timeline (figure 11).

Heart rate monitoring immediately after birth and during handling of the newborn, are prone to ECG distortion due to motion. To ensure reliable measures, the heart rate algorithm of the NeoBeat is based on a zero-crossing count algorithm adding a proprietary layer that includes noise detection and noise handling[144]. This algorithm takes into account different sources of ECG distortions, such as acceleration energy,

amplitude, and rate variability, to determine when there is likely too much motion to get a reliable heart rate.

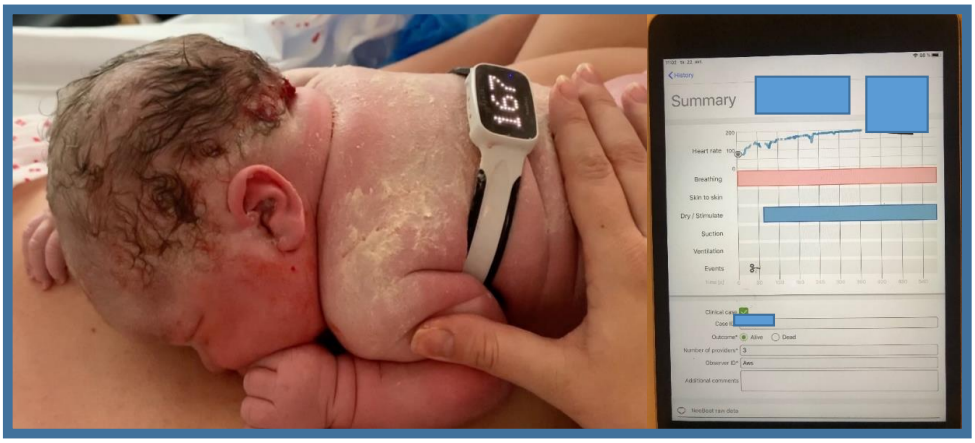


Figure 11 Photo of heat rate recording and the Liveborn app timeline. Photo of the newborn is printed with permission from the parents. The Liveborn registration is not representing the newborn in the photo. Photo: S. Rettedal and P. Bjorland

The Laerdal Newborn Resuscitation Monitor

The Laerdal Newborn Resuscitation Monitor (LNRM) is a patient monitor designed by Laerdal Global Health (Laerdal, Stavanger, Norway) for research purposes[145]. It has sensors to detect newborn heart rate and respiratory parameters such as airway pressure, flow, volume and expired CO_2. For our study, we used the LNRM as a respiratory monitor, measuring only pressure, flow, and volume. The CO_2 sensor was disconnected, as the required maintenance of the CO2 sensor was not feasible within our project.

The LNRM has a hot-wire anemometer flow sensor (MIM Gmbh, Krugzell, Germany) to measure airflow and volume, and a piezo resistive pressure sensor (MPXV5010, Freescale Semiconductor Inc, Austin, TX) to measure airway pressures. Both sensors were connected between the T-piece and the facemask. The flow sensor and its

electronics are the same as used in the Florian respiration monitor and has negligible flow resistance and dead space (1 ml).

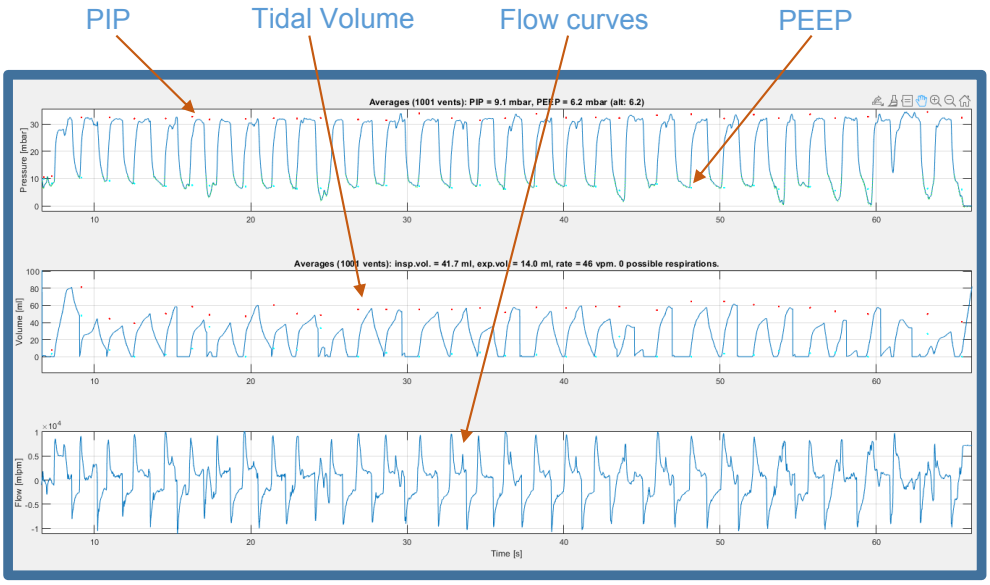


Figure 12 Graphical presentation of pressure-, volume- and flow-curves from a resuscitation episode. PIP: Peak inflating pressure, PEEP: Positive End-Expiratory Pressure.

The LNRM function monitor has a lever formed to hold the T-piece and mask when not in use, and lifting up the T-piece will initiate recording. Events are stored the LRNM`s internal memory as reports that are tagged with the date and time of recording. The reports can be uploaded to a computer through a USB-port.

3.3 Study design, timeline, and population

3.3.1 Design

All four studies in this thesis are prospective observational studies. *Study I* and *III* are descriptive, whereas *study II* and *IV* are both descriptive and analytic.

3.3.2 Study timeline

The studies in this thesis are based on data collected in two time periods.

In 2016, we planned and launched a project of video recording newborn resuscitation for research purposes. After acquiring ethical and legal approval, we installed camera equipment and tested the routine and equipment during a pilot phase. Finally, resuscitations were recorded and analysed from October 1st 2016 until September 30th 2017. Studies I and II are based on data from this data collection.

In 2019, we implemented a larger research program in our hospital, the Safer Births Bundle, collecting data on newborn transition and resuscitation. In addition to the camera equipment already installed, the data collection was extended to include heart rate measurements of all newborns immediately after birth obtained by the NeoBeat and time of birth and cord clamping logged in the Liveborn app, and collection and storage of ventilation data during PPV by the LNRM. The data used in *Study III* and *IV* were collected as part of the Safer Births Bundle project.

3.3.3 Sample size calculations

Study I

Incidence of resuscitative measures are reported to be between three and eight percent in different settings[67-69,75,78-80]. With a sample size of 5000, we would then be able to estimate an incidence of 5% with a precision of +/- 0.6 percentage points and an incidence of 0.5% with a precision of +/- 0.2 percentage points. By collecting data over a one-year period, we aimed at a sample size of 4500-5000 newborns.

Study III

Using a standard deviation for the heart rate of 21 bpm, as reported by Linde et al.[103], a sample-size calculation showed that ≥ 68 observations were needed at each second to estimate the median heart rate with a margin of error of less than ±5 bpm. To obtain a margin of error of less than ±5 bpm for the estimate of the 10th and 90th centiles, sample size calculations showed that at least 482 observations were required[146]. We planned to include 500-1000 newborns to ensure sufficient good-quality data.

Due to the explorative nature of the studies, no sample size calculations were considered necessary for *study II* and *IV*.

3.3.4 Study population

The inclusion criteria and periods of data collection differed between the four studies:

Study I

For reporting incidence and characteristics of resuscitative interventions, we included all inborn newborns from October 1st 2016 through September 30th 2017. All premature newborns <34 weeks of gestation are routinely admitted to the NICU, and the level of intensive care and outcome is strongly related to their prematurity and difficult to separate from consequences of resuscitative interventions. Thus, we included only newborns ≥34 weeks of gestation for the description of short-term outcomes after resuscitation.

Study II

For the assessment of guideline compliance and heart rate monitoring during newborn resuscitation, all newborns of GA≥34 weeks born from October 1st 2016 through September 30th 2017, and who received PPV at birth, were eligible for inclusion. Only newborns who were apnoeic or with inadequate respiratory effort (e.g. grunting or severe retractions) were included.

Study III

This study used data collected from March 2019 through august 2019. All vaginally delivered term newborns (GA≥ 37) were eligible for inclusion. We excluded newborns in need of assisted delivery (i.e. vacuum or forceps), and newborns who received any medical interventions (e.g. supplementary oxygen or assisted ventilation) after birth.

Study IV

This study used data collected from June 2019 through March 2021. All apnoeic term newborns who received PPV by NeoPuff after birth were eligible for inclusion. We excluded newborns for whom we did not have LNRM data. In addition, newborns

ventilated with a self-inflating bag and newborns with congenital malformations were excluded.

3.3.5 Data collection

Study I and II

During the study period, an *incident report form* (figure 13) was completed for every newborn, documenting the time and mode of delivery (vaginal delivery or caesarean section), gestational age and if the newborn received resuscitative interventions within the first five minutes after birth. We defined resuscitative interventions as one or more of the following: CPAP, PPV, endotracheal intubation, chest compressions, and intravenous administration of fluids or drugs. The incident report forms were continuously crosschecked against the birth record, ensuring that every birth was included. Waiver of consent was approved for the completion of the incident report forms, so that the data collection were complete and population-based.

When video recordings were available (that is if the newborn was treated at one of the main resuscitation bays with a camera installed, or in case of preterm deliveries, the mobile camera was attached and connected) we approached parents and asked to analyse the video recordings and to obtain relevant data from the newborns medical journal. Parents were entitled to watch the recordings at their own request, but no copies were provided. To protect patient and provider privacy, all recordings were automatically erased three weeks after capture. Thus, the video had to be analysed within this timeframe.

To determine the time from birth to resuscitative interventions the nurse-assistants were instructed to start a stopwatch at all deliveries, at the time when the whole body was delivered. If newborns were brought to the resuscitation bay, the stopwatch showing the exact time from birth was to be presented to the camera.

Gender, weight, APGAR score and umbilical cord blood samples were retrieved from the electronic medical journals.

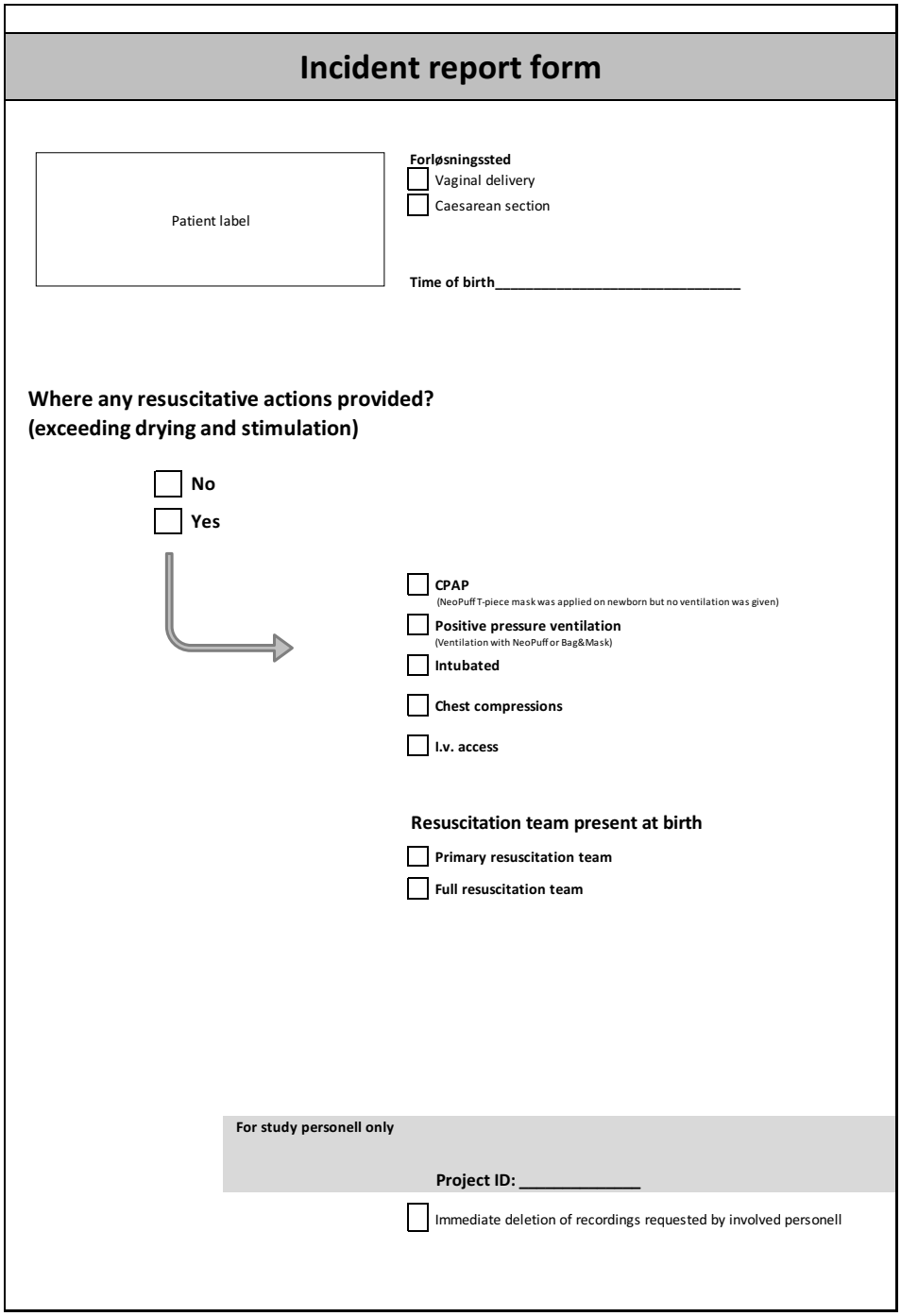


Figure 13 Incident report form used for documenting if the newborns received resuscitative interventions after birth.

Study III

As part of the Safer Births Bundle project, parents received written information and were invited to consent to their newborn's participation in the study at routine ultrasound screening in pregnancy week 20 and participation was registered in the maternal medical journal. When parents were admitted to the birth department in labour, birth attendants asked whether they had – or would – consent to participation. If so, a study ID was assigned.

Each delivery room was equipped with a NeoBeat, and each delivery site had several tablets (iPad, Apple, Cupertino, CA) with the Liveborn app installed. If parental consent was obtained, an assisting midwife or the nurse assistant attending the birth carried a tablet and marked the exact time of birth (i.e. time when the whole body was delivered) in the Liveborn app and the NeoBeat was applied to the newborn immediately after birth. Heart rate was then measured for at least five minutes, or until the cord was clamped if this occurred beyond five minutes. Heart rate was recorded every second and consecutively transferred to the Liveborn app, where also the time of cord clamping was registered. The NeoBeat would not provide heart rate if it detected that the signal was too distorted with noise or motion artefacts. Upon completion of the registration, the report would be labelled by the study ID.

Before study commencement, midwifes and nurse assistants were trained in the use of the NeoBeat and the Liveborn application using manikins, and data collection was trialled during a pilot phase. Data collection did not interfere with the routine management of the newborns after birth. Patient and birth characteristics were extracted from the medical record.

Study IV

The process for obtaining parental consent was the same as for study III. Whenever a term newborn received PPV, video recordings were analysed to assess the respiratory state of the newborn on arrival at the resuscitation bay, to confirm that PPV was provided by the NeoPuff, and the duration of PPV. The time from birth to initiation of PPV was identified by comparing the time of birth in the Liveborn app and the time

counters on the video recordings (both having their timestamps automatically synchronized by a *network time protocol server*).

The ventilation parameters would then be manually uploaded through a USB-port on the LNRM. Although the internal time stamp of the LRNM was not fully synchronized with the video and Liveborn, the reports closest in time would be uploaded. The correct report would then be confirmed by comparison with the video recordings.

3.4 Data analyses and statistics

The statistical analyses and the drafting of plots and figures for all papers included in this thesis were done by the PhD-candidate using SPSS (SPSS Inc., Chicago, IL, USA) for *Paper I* and R-studio (R Core Team 2019, Vienna, Austria) for papers II-IV. Supervisors Siren Rettedal, Hege Ersdal, and Knut Øymar participated in choices of outcome measures and presentation of results. Anastasia Ushakova from the department of Biostatistics aided with statistical advice for *Paper III*, and contributed significantly to fitting the statistical models of *Paper IV*, where she was also invited as co-author.

Study I

The PhD candidate analysed all video recordings according to a Standard Operating Procedure (figure 14). We defined short-term outcomes as either death, survival and returned to parents, or survival and admitted to the NICU. Further, we characterized level of intensive care by length of stay, therapeutic hypothermia, mechanical ventilation, pneumothorax, hypoxic ischemic encephalopathy, and death.

Statistical analyses were mainly descriptive, estimating incidence of categorical outcomes and medians and interquartile ranges of continuous outcomes. Comparison between groups was done by Mann-Whitney U test for continuous variables and Chi-square test for categorical variables (Fisher`s exact test if expected counts were <5). A p-value <0.05 was considered statistically significant.

SOP

Time from birth to arrival at the resuscitation bay (if the stopwatch is presented to the camera during treatment)		
Respiratory effort: (at arrival)	Apneic	
	Inadequate (e.g. grunting or severe retractions)	
	Adequate (e.g. crying or showing mild or moderate retractions)	
Drying and stimulation:	Consider adequate if the newborn received tactile truncal stimulation (drying, chest- and back rubs) prior to respiratory support	
Initial heart rate assessment:	By stethoscope	
	By palpation	
	None	
Application of PO:	Time to (first attempted) application.	
	Time to reliable signal (≥3 seconds with continuous pulse waves and stable pulse)	
Application of EKG:	Time to application (when all three electrodes are attached to the newborns chest)	
	Time to reliable signal (regular QRS complexes and heart rate corresponds to RR-intervals)	
PPV	Time to initiation of PPV	
	Duration of PPV	
Intubation:	Indication for intubation	Failed mask ventilation
		Chest compressions
		Need for prolonged respiratory support)
	Intubation attempts (each laryngoscopy counting as one attempt)	
	Duration of intubation (defined as time from PPV ceases prior to intubation until PPV resumes after intubation).	
Chest compressions	Time to initiation of chest compression from birth and arrival at resuscitation bay	
	Duration of chest compressions	
Intravenous access	Type of access	
	Fluid bolus	
	Epinephrine	

Figure 14 Standard Operating Procedure (SOP) for analyzing resuscitations

Study II

Video recordings confirmed whether the newborn was apnoeic or had inadequate (e.g. grunting or severe retractions) respiration. Drying and stimulation was considered adequate if the newborn received tactile truncal stimulation (drying, chest- and back rubs) prior to respiratory support as opposed to excessive stimulation for longer than 15 seconds, or none at all[147]. We registered time to and mode of initial heart rate assessment, time to initiation of and duration of PPV, and time to PO and/or ECG sensor application as well as time to reliable heart rate signals. Reliable PO signals were defined as a continuous pulse wave and heart rate values for at least three seconds. Reliable ECG signals were defined as regular QRS complexes. These definitions of reliable PO- and ECG-signals were in accordance with previously published studies[100,101,148]. The time to reliable heart rate monitoring were compared between newborns with 5-minute Apgar <7 and ≥7[149].

Groups were compared with Mann-Whitney U test for continuous variables and Fisher`s exact test for categorical variables. A p-value <0.05 was considered statistically significant.

Study III

Before statistical analysis, the collected heart data was processed using Mathlab (MathWorks, Natric, MA) where heart rate registrations suspected to be erroneous were filtered. After analysing heart rate reports and potential sources of error during data collection, there was consensus in the group in exclusion of data when the heart rate was registered by the ECG before the recorded time of birth (suggesting birth registered too late, n=75). Feedback from birth attendants did in fact reveal that the NeoBeat occasionally was applied to the newborn before the whole body was delivered, probably explaining some of registrations where ECG signals preceded time of birth. However, the number of registrations were relatively few the first 10-15 seconds, so that biased registrations would have had a relatively large impact.

We also excluded data if less than 30 seconds of heart rate was recorded during data collection (suggesting low signal quality, n=19).

With the database being completed, further calculations and drawings of centile charts where performed in R-studio. The 3rd, 10th, 25th, 50th, 75th, 90th, and 97th centile were calculated for each second until five minutes after birth. Then centile charts were fitted using Local Polynomial regression (LOESS, or Locally Estimated Scatterplot Smoothing)[150]. LOESS is a non-parametric regression model fitting localized subsets of data in series. This means that it estimates a “true” mean at any given point (here second) by also including nearby points in the model (here meaning one second before or after).

In accordance with our power-calculations (chapter 3.4.3), we did not present curves until we had at least 68 heart rate registrations, which occurred from five seconds after birth.

Study IV

Every report contained PIP, PEEP, tidal volume, leak, dynamic lung compliance, inflation time and instant inflation rate of each inflation. PIP and PEEP was measured in mbar, where one mbar equals 1.02 cmH_2O. Leak was defined as the difference between inflated and expiratory volume as percentage of inflated volume. The dynamic lung compliance was calculated as the inflated volume divided by PIP. Instant inflation rate was defined as 60 divided by the time interval between current and previous inflation.

We were most interested in the first minutes of ventilation. Our data confirmed the findings of study one, that most newborns were only ventilated for a few minutes. Hence, to prevent the overall statistics from being biased by those few newborns who were ventilated for a considerably longer period, we decided to only include the first 100 inflations from each newborn.

We defined the first 20 inflations as a phase of lung recruitment and establishing FRC[106]. The following 80 inflations were defined as a phase of ventilating lungs with established FRC. We then compared variables between the early and the late phase using Mann-Whitney U-tests.

We used Generalized Estimating Equations (GEE) to model the dynamics of different variables throughout the resuscitation. GEE reveals a population average effect as opposed to a more individual specific effect from the general linear mixed models[151]. The inflation number was used as the predictive value, and to correct for the dependencies between measurements from the same newborn, we chose a first-order autoregressive covariance structure.

When studying the relationship between PIP, inflation time, and inflation rate and the tidal volume, we excluded extreme values of PIP, inflation time, and inflation rates that we considered irrelevant in this setting.

The smoothed estimates of the correlations revealed a relationship with a sudden shift in slope. Using breakpoint analysis, we identified breakpoints suggesting thresholds

where e.g. further decrease in PIP or inflation time would lead to a marked reduction in tidal volumes.

3.5 Ethical approval, consent and safety issues

Study I and II

The regional ethical committee (2015/1162/REK vest) first evaluated the project. They considered the study to be mainly health service research and non-interventional, thus it was outside their mandate to approve. Instead, they recommended local approval by the hospital data protection officer. The data protection officer then approved the project after consulting with the national Data Inspectorate. Acknowledging the sensitivity in storing video recordings of critical situations, security and access restriction of the stored data was prioritized. In addition, the maximum length of storing the video recordings was set to three weeks.

In order to ensure that the reported incidence was complete and population based, the hospital data protection officer gave permission to record incidence data (i.e. the *observational incident report form*) without parental consent (waiver of consent). We video recorded all resuscitations, and then subsequently asked for parental consent to analyse the video recordings (Deferred consent).

If personnel wanted reservation from participating, this was anonymously marked on the observational incidence report form. If this was marked, parental consent would not be obtained and the video would be deleted without further analysis.

Both parents and personnel involved in a resuscitation were permitted to watch the recordings upon request. However, we did not provide copies.

Study III and IV

The data for *study III* and *IV* were collected as part of the Safer Births Bundle project. As the Safer Births Bundle project includes an interventional study[152], and extends data collection to also include newborns not resuscitated, parental consent needed to be obtained before data collection. Written information about the study was handed out to

the parents at the routine ultrasound screening in pregnancy week 20, with an invitation to participate in the study. The consent included all parts of data collection as part of the project, including heart rate data, ventilation data and video recording of resuscitations. This project was approved by the regional ethical committee as well as the local data protection officer (REK Vest 2015/2056).

4. Summary of the results

4.1 Paper I

4.1.1 Incidence of resuscitative measures

We included 4693 newborns in the incidence analyses, of which approximately 5.7% were born premature (GA<37). In total, 291 (6.2%) newborns were respiratory and/or circulatory supported after birth. The provided support was mainly respiratory, with 170 (3.6%) and 121 (2.6%) receiving PPV or CPAP, respectively. Circulatory support was rare with 18 (0.4%) newborns receiving intravenous fluid boluses or adrenaline and 10 (0.2%) newborns receiving chest compressions. Chest compressions were most commonly discontinued within a few minutes. The incidence of resuscitative measures was unevenly distributed between different gestational age groups, and are presented in Paper I/Table I.

Paper I/Table 1 - Incidence of resuscitative interventions during one year at Stavanger University Hospital

Gestational age group	**<28**	**28-33**	**34-36**	**37-41**	**≥42**	**Total**
Total number of newborns	**13**	**61**	**190**	**4318**	**111**	**4693**
Interventions provided in	**13 (100%)**	**47 (77%)**	**19 (10%)**	**199 (4.6%)**	**13 (12.6%)**	**291 (6.2%)**
CPAP only	0	24 (39%)	7 (3.7%)	85 (2.0%)	5 (4.5%)	121 (2.6%)
Positive Pressure Ventilation	13 (100%)	23 (38%)	12 (6.3%)	114 (2.6%)	8 (7.2%)	170 (3.6%)
Intubation	7 (54%)	2 (3.3%)	1 (0.5%)	9 (0.2%)	0	19 (0.4%)
Chest compression	0	1 (1.6%)	1 (0.5%)	8 (0.2%)	0	10 (0.2%)
Intravenous Adrenaline	0	0	0	3 (0.1%)	0	3 (0.1%)
Intravenous Fluid Bolus	0	1 (1.6%)	2 (1.1%)	12 (0.3%)	0	15 (0.3%)

Incidence is presented as n (percentage of newborns in the same group) CPAP = Continuous Positive Airway Pressure

4.1.2 Short term outcomes of resuscitated near-term and term newborns

We obtained parental consent to retrieve data from the medical journal in 204 of the resuscitated newborns GA ≥34. Of those, 128 (63%) were returned to parental care after stabilization, including two newborns who were given chest compressions. The

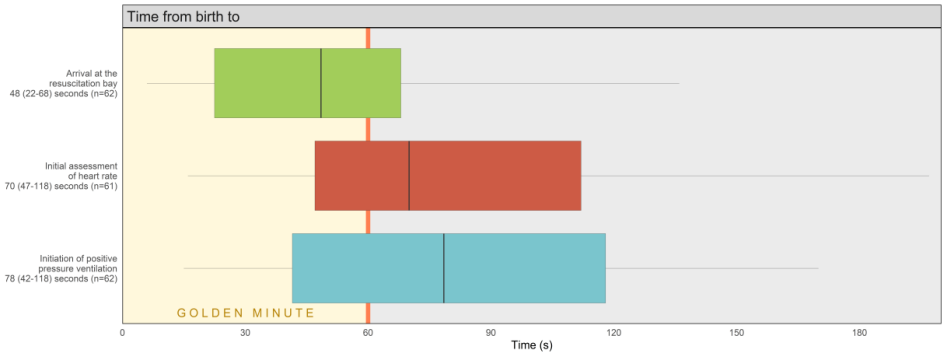
remaining 75 (37%) newborns were admitted to the neonatal intensive care unit for further monitoring or treatment. Of those admitted to the intensive care unit, 70% were discharged within the first week. We found no difference in arterial umbilical blood gasses between newborns returned to parental care and those admitted to the intensive care unit.

4.2 Paper II

In this paper, we analysed videos from the resuscitation of 104 newborns, either apnoeic or with inadequate respiratory effort after birth.

4.2.1 Initial assessment and time to initiate PPV

After arriving at the resuscitation bay, 78/104 (75%) were considered to be adequately dried and stimulated. 99/104 (95%) of the newborns had their heart rate assessed by stethoscope (n=84) or through palpation (n=15). We recorded time from birth to arrival at the resuscitation bay in 62 ventilated newborns. Within the first minute from birth, 22 (35%) had their heart rate assessed and 22 (35%) had received PPV. The median (IQR) time from birth to initiating PPV was 78 (42-118) seconds (Paper II/Figure I).

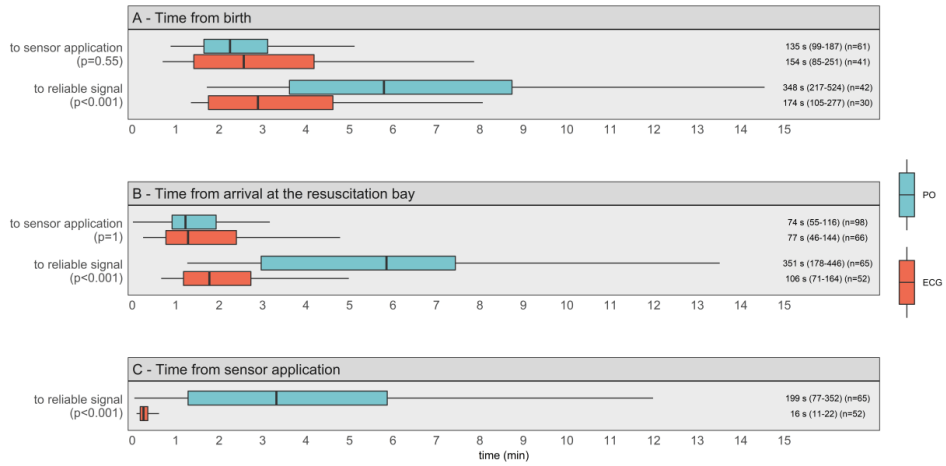


Paper II/ Figure I. Timelines from birth to arrival at the resuscitation bay, assessment of initial heart rate and initiation of positive pressure ventilation for apnoeic or inadequately breathing newborns. The boxes represent the median, first and third quartile and the whiskers represent the range without outliers. Values in headings are shown as median (IQR).

4.2.2 Heart rate monitoring by PO and ECG

A PO sensor was applied in 94% of the analysed resuscitations, whereas ECG electrodes were applied in only 63%. The time from arrival at the resuscitation bay to application of sensors did not differ between PO and ECG. In total, 85 monitor recordings of PO and 58 monitor recordings for ECG were eligible for analysis. Reliable heart rate signals were not provided in 20/85 (24%) PO recordings and 6/58 (10%) ECG recordings (p=0.110). The time from sensor application to reliable signals were significantly shorter for ECG than for PO: 16 (11-22) seconds versus 199 (77-352) seconds, respectively (p<0.001).

The time to reliable heart rate signals by PO were longer in newborns with 5-min Apgar score <7: 296 (149-393) seconds (n=25) versus newborns with 5-min Apgar score ≥7 134 (63-291) seconds (p=0.03). No such difference was seen when using ECG; 14 (11-19) seconds in the 5-min Apgar <7 group (n=20) versus 16 (12-24) seconds in the 5-min Apgar ≥7 (n=32) group (p=0.332). The difference between PO and ECG in time to obtaining reliable heart rate signals was significant for newborns in both groups (p<0.001).

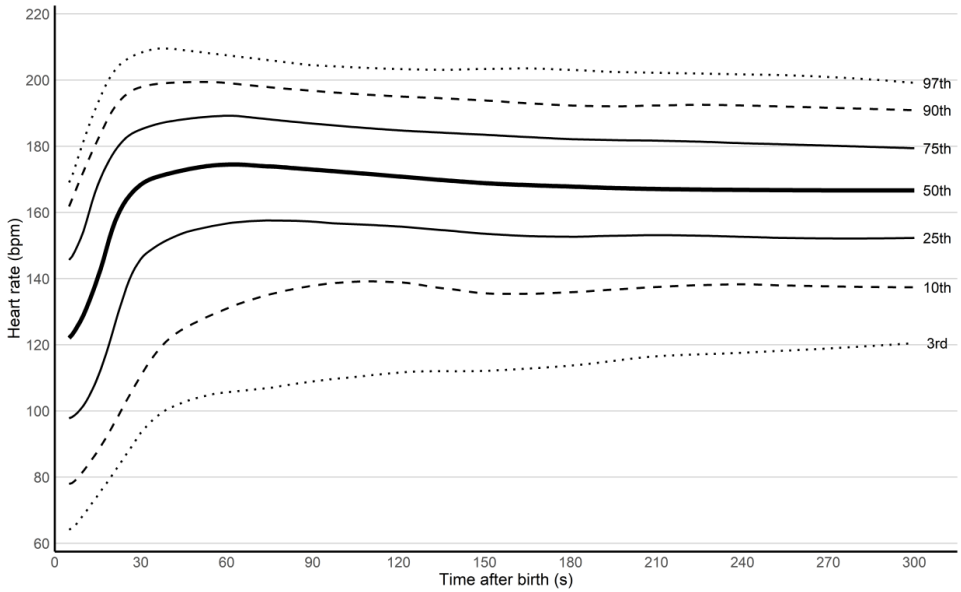


Paper II/ Figure II. Efficacy of ECG and PO in achieving a reliable heart rate monitoring during real-life newborn resuscitation. The boxes represent the median, first and third quartile and the whiskers represent the range without outliers. Values to the right of the boxplots are presented as median seconds (IQR). P-values are calculated with two-sided Mann-Whitney-u-test.

4.3 Paper III

Heart rate recordings from 898 newborns were included in the analysis. At least 68 individual heart rate measures were recorded from five seconds (n=77), and at least 482 individual heart rate measures were recorded from 14 seconds (n=510) after birth.

At five seconds after birth, the median heart rate was 123 (98-147) bpm. The heart rate rapidly increased the first minute of life until levelling at approximately 175 bpm at 61 seconds after birth. Heart rates below 100 bpm were rarely seen after the first 30 seconds of life. The median time from birth to cord clamping was 319 (244-412) seconds, and beyond the timeline of the heart rate centile chart.

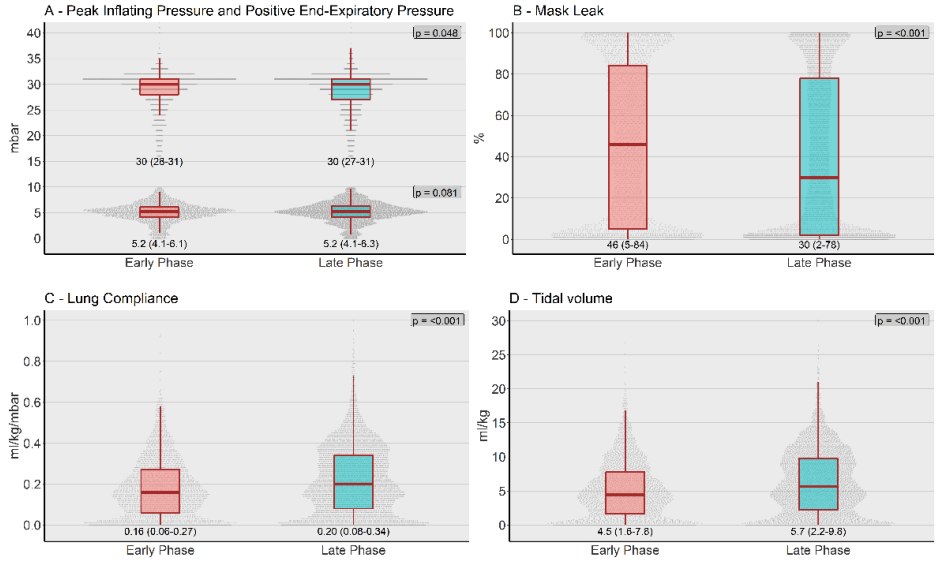


Paper III/ Figure III. The 3rd, 10th, 25th, 50th, 75th, 90th, and 97th heart rate centiles from five seconds after birth for vaginally born term newborns with delayed cord clamping and no medical intervention.

4.4 Paper IV

Respiratory data from the resuscitation of 129 term born newborns were included in the analysis, resulting in 2393 inflations in the early phase (i.e. first 20 inflations) and

4148 inflations in the late phase (i.e. inflation 21-100). Video recordings were eligible in 124 resuscitations, revealing that 109/124 (88%) of the newborns were apnoeic on arrival on the resuscitation bay, whereas 15/124 (12%) were breathing but with insufficient respiratory efforts (i.e. gasping or severe retractions).



Paper IV/ Figure II Swarm plots and boxplots of A) Peak inflating pressures and Positive End-Expiratory pressures, (B) Mask leak, (C) Lung compliance, and (D) Tidal volumes of the first 100 inflations during positive pressure ventilation of 129 term newborns after birth, and divided into an early phase (first 20 inflations, n=2393) and a late phase (inflation 21-100, n=4148). The swarm plots displays the distribution of individual observations on the y-scale. The boxes extend from the 25th to the 75th percentile; the horizontal line within the box denote median values; vertical extending lines denote range excluding outliers. Mann-Whitney U-test was used to compare variables between the early and late phase.

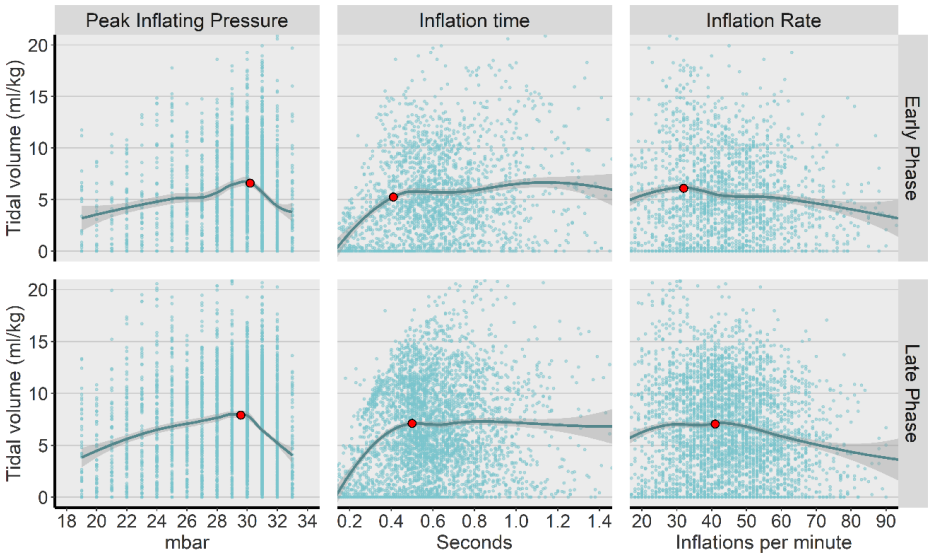
4.4.1 Delivered tidal volumes

Despite a relatively consistent delivered PIP and PEEP, the measured tidal volumes variated substantially. The median (IQR) tidal volume during the early phase was 4.5 (1.6-7.8) ml in the early phase, thus lower than the recommended range. During the late phase, the median (IQR) tidal volume was 5.7 (2.2-9.8) ml, thus in the lower end of the recommended range. Tidal volumes slowly increased throughout the first 20

inflations of the early phase, accompanied by an increase in compliance and a decrease in mask leak.

4.4.2 The impact of PIP, inflation time and inflation rate

The tidal volumes increased with increasing PIP up to 30 mbar in both the early and the late phase. Inflations where the measured PIP exceeded the set-PIP of 30 mbar were associated with lower tidal volumes. Analysis of the volume flow curves of said inflations suggested interference.



Paper IV/ Figure IV. Scatterplots illustrating the association between peak inflating pressure, inflation time, and inflation rate on delivered tidal volumes from positive pressure ventilation of 129 term newborns after birth. The blue line represents the mean value smoothed through local regression (Local Estimated Scatterplot Smoothing) with the grey band representing 95% confidence intervals. The red dots represent breakpoints from the segmented regression analysis.

Increasing inflation times resulted in a rapid increase in tidal volumes until reaching a plateau at 0.41 seconds in the early phase and 0.5 seconds in the late phase. Longer inflation times had an inferior effect on tidal volumes.

Tidal volumes started to decrease with inflation rates increasing beyond 32 per minute in the early phase and 41 per minute in the late phase.

5. Discussion

5.1 Methodological considerations

This thesis includes four prospective observational studies describing aspects of newborn transition, and more precisely the support thereof. The implementation of data collection from such critical and often unexpected events has both practical and ethical implications. In the following section, I will reflect on the strengths and weaknesses in relation to the study design and the methods of data collection, potential biases and ethical considerations.

5.1.1 Study design

As in most medical research, an overall aim when studying newborn resuscitation is to assess the causality between the different interventions and the outcome of resuscitated newborns. Although randomized controlled trials are commonly referred to as "gold standard" for investigating such causality, they are not appropriate in all clinical settings. Randomizing newborns to different treatment options during newborn resuscitations with potential lifesaving interventions raises ethical issues, and is likely to hinder recruitment.

The observational study design offers a feasible and scientifically valid alternative method[153,154]. Observational studies typically generate new hypotheses and may also reveal areas for targeting future research. Furthermore, meta-analyses suggest that estimates of treatment effects do not differ substantially between randomized controlled trials and observational studies in general[155]. As opposed to the often more controlled setting of randomized controlled trials, observational studies produce "real world data", which may strengthen their external validity. On the other hand, this "uncontrolled" setting typically makes observational studies at high risk of error through random effects. It is therefore important to include a high enough number of observations do balance out these random effects. Furthermore, thorough planning of the data collection such as a representative study population, a clear definition of the

variables, and appropriate statistical methods, may reduce the typical sources of bias in observational studies; selection bias, information bias and confounding.

Study Site

All data for this thesis were collected at Stavanger University Hospital. With approximately 4500 annual births, it is a relatively large birth centre in a national setting: it has been the fourth largest in Norway the last five years with regards to number of births[156]. Stavanger University Hospital is the only birth centre in the region, which makes it a good location for population-based studies. The rate of home-deliveries is low, and accounts for around 10 annual deliveries in our region. We offer care for premature newborns from GA 23, and only newborns with known malformations possibly in need of surgery shortly after birth are referred for delivery elsewhere. We have estimated that this account for approximately 5-10 deliveries each year. The two nearest birth departments are Helse Fonna in Haugesund, approximately 80 kilometres to the North, and Sørlandet sykehus Flekkefjord, approximately 130 kilometre to the South. Haugesund provides care for premature newborns GA>28, and Flekkefjord provides care for term newborns. Although both hospitals have other primary referral centres for premature births (Helse Bergen and Sørlandet sykehus Kristiansand, respectively), they occasionally transfer women in premature labour to Stavanger for capacity or geographical reasons. These newborns were not included in the data collection. We did not take into account newborns from our region who were delivered elsewhere (unplanned, or planned). However, this is most likely a very low number and dose not interfere with the conclusions of our studies.

Despite the hospital being suited for population-based studies, the fact that all data in this thesis are from a single centre is one of the major weaknesses. Above all, this weakens the external validity of our results. In low-resource settings, the newborn population will differ due to different access to obstetrical care and monitoring during both pregnancy and labour. Also in high resource settings, the availability of different professions and their training and experience will differ. *Paper I* measures incidence of respiratory and circulatory support after birth, without being able to evaluate if

resuscitative measures were required. The ventilatory parameters measured in *study IV* are dependent on the skill of the staff providing airway support.

5.1.2 Selection bias

Selection bias may arise if the inclusion of newborns systematically leaves out certain subgroups of the population. Even a well-planned study is at risk of excluding selected individuals. Consequently, the results may be unrepresentative for the population they were meant to describe. Our aim was to include all resuscitated newborns from an unselected population. Our primary sources of errors due to selection are missing consent and missing data.

Selection due to missed consent

For studies I and II, where parents were approached after the newborn had been resuscitated, only 12% and 7% of the newborns were excluded from analysis due to missing consent. In *study III* and *IV*, where consent was asked for before birth, the rate of missing consent was higher: 25% and 20% respectively.

It would seem that the time of approach affects the rate of parents consenting to participate in these studies. Parents of newborns who recently were in need of treatment after birth are probably more aware of the value of the project. Also, in *study I* and *II*, informed consent was mostly asked for by the doctoral candidate, who is also a consultant neonatologist at the NICU. Hence, their decision to participate may be motivated by a sense of dependency towards the NICU department. This may explain the higher rate of missed consent in *study III* and *IV*, where consent was obtained by midwifes during either early screening or admission in labour.

In *study I* and *II*, we aimed to approach parents to ask for consent while they were still at the hospital. As most newborns are discharged from the hospital within a few days from birth, this was not always applicable, and consent was occasionally requested by mail. It was our experience that parents, with only a few exceptions, consented to participation when asked during hospital stay. The response rate on consent requested by mail however was low, or often did not reach us within the allowed video storage time of three weeks. This way, the missed consent group are mostly represented by

newborns either not severely compromised, or rapidly responding to treatment, affording them an early discharge. The suspected higher rate of missing consent among the mildly compromised newborns is also implied by the higher rate of missed consent in *study I* (including both newborns treated with PPV and CPAP) than in *study II* (including only newborns treated with PPV, i.e. more severely affected newborns). This potential bias is avoided in *study III* and *IV* where consent was asked in advance.

Selection due to missing data

Of greater concern is the high number of excluded newborns due to technical malfunction, mainly due to missed recordings from the video cameras, the patient monitor recordings and the respiration monitors. The software responsible for decoding the signals from the patient monitors into video formats would occasionally freeze. In addition, although less frequent, the video cameras mounted on the resuscitation table would shut down. A reboot of the system would then be necessary for the data collection to continue. Despite regular system checks, recordings could be paused for several days before it was noticed. These episodes however occurred randomly and should not in our opinion cause any selection bias.

Some newborns were treated on resuscitation tables not equipped with cameras. For the most, this applied to preterm newborns GA<34, as they were frequently stabilized on mobile incubators. These newborns were not eligible for inclusion in any of the studies needing recordings, and should not affect the results. Occasionally, there would be simultaneous use of both the primary resuscitation bay and the secondary (reserve) resuscitation bay, e.g. after delivery of twins. The choice of only mounting cameras to the primary resuscitation bay at each birth site was made based on the experience that the reserve resuscitation bays were seldom used, and the financial costs associated with extra cameras. Whether this has resulted in a minor bias is not clear.

The ventilation monitor was dependent on the t-piece being placed at the lever before initiation of ventilation, so that recordings could be activated. Often, the T-piece was placed on the resuscitation bay. The respiration monitor was blinded to the resuscitation team, so they had no indication whether the monitor was active or not. We set up prints on the wall to remind the staff, and constantly reminded the midwives who did the

equipment checks. This had some effect, but did not prevent 25% of missed respiratory data in Study IV.

5.1.3 Information bias

Information bias or measurement bias may arise through inaccurately or falsely measured key variables. This can be reduced by thorough planning, clearly defining variables, and strict management and control of the data collection.

Prior to the data collection for *study I* and *II*, we completed a Standard Operating Procedure (see chapter 3.5), defining variables for the analysis of video recordings. However, all recordings were analysed by a single observer (the doctoral candidate). This will weaken the validity of the results, as many of the variables are dependent on the perception of the observer such as defining if the newborn is adequately stimulated, or if respiration is adequate. The observations would be more reliable if assessed by two – or more – independent observers. Although all personnel involved in newborn resuscitation are instructed in how to apply PO and ECG sensors, the stress of managing a compromised newborn occasionally led to unfavourable placements of both the PO sensor and ECG electrodes, affecting the detection of heart rate signals. We did not define whether the sensors were placed suboptimally. This could have provided useful information when interpreting the results of the study.

Study II and *IV* included newborns who were apnoeic upon arrival at the resuscitation bay. However, we have no information about the respiratory effort prior to arrival at the resuscitation bay. Some newborns may have had an initial short cry or a few breaths before they became apnoeic and were moved to the resuscitation bay for support. This will affect the time to arrival at the resuscitation bay. Furthermore, the video recordings cannot reveal whether the newborn is in a state of primary or secondary apnoea. For some newborns, only seconds passes from arrival at the resuscitation bay until they received airway support, and it is possible that some of these newborns would have responded to stimulation alone. Thus, the included newborns in *study II* and *IV* represent a heterogeneous group, and some may not be representative of the newborns we intended to study.

Study III aimed to assess heart rates immediately after birth. We intentionally left the data collection to personnel already attending the birth as it was considered less intrusive to the parents. Consequently, the data collection was spread over many hands. In addition, the birth attendants must perform other tasks, possibly interfering with the data collection. Although involved personnel were trained, and the data collection was preceded by a pilot phase, this weakens the quality of the collected data. Our biggest concern in this regard, was the accuracy of the variable: time of birth. During analysis, we defined algorithms to filter out erroneous registrations such as events where NeoBeat registered skin contact prior to time of birth. Not all of these were necessarily erroneous. Reports from birth attendants revealed that the NeoBeat was in fact occasionally applied to the newborn before the whole body was delivered. The number of registrations the first seconds were relatively few, so that erroneous registrations would have a major impact, which is why we did not present results until reaching a minimum of 68 observations. Reducing the data collection to fewer birth attendants may have improved the validity of the collected data. However, it would greatly affect the number of inclusions. Eventually, the high number of included observations were thought to diminish errors during data collection.

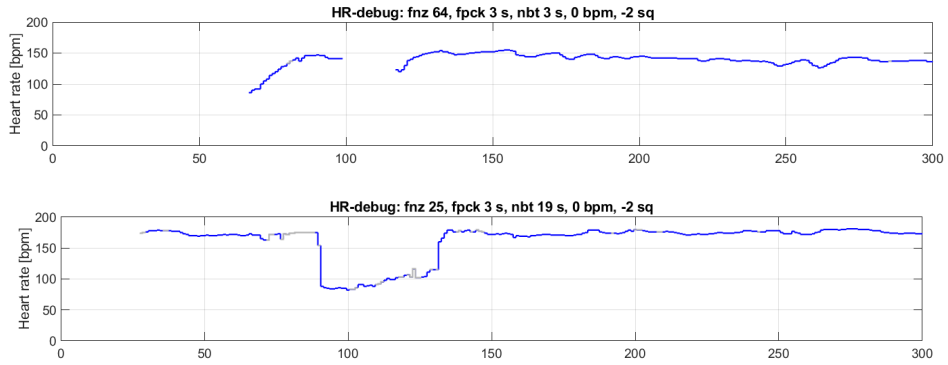


Figure 15 Examples of potential erroneous heart rate registrations. The upper diagram may represent a case where birth is registered too early. The lower graph may represent an erroneous reading (i.e. detecting the heart rate of the mother as the newborn are placed skin to skin on the mother's chest?).

We also discussed excluding data when the NeoBeat did not detected any signal the first 30 seconds (suggesting that birth were registered too early n=34), or when there were sudden changes in heart rate (suggesting erroneous QRS read, n=21). (figure 15). However, when running statistical analysis with one or both groups removed, results were seemingly not affected.

In study IV, we recorded ventilation support during resuscitation of apnoeic newborns. As newborns respond to ventilation support, they will gradually initiate breathing, which in turn interferes with the measured pressures, tidal volumes and leak. This probably contributes to the variance in the results. For instance, we suggested that respiratory efforts of the newborns explains that the highest measured inflation pressures (exceeding 30 mbar) are associated with a decrease in tidal volumes (Paper IV, Figure IV)

As the t-piece device is set to a PIP of 30 cmH_2O, all inflations with a peak pressure deviating from the set-value may be suffering from erroneous ventilation techniques or other unknown- or undetected disturbances during ventilation. This weakens the validity of the reported association between PIP and delivered tidal volumes.

Medical personnel may act differently when they are aware of being observed, a phenomenon known as the Hawthorn effect. Typically, this will have a positive effect on their performance. While this potential bias is certainly present in our study, we suspect that the personnel soon became unaware of the camera in the everyday routine. This was also been communicated by the staff throughout the project.

5.1.4 Statistical considerations

Number of participants

We performed power calculations prior to data collection for the incidence study (*Study I*) and the study on normal newborn heart rate (*Study III*), to ensure that sufficient data would be collected for valid estimates. No power calculations were performed for *study II*, which included the newborns from *study I* who received PPV and where we had video- and monitor recordings for analysis. Nor was there performed any power calculation prior to collection of data for study IV. When we started the analyses for

Paper IV in early 2022, we included all newborns for whom we had complete data from the respiratory monitor up to that point. Thus, the length of data collection ultimately determined the number of included newborns in this study.

Important factors affecting the final number of inclusions were the rate of consent to participate and the rate of missed recordings. Extending the duration of data collection, or expanding the project to other study sites, would have increased the number of included newborns. In addition, refined technical solutions may have reduced the rate of missing data. Although the rate of missing data due to technical errors was relatively high, we consider the high rate of parental consent to participate in the different studies as a strength in our project. Although acknowledging the limitations associated with small numbers of observations, we observe that the number of inclusions in our study is not inferior to comparable studies on newborn resuscitation.

Smoothing centile charts

In the presentation of heart rate estimates in healthy newborns in *Paper III*, we smoothed the centile charts using LOESS (see also chapter 3.4). When smoothing a curve from a scattered plot like this, a "span" is set between 0 and 1, which defines the level rate of which the model should weight nearby values. A low span (near 0) captures more trends but introduces noise in the centile charts, whereas a too high span (near 1) may over-smooth the line and thus risking missing important variations. We considered an acceptable balance was achieved by using a span of 0.7 for the 3rd and 10th centile, and 0.5 for all other centiles.

Fitting the models in paper IV

Finding a model with the best fit for modelling the relationship between different variables and tidal volumes was challenging. A linear mixed model was tried but rejected, as the residuals were not normally distributed. We considered robust methods, i.e. reducing the effect of outlying data points and allowing data with better fitted residuals to primarily determine the results. However, our dependent variable (tidal volume) showed great variability, many of the observations had large deviations in residuals, and it was unclear what clinical relevance it would have to reject all those

observations. We tried non-linear models through transformations (log, sqrt, cube root) without achieving a better fit. Generalized Estimating Equations was found appropriate for our population model, as it does not depend on normally distributed residuals.

All models were univariable. This was chosen as univariable models describe the mutual relations. In addition, we found it difficult to interpret models that include several highly interrelated processes as explanatory variables. As a quality check, we ran a multivariable model including PIP, inflation rate and inflation time. This did not alter the statistical significance of any associations compared to the univariable model. Thus, our model of mutual relations seems accurate.

5.1.5 Ethical considerations

We have video-recorded newborns in a most critical situation. This raises many ethical concerns[157]. When and how to ask for parental consent for participation in the study? How to collect data without interfering in the treatment of the newborn? How to guarantee safety of both the newborns and the caregivers?

Usually, informed (parental) consent must be obtained before collecting any data for research purposes. Obviously, this is challenging when studying newborn resuscitation as it (for the most) occurs unexpectedly, and there is no time to ask for consent. Deferred consent is a commonly used strategy in emergency care research like this, whereby the data is collected before asking consent[158]. The parents are then approached after the event to ask for consent to include the recorded data. Alternatively, parents must be approached before birth to consent to data collection in any case where the newborn needs support after birth.

During the planning of the data collection for *study I* and *II*, we consulted with a research group at the University Hospital in Oslo, Norway, having recently performed a similar study of video recording newborn resuscitation[67,159]. They had asked consent from all parents admitted to the birth department in labour. In their experience, this acted as a reminder of the chance of a complicated delivery, evoking unnecessary stress and anxiety. Unnecessary, as only a small percentage of newborns are in need intervention after birth. In large part based on their experience, we landed on using

deferred consent for the data collection of the first two studies. For *study III* and *IV*, the data was collected as part of the Safer Births Bundle project, collecting data on both healthy newborns and those needing resuscitation after birth. Hence, the obvious approach was to obtain parental consent before birth.

It was important to us that the data collection did not interfere with the treatment of the newborn. We installed cameras and other equipment for data collection in a way which should not distract the personnel. The task of marking the time of birth using either a stopwatch (*study I* and *II*) or on the tablet (*study III* and *IV*) was delegated to the birth attendants, who have many other tasks during labour. Still, we found this less interfering than the alternative of having study personnel attend the birth.

Video recordings of resuscitations are potent and highly sensitive data. Unauthorized access may have had grave consequences for the involved newborns, and for the medical personnel involved in the event. This was also a repeated worry among the personnel prior to data collection. To reduce concern, we regularly visited departments and attended staff meetings of the included departments, to clarify the aim of the project, and inform about data security.

Both personnel involved in the treatment of a newborn, and the newborns parents were offered the opportunity to watch the video recording of the event. To our surprise, this was seldom requested. Only three sets of parents asked to see the video showing the treatment of their newborn, all thee being – in this context – short and uncomplicated events. When involved personnel asked to watch a video, it often involved more complicated events, where the caregivers felt a need to assess their own resuscitation efforts. No one profession predominantly requested to view videos, and included midwifes, nurse assistants, paediatric residents, and consultant neonatologists. The feedback from parents and personnel who watched a video was exclusively positive. While generally encouraging all personnel to watch videos where they had been involved, we deliberately avoided approaching staff directly, as we feared this could raise the notion of surveillance. While we identify video recordings of newborn resuscitation as a great potential for learning and quality improvement, we acknowledge how one may feel this is a potent tool for criticism or even reprimand if

something went wrong. Only twice did someone (anonymously) mark the incident report form to ask for deletion of the video. Both episodes occurred during the first weeks of the project. To us, this suggests a general endorsement of the project. We believe establishing confidence among the involved personnel was essential.

The restriction of allowing storage of video recordings for only three weeks before they had to be deleted reduced the risk of videos going astray. However, this had implications for the further processing of data, as the video recordings had to be analysed frequently to avoid missing any data. In addition, there was no possibility of re-checking video recordings. In retrospect, we should have applied for a longer storage time for the video recordings.

Our studies have been conducted in collaboration with Laerdal Global Health, the non-profit sister company to Laerdal Medical. Laerdal Global Health has also provided this PhD grant. The Laerdal Global Health team has a long tradition of collaborating with different research projects globally, and has a unique competence in collection of research data during newborn resuscitation. Some of the equipment that has been made available to us by them has been crucial for our data collection. Our project demonstrates that public-private partnership can be a great contributor to facilitate research, and may enable projects that would otherwise not be possible. However, Laerdal Medical is a large global operator, and producer of both self-inflating bags and the NeoBeat. Hence, high transparency and awareness are imperative not to let economic interest affect the results. Laerdal Medical has not participated in the planning of the studies, nor in the interpretation of the results.

5.2 Discussion of the main results

5.2.1 Incidence of newborn resuscitation

We found that more than 6% of all newborns received resuscitative interventions in the first minutes after birth in our hospital. As expected, the majority of newborns responded to respiratory support alone, which remains the most important intervention during newborn stabilisation after birth. We defined CPAP as a resuscitative

intervention as the ILCOR guidelines suggest CPAP as a means to support transition after birth[63]. However, as this is not part of the resuscitation algorithm, we find it more appropriate to look at the incidence of PPV when comparing our results with studies from other settings.

Studies reveal a substantial variation in the incidence of PPV between different high-resource settings around the world. In our hospital, the incidence of PPV was 3.6%, similar to the 4 % found in a study from Oslo, Norway, where both the setting and caesarean section rate are comparable to ours[67]. A study from a tertiary level hospital in Philadelphia found that 6% of all newborns were treated with PPV after birth[69]. They did however have a higher caesarean section rate of near 30%, almost twice that in our hospital. A tertiary level hospital in Iran reported an incidence of PPV of only 2.8%, despite being a referral centre for high-risk deliveries, and having over 20% premature newborns of GA<37 weeks in the studied population[75]. However, this study likely suffers from underreporting as it is based on medical records alone. Studies from low resource settings generally report a higher incidence of PPV[4,77-79]. Poorer maternal health and follow-up in pregnancy, and foetal monitoring during labour and obstetric care may very well explain a higher risk of newborns in need of resuscitation after birth. In addition, these settings are usually not equipped to deliver CPAP, and may rely on PPV to stabilize newborns with grunting or severe retractions. Another reason for the increased incidence of PPV seen in studies from low resource settings could be that most of these studies are from sites where Helping Babies Breathe training programs for newborn resuscitation had been recently implemented, or are currently under implementation. This may very well have altered the readiness of birth assistants to provide airway support (Hawthorne effect).

Common for all studies reporting on the incidence of PPV are that they merely report what has been provided, and not necessarily what was actually needed. Thus, the variation in incidences between sites could just as well be a result of variation in clinical practice. Regardless, newborn resuscitation remains a frequent concern in all settings, and trained personnel should always be available and prepared.

Several intra-partum risk factors are identified as predictors for newborns needing resuscitation after birth, including prematurity[75,81,82]. *Paper I* confirms that the incidence of interventions increases with lower gestational age. This is not surprising, as the transition in premature newborns is highly different from that of term-born newborns. We did however also see a marked increase in interventions in post term newborns (GA>42). Post term pregnancy is associated with an increased risk of foetal and neonatal mortality and morbidity, and should be suggested among the risk factors.

5.2.2 Heart rate

Normal heart rate after birth

In *Paper III*, we presented centile charts of the normal heart rate in healthy, vaginally delivered term newborns, during the first five minutes after birth. In 2010, Dawson et.al published what have since been widely used references of newborn heart rate during normal newborn transition[84]. Our study primarily differs from that of Dawson in three areas. We detected heart rate by ECG whereas Dawson et al. used PO. We conducted the study on newborns undergoing delayed cord clamping. Finally, our centile charts include the first minute after birth, as opposed to the centiles of Dawson et al. starting from one minute.

Both the use of ECG and the delayed cord clamping are likely to have an impact on the measured heart rate. Indeed, our results, in particular the first two minutes, deviate significantly from those of Dawson et al. Whereas their results suggest that heart rates below 100 bpm are common the first minutes after birth, our results suggest that heart rates below 100 bpm rarely occurred after 30 seconds of life. This makes them more in line with current resuscitation guidelines, suggesting that a heart rate below 100 bpm is a sign of severe distress. Based on our results one may even argue that a heart rate below 120 bpm may be a more suitable threshold to indicate distress in a newborn after birth. Studies of heart rate in compromised newborns requiring support are warranted to further address this question.

We suggest that the difference between the centile charts of Dawson et al. and ours, are primarily due to an underestimation of heart rates when measured by pulse oximetry

early after birth[100]. There are also several studies suggesting that delayed cord clamping ensures a smoother transition after birth. Padilla-Sanchez et al., also using PO to study heart rate after birth in the era of delayed cord clamping, found an earlier rise in heart rate compared to Dawson et al[27]. They attributed the difference to the effects of delayed cord clamping on the hemodynamics. However, they too found heart rates below 100 bpm in more than 10% of all healthy newborns at one minute from birth. In 2016, Linde et al. published changes in heart rates after birth in 55 healthy newborns in Tanzania using a predecessor of the NeoBeat, with a mean heart rate in alignment with our findings[103]. The newborns included in their study did have their cord clamped within one minute from birth. However, most initiated breathing before cord clamping.

ILCOR suggests using ECG to achieve rapid and accurate heart rate monitoring during resuscitation. Novel ECG-application methods such as NeoBeat will make it feasible to monitor heart rate data with an intact umbilical cord. Hence, the centile charts for heart rates obtained by ECG immediately after birth are required. Moreover, our centile charts fill a gap in the existing literature, which is of importance, as it is the time where the newborn heart rate, together with breathing, could determine whether the newborn needs resuscitative interventions.

Assessing and monitoring heart rate during newborn resuscitation

In *Paper II*, we describe how most newborns in our hospital have their initial heart rate assessed by stethoscope. Auscultation by stethoscope is simple, rapid, and provides a reasonably accurate heart rate for the initial assessment. Furthermore, heart rate monitoring through ECG and PO was not available within the time frame suggested for initial assessment. Furthermore, *Paper II* clearly revealed that ECG provides accurate heart rate monitoring earlier than PO. This is in line with previous studies[160]. However, the difference between time from arrival at the resuscitation bay to reliable heart rate signals from PO and ECG is more prominent in our results: 351 and 106 seconds respectively. We also found a larger proportion of failed heart rate monitoring with PO than was the case for ECG. Why does PO so dramatically fail in our setting? It would certainly be interesting to do similar audits in comparable sites.

The widely referenced study of van Vonderen from 2015 compared ECG and PO in 53 newborns, managing to obtain reliable heart rate signals from PO and ECG at 99 and 82 seconds from birth respectively[100]. However, these were stable newborns without the need for intervention, and may not be comparable to compromised and possibly circulatory unstable newborns, with constant signal disturbances through stimulation and interventions.

Katheria et al. compared PO and ECG in 40 preterm newborns and obtained reliable heart rate signals 62 and 28 seconds respectively from placement at the resuscitation bay[102]. Iglesias et al. observed 39 premature births and found that 113 and 43 seconds passed from placement at the resuscitation bay before reliable heart rate signals were obtained by PO and ECG respectively[161]. Mizumoto, observing 20 resuscitations from high risk deliveries, found similar results: 122 seconds for ECG and 38 seconds for PO[98]. In contrast to our study, these studies were conducted on high-risk deliveries where there are healthcare workers, or even dedicated study personnel, tasked to immediately and properly apply PO and ECG sensors on the newborns after birth. This does not however reflect most real-life situations. Normally, the person who applies PO or ECG sensors will do this in between other equally critically important tasks during the first minute of resuscitation. Hence, thorough skin cleaning and proper fixation of the sensors will not always be prioritized. We therefore claim that our study may paint a more realistic picture of the feasibility of instrumental heart rate monitoring during resuscitation.

Interestingly, a more recent study on 60 newborns revealed a difference in speed and reliability between two different and commonly used PO sensors. Massimo and Nellcor, finding that the Nellcor obtained a heart rate signal almost twice as fast as Massimo[162]. The group of Murphy et al. also suggests the superiority of the Nellcor PO sensor in the delivery room[163-165]. We used the Massimo sensor in *Paper II*, and the results may have been different with the Nellcor PO.

Our assumption that poor peripheral circulation in compromised newborns explains the delay in heart rate detection by PO is further strengthened by our findings of a significant delay in detecting reliable PO signals when 5-minute Apgar scores are

below 7. This highlights the value of PO in severely compromised newborns, where reliable feedback on heart rate, perhaps of greatest importance, is limited. Moreover, a recent pilot study suggests that interventions may start earlier when the healthcare personnel have early reliable heart rate monitoring[166]. We suggest that ECG should be the primary source for heart rate monitoring during newborn resuscitation.

The challenges of attaching ECG electrodes on wet skin has been claimed a disadvantage of the ECG[89]. During our study, we observed that the challenge of proper fixation of sensors applied to PO as well. Both the vigorous handling of the newborn, and wet skin, affected the attachment of the ECG gel electrodes as well as the PO wrap-around sensor. In consequence, the personnel needed to reapply the sensors, sometime several times during the same event. Novel ECG-application methods may solve this problem[167].

The 2020 treatment recommendations by ILCOR have not changed their statement that ECG may be used to monitor heart rate in babies requiring resuscitation, and that the recommendation is still weak and with low certainty evidence[168].

5.2.3 Positive pressure ventilation

Time to initiating PPV

Resuscitation guidelines stress the onset of PPV within 60 seconds from birth in apnoeic newborns. *Paper II* reveals that we are mostly not able to comply with this fundamental recommendation. McCarthy et al. studied high-risk deliveries attended by alerted teams and found that heart rate assessment and initiation of PPV was not achieved within the first minute of life in 2/3 of the resuscitations[70]. Our results suggest that the main reason for a delay in initiating PPV in our hospital is the time that passes before the newborn arrives at the resuscitation bay.

We have centrally located resuscitation bays, which may have prolonged the time to arrival. However, Niles et al. had similar results despite each delivery room being equipped with a resuscitation bay[69]. This suggests that the distance to the resuscitation bay may not be the decisive factor. The concept of immediate skin-to-skin contact and delayed cord clamping is well founded in our birth department and is strongly endorsed

by our birth attendants. We therefore speculate that birth attendants may delay the relocation of newborns to the resuscitation bay in the hope that the infant responds to stimulation, and thereby avoid separating the newborn from the mother. This notion is strengthened when observing that the time to arrival at the resuscitation bay, and therefore the time to initiate PPV, was markedly shorter following caesarean sections.

The effect of delayed cord clamping depends on the aeration of the lungs. One could therefore argue that spending some extra seconds stimulating the newborn with an intact cord may in fact be time well spent. The natural extension of this would then be to provide PPV on an intact cord for those not responding to stimulation. Bedside resuscitation units allowing resuscitation with an intact cord may reduce the time to initiating PPV[169,170]. This is a concept that is gaining increasing support among clinicians, and there are several ongoing and completed trials investigating the benefits[171]. Obvious challenges may be the reduced workspace and accessibility to the newborn when having to complete tasks beyond PPV. However, both parents and healthcare workers included in surveys had a generally positive experience[169,170]. Most likely, this method works very well in newborns responding quickly to intervention, which is the case in most events.

5.2.4 PPV by T-piece resuscitators.

Study I showed that the NeoPuff was the preferred device for providing PPV during newborn resuscitation in our hospital. This is probably primarily a matter of habit, but may also suggest that the healthcare workers feel that the t-piece resuscitator is easier to use. The 2020 ILCOR guidelines state that the direction of evidence is shifting towards support for the use of T-piece resuscitators, but still does not make a clear recommendation on the subject[168]. *Study IV* clearly shows an overall consistent delivery of PIP, suggesting that most healthcare workers have an acceptable technique for fitting the mask during ventilation. Still, the results also confirm that steady inflating pressures by no means guarantee adequate ventilation support. Clinicians must be aware of the generally low compliance of the liquid filled lungs, and keep a continuous focus on maintaining open airways.

Tidal volumes

Studies show that spontaneously breathing term newborns achieve tidal volumes of 4-6 ml/kg shortly after birth[110-112]. Still, resuscitation guidelines recommend tidal volumes between 5-8 ml/kg during newborn resuscitation[64]. The rationale behind this is that some of the inflated air will remain in the lungs to build up the FRC. Hence, during lung recruitment, the volume of inflated air is probably higher than the volume measured during expiration. The gradual increase in expired tidal volumes throughout the first 20 inflations visualize this effect (Paper IV, Figure III).

After initial lung recruitment, measured tidal volumes are within recommended values, however at the lower end of the range. This is in line with the findings of Ersdal et al., who studied more than 800 newborns receiving PPV after birth, and found that that PIP of 37 cmH_2O was sometimes be necessary to achieve tidal volumes in the target range[106]. An earlier study by Linde et al. from the same study site, including 215 near-term and term newborns, suggested that to achieve an increase of heart rate in apnoeic newborns, tidal volumes above 6 ml/kg were required. Furthermore, tidal volumes between 9 and 10 ml/kg ensured the most rapid heart rate increase, as a marker of successful lung aeration[114]. Holte et al. investigated expired CO_2 in 434 late preterm and term newborns, and demonstrated the highest CO_2 clearance was achieved with tidal volumes of 10-14 ml/kg[113].

Despite delivering tidal volumes at the lower end of the recommended range, our cohort of resuscitated newborns largely consisted of newborns rapidly responding to the treatment. As such, we have no indication that they were receiving insufficient support. Thus, optimal tidal volumes during PPV in the delivery room remain unknown.

More concerning is the large variation in the delivered tidal volumes. In consequence, a large proportion of the inflations had tidal volumes falling outside the target range. A small study including 20 preterm newborns receiving PPV in the delivery room, showed that a PIP of approximately 30 cmH_2O resulted in tidal volumes between 0 and 30 ml/kg, implying a weak correlation between PIP and delivered tidal volumes[128]. In our paper, we have speculated that both the variation in airway resistance and lung compliance during the establishment of FRC contributes to this variation. Perhaps more

important is the challenge of maintaining an open airway while the newborn is repeatedly handled and stimulated. It is also likely that the newborns gradually changing tone and respiratory effort in response to the treatment will interfere with inflations. Despite a relatively high mask leak, the T-piece resuscitator managed to maintain a relatively stable PIP, and the mask leak should not affect the actual delivered tidal volumes. However, the measured expired tidal volumes may very well be erroneous when mask leak increases.

Our findings are in line with several other studies of mask ventilation at birth [106,113,127,128,130,132,172-175], illustrating the difficulty for clinicians to estimate the delivered tidal volume, or even to detect if the newborn receives any tidal volume at all.

We have clearly demonstrated that a steady PIP pressure is no guarantee of adequate tidal volumes. This weakens one of the cited advantages of T-piece resuscitators. Newborn ventilation strategies are focused on volume-targeted ventilation[176], and we cannot see why this should not apply to PPV in the delivery room. This could be achieved by implementing respiratory monitors to assist healthcare workers during newborn resuscitation. Considering the indisputable acknowledgement that optimal respiratory support is key to newborn resuscitation, it may seem somewhat surprising that respiratory function monitors are not standard equipment during newborn resuscitation in high resource settings. In comparison, instrumental heart rate monitoring has long been standard in those same settings. However, advanced and expensive equipment is required, and there is as yet no certainty of its benefit. Admittedly, no clear recommendations on delivered tidal volumes exist; even so, any feedback on actual delivery of tidal volumes is reassuring for the healthcare provider.

Peak inflation pressure

As recommended in the resuscitation guidelines, the PIP was set to 30 cmH_2O. Our results clearly illustrate that the healthcare workers were able to maintain a stable pressure using the NeoPuff. Furthermore, the association between PIP and tidal volumes shown in *Paper IV* suggest that a pressure close to 30 cmH_2O is warranted to support initial lung recruitment. Traditionally, high PIP has been avoided for fear of causing barotrauma to the lungs. However, modern newborn ventilation strategies

acknowledge volutrauma as more important than barotrauma and endorse volume-targeted ventilation[176]. Our results demonstrate that PIP should preferably be adjusted to lower values as the resuscitation advances, to adapt to the increased compliance. It was, however, our experience that the inflation pressure was rarely adjusted. Obviously, the healthcare workers are not used to adjusting the PIP on the t-piece resuscitator during resuscitation. It could also be that this reflects the challenge when using the t-piece resuscitator, of sensing the decrease in lung resistance as the compliance increases with successful lung recruitment. This would probably be easier to notice and adapt to when using a bag-mask ventilator.

Inflation time and rate

As expected, there was a positive correlation between the inflation time and tidal volumes. The air entering the lungs during inflation will increase the intrathoracic pressure. Hence, air will flow into the lungs until the intrathoracic pressure equalises with the inflation pressure. Extending the inflation beyond this equilibrium will not affect the tidal volume. This is nicely illustrated in the graph presenting the association between inflation time and tidal volumes (Paper IV, Figure VI). This is also suggested in the paper as the rationale behind the decrease in tidal volumes with increasing inflation rate, although low inflation rates do not automatically involve long inflation times. We can use these estimates to make suggestions about ideal inflation times and rates during resuscitation.

There is a slight difference between recommended inflation times and rates in different guidelines. ERC and AHA suggest inflation times <1 second, ANZCOR suggests 0.3 – 0.5 seconds. ERC recommends inflation rates of 30 per minute, AHA and ANZCOR suggest 40-60 per minute[177-179]. Our results imply that after the initial phase of lung recruitment, the highest tidal volumes are ensured by an inflation time of 0.5 seconds and inflation rates of 30-40 per minute. However, it is not certain if this would change with different inflation pressures.

5.2.5 Full cardiopulmonary resuscitation

The incidence of full cardiopulmonary resuscitation (including chest compression and/or i.v. administration of adrenaline and/or fluid boluses) was rare. This is in alignment with other reports. In addition, we cannot rule out that some of the newborns receiving chest compressions would have responded to airway support alone. In our first paper, three newborns received chest compressions for less than one minute. There were also two episodes where the newborns did not receive any airway support prior to initiation of chest compressions. Thus, the actual need for chest compressions may even be rarer than suggested by our results. We comment on this not to advise against chest compressions, but to emphasise that proper airway support should remain the primary focus during newborn resuscitation. The 2015 revision of ILCOR guidelines on newborn resuscitation recognized this by prolonging the recommended duration of PPV.

5.2.6 Short term outcome of near- and term newborns after resuscitation.

The majority of the term- or near term newborns (GA>34) included in our one year survey were returned to parental care either immediately following stabilisation, or after a few days stay on the neonatal intensive care unit. The mean umbilical artery BE in non-asphyxiated newborns is -4 - -4.8 mmol/L[180,181], and asphyxial injury mostly does not occur until foetal BE is ≤ -12 mmol/L[182,183]. The overall good prognosis suggests that most newborns in need of treatment after birth in our setting are not severely affected. Nevertheless, swift and correct management of compromised newborns is required to avoid complications. There was a significant difference in Apgar scores between newborns returned to the parents and those admitted to the NICU after stabilisation. This is to us not very surprising, as both the Apgar score and the decision whether to admit the newborn to the NICU after resuscitation are based on clinical evaluation. However, we found no difference in the in blood gasses from the

umbilical artery between the two groups. This is in alignment with studies showing no certain predictive value of umbilical cord blood gasses alone on outcomes[184-186].

6. Conclusion

- In an unselected population in a high risk setting, 6.2% of all newborns received resuscitative measures in the first minutes after birth.

- Most newborns responded to airway support alone, and the need for circulatory support was rare.

- Nearly two thirds of all newborns who received respiratory and/or circulatory support after birth were immediately returned to parental care. Of those admitted to the NICU after stabilization, 70% were discharged within one week.

- The time to assess heart rate and initiate PPV in apnoeic or inadequately breathing newborns exceeded the recommended 60 seconds from birth in near two thirds of the events.

- 3-lead ECG was able to provide a reliable heart rate signal significantly earlier than PO during resuscitation of term newborns.

- We have presented heart rate centiles from five seconds to five minutes of vaginally delivered term newborns undergoing delayed cord clamping.

- When providing PPV in apnoeic newborns by the T-piece resuscitator, there was a consistent delivery of PIP and PEEP, and the lung compliance was generally low. There was a substantial variation in both mask leak and tidal volumes.

- A set-PIP of 30 cmH_2O resulted in delivered tidal volumes at the lower end of the target-range. Inflation time of approximately 0.5 seconds and inflation rates between 30-40/minute ensures the highest delivered tidal volumes.

7. Clinical implications and future perspectives

The projects overall aim has been to bring new insight into the management of compromised newborns after birth. We hope our results will contribute in further developing evidencebased treatment recommendations. We have accentuated the challenge of complying with guidelines and of monitoring heart rate during stabilisation of unanticipated compromised newborns. We have demonstrated how novel technology may provide early and continuous heart rate monitoring in the delivery room, only seconds after birth in healthy newborns. Our heart rate centiles also fill a gap in the literature. As novel technology enables early heart rate monitoring, this necessitates knowledge on normal heart rate values in the first minute of life. Furthermore, our results solve the paradox of assuming that the majority of healthy newborns have a heart rate below 100 bpm at 60 seconds after birth, and at the same time having guidelines recommending resuscitative measures at heart rates <100 bpm. Future research may reveal whether early heart rate monitoring is feasible also in compromised newborns in need for resuscitation, and more importantly whether this may improve guideline adherence.

In addition, this project has had large effects locally. Inspired by other research environments, we have gradually established systematic and continuous data collection during newborn resuscitation. This has in turn facilitated new projects in close collaboration with the University of Stavanger and Laerdal Medical. The close proximity between the research environment and the neonatal- and birth departments enables transferability of results directly back into clinical work through instruction, training and simulation.

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9. Errata

Paper I

Two errors have been found in the manuscript after publication in the BMJ Pediatric Open. In the result section of the abstract, it says Duration of PPV was median (IQR) 106 s (54-217). It should say: Duration of PPV was median (IQR) 106 s (54-221). In Table 1, in the column with Gestational age group: 37-41, it says that CPAP only was provided in 85 (0.2%). It should say 85 (2.0%).

10. Reprint of publications

I

BMJ Paediatrics Open

Incidence of newborn resuscitative interventions at birth and short-term outcomes: a regional population-based study

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To cite: Bjorland PA, Øymar K, Ersdal HL, *et al*. Incidence of newborn resuscitative interventions at birth and short-term outcomes: a regional population-based study. *BMJ Paediatrics Open* 2019;**3**:e000592. doi:10.1136/bmjpo-2019-000592

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjpo-2019-000592).

Received 16 October 2019
Revised 6 December 2019
Accepted 10 December 2019

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ABSTRACT

Objectives To determine the incidence and characteristics of resuscitative interventions at different gestational ages and short-term outcomes after resuscitation.

Design, setting and patients A prospective observational study in an unselected population at Stavanger University Hospital, Norway, from October 2016 until September 2017.

Interventions Using a data collection form and video recordings, we registered and analysed resuscitative interventions.

Main outcome measures Incidence of continuous positive airway pressure (CPAP), positive pressure ventilation (PPV), intubation, chest compressions and intravenous fluid or epinephrine boluses. Short-term outcomes of resuscitated newborns.

Results All 4693 newborns in the study period were included in the study. Two hundred and ninety-one (6.2%) newborns received interventions in the first minutes of life beyond drying and stimulation. PPV was provided in 170 (3.6%) while CPAP (without PPV) was provided in 121 (2.6%) newborns. Duration of PPV was median (IQR) 106 s (54–221). Intubations were performed in 19 (0.4%) newborns, with a mean (SD) intubation time of 47 (21) s. Ten (0.2%) newborns received chest compressions and epinephrine was administrated in three (0.1%) newborns. Sixty-three per cent of the treated newborns from 34 weeks' gestational age were returned to parental care without further follow-up.

Conclusions The need for resuscitative interventions after birth was frequent in this unselected population in a high-resource setting, but full cardiopulmonary resuscitation was rare. Short-term outcomes were good, suggesting that most newborns treated with resuscitative interventions were not severely affected.

What is known about the subject?

- A significant percentage of newborns require some assistance to enable the transition to independent life.
- The incidence of different resuscitation measures is likely to vary between different settings and gestational age (GA) groups.

What this study adds?

- Most compromised newborns respond to airway support alone and full cardiopulmonary resuscitation is rare.
- There is a similar increase in resuscitation measures in near-term (34–37 weeks' GA) and postmature (>42 weeks' GA) deliveries.
- Most newborns treated with resuscitative interventions are not severely affected and short-term outcomes are good.

INTRODUCTION

The transition from intrauterine to extrauterine life is a critical time for survival and involves considerable changes to the newborn's cardiovascular and respiratory systems.[1–3] Although most newborns initiate spontaneous breathing within the first 30 s of birth, or respond to drying and stimulation, a significant percentage require some assistance to enable this transition to independent life.[4] The literature suggests that 3%–8% of newborns receive respiratory support during the first minutes of life, and 0.1%–0.3% require advanced cardiopulmonary resuscitation.[5–12] However, current estimates are widely based on studies conducted in low or middle-resource settings, and the incidence of resuscitative interventions such as continuous positive airway pressure (CPAP), positive pressure ventilation (PPV), intubation, chest compressions and administration of intravenous fluids or drugs is likely to vary between different settings and countries. Recent studies imply that newborn resuscitation is a frequent concern also in high-resource settings,[13–16] however most studies are not population based or they are conducted in tertiary referral hospitals accumulating high-risk deliveries. Furthermore, knowledge on

short-term outcomes of near-term or at-term newborns after resuscitation is limited.[17 18] The aim of this study was (1) to describe the incidence and characteristics of newborn resuscitative interventions during the first minutes of life in an unselected population, and (2) to assess short-term outcomes after resuscitation.

MATERIALS AND METHODS

Study site

This prospective, observational study was conducted at Stavanger University Hospital, Norway, including all newborns born in the region from 1 October 2016 until 30 September 2017. Stavanger University Hospital serves a population of 350 000 with approximately 4600 deliveries annually, and is the only hospital in the region with delivery and newborn services. The hospital has an obstetric and neonatal department, providing care for newborns ≥23 weeks' gestational age (GA). Newborns with antenatally diagnosed severe cerebrospinal, cardiac or gastrointestinal malformations requiring surgery immediately after birth are delivered elsewhere, accounting for approximately seven pregnancies each year.

The department of obstetrics includes a midwife-run low-risk delivery unit, a general labour ward and an operating theatre for elective and emergency caesarean sections. Each site has a centrally placed main resuscitation crib with resuscitation and monitoring equipment, and a backup resuscitation crib in case of, for example, twin deliveries. In cases of extreme preterm deliveries (<28 weeks' GA), a fully equipped mobile resuscitation crib is brought from the neonatal intensive care unit (NICU) for convenient transportation back to the NICU after stabilisation.

The resuscitation cribs are equipped with a radiant heater, suction device, patient monitor (Carescape B450, General Electric, Boston, MA), oxygen blender, self-inflating bag without positive end expiratory pressure (PEEP) (Laerdal Medical, Stavanger, Norway), T-piece resuscitator (NeoPuff, Fisher & Paykel Healthcare, Auckland, New Zealand) and instruments for endotracheal intubation and intravenous access (online supplementary file 1). CPAP is provided with the NeoPuff T-piece resuscitator with adjustable PEEP, routinely set at 5 cm H_2O.

The primary resuscitation team consists of the midwife and/or nurse assistant responsible for the birth and a paediatric resident. A consultant neonatologist is present in cases of extreme preterm deliveries or risk of severe asphyxia. The primary resuscitation team may also call on a full resuscitation team including a consultant neonatologist (if not already present), a neonatal nurse, an anaesthesiologist and an anaesthetic nurse. All staff undergo regular training. The resuscitation teams follow the Norwegian Resuscitation Council guidelines for newborn resuscitation,[19] based on the International Liaison Committee on Resuscitation (ILCOR)[4] and European Resuscitation Council[20] guidelines.

Data collection

During the study period, an 'observational incidence report form' was completed for every newborn, documenting the time and mode of delivery (vaginal delivery or caesarean section), GA and if the newborn received resuscitative interventions within the first 5 min after birth (online supplementary file 2). We defined resuscitative interventions as one or more of the following: CPAP, PPV, endotracheal intubation, chest compressions and intravenous administration of fluids or drugs. The incidence report forms were continuously cross-checked against the birth record, ensuring that every birth was included.

Video recordings were used to supplement the report forms regarding the resuscitative interventions provided. For this purpose, a video and voice recording camera with motion sensors was mounted above all main resuscitation cribs, and on some of the NICU's mobile resuscitation cribs, during the entire study period. Due to economic and technical limitations, secondary resuscitation cribs and some of the NICU's mobile resuscitation cribs were not equipped with a camera. During the data collection period, study personnel would continuously, at a minimum of twice weekly, collect the 'observational incidence report form' filled out after every birth. Parental consent to analyse the video recordings and to

Table 1 Incidence of resuscitative interventions during 1 year at Stavanger University Hospital

Gestational age group	<28	28–33	34–36	37–41	≥42	Total
Total number of newborns	**13**	**61**	**190**	**4318**	**111**	**4693**
Interventions provided in	**13 (100%)**	**47 (77%)**	**19 (10%)**	**199 (4.6%)**	**13 (12.6%)**	**291 (6.2%)**
CPAP only	0	24 (39%)	7 (3.7%)	85 (0.2%)	5 (4.5%)	121 (2.6%)
Positive pressure ventilation	13 (100%)	23 (38%)	12 (6.3%)	114 (2.6%)	8 (7.2%)	170 (3.6%)
Intubation	7 (54%)	2 (3.3%)	1 (0.5%)	9 (0.2%)	0	19 (0.4%)
Chest compression	0	1 (1.6%)	1 (0.5%)	8 (0.2%)	0	10 (0.2%)
Intravenous epinephrine	0	0	0	3 (0.1%)	0	3 (0.1%)
Intravenous fluid bolus	0	1 (1.6%)	2 (1.1%)	12 (0.3%)	0	15 (0.3%)

Incidence is presented as n (percentage of newborns in the same group).
CPAP, continuous positive airway pressure.

Table 2 The characteristics of resuscitated newborns at Stavanger University Hospital by gestational age (GA) and in total

	GA <28		GA 28–33		GA 34–36		GA 37–41		Ga ≥42		Total	
	n=12		n=39		n=14		n=177		n=13		n=255	
Characteristics of newborns												
Weight (g)	790	(743–899)	1485	(1325–1804)	2545	(2190–2970)	3566	(3142–3946)	3746	(3654–3924)	3310	(2375–3832)
Male gender	8	(67%)	23	(59%)	10	(71%)	105	(59%)	7	(54%)	153	(60%)
Apgar scores												
1 min Apgar	5	4–7	7	6–8	6	5–8	6	5–7	5	4–7	6	5–7
5 min Apgar	8	7–8	8	7–9	8	7–8	8	7–9	7	7–9	8	7–9
10 min Apgar	8	7–9	9	8–9	8	7–8	9	8–10	9	8–10	9	8–10
Umbilical blood values*												
Arterial pH (n=198)	7.35	(0.05)	7.32	(0.13)	7.25	(0.08)	7.18	(0.14)	7.16	(0.1)	7.20	(0.13)
Arterial BE (n=194)	−2.5	(1.2)	−2.7	(3.5)	−2.6	(1.9)	−5.2	(3.5)	−4.7	(4.9)	−4.7	(3.6)
Venous pH (n=232)	7.34	(0.10)	7.37	(0.13)	7.31	(0.10)	7.28	(0.11)	7.27	(0.1)	7.29	(0.14)
Venous BE (n=229)	−4.3	(1.9)	−1.9	(2.6)	−3.7	(3.0)	−5.8	(3.8)	−4.9	(2.5)	−5.0	(3.4)
Characteristics of births												
Vaginal	5	(42%)	13	(33%)	7	(50%)	115	(65%)	7	(54%)	147	(58%)
Planned caesarean section	2	(17%)	5	(13%)	1	(7%)	4	(2%)	0		12	(5%)
Acute caesarean section	5	(42%)	21	(54%)	6	(43%)	58	(33%)	6	(46%)	96	(38%)
Breech	6	(50%)	10	(26%)	5	(36%)	14	(8%)	1	(8%)	36	(14%)
Vacuum	0		1	(3%)	1	(7%)	60	(34%)	5	(38%)	67	(26%)
Forceps	0		0		1	(7%)	11	(6%)	0		12	(5%)
Induced labour	0		1	(3%)	1	(7%)	59	(33%)	7	(54%)	68	(27%)

The table shows the characteristics of the 255 newborns for which consent was provided to access further details. Weight and Apgar given as median (IQR). Umbilical cord blood values given as mean (SD). All others presented as n (percentage of resuscitated newborns in the same group).
*Umbilical blood samples were not available for all patients.
BE, base excess.

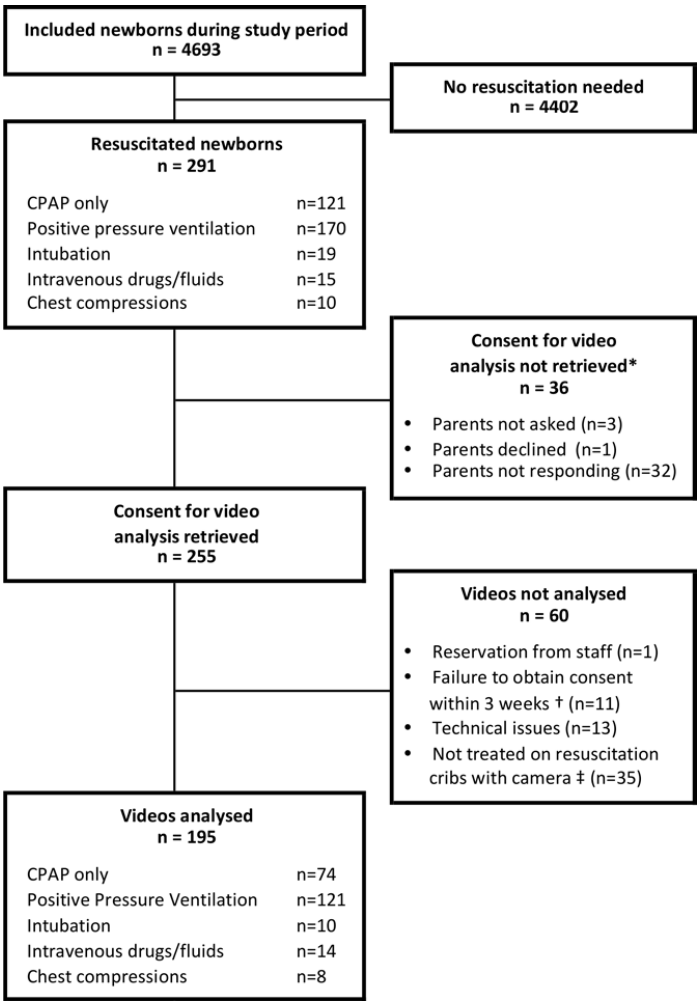

Figure 1 Overview of the studied population *Parental consent was preferably obtained during hospital stay, or else by letter (n=112). Three parents were not asked due to language difficulties. †Videos were automatically deleted after 3 weeks. Consent obtained after 3 weeks resulted in data extraction from patient records alone. ‡Only main resuscitation cribs were equipped with cameras. CPAP, continuous positive airway pressure.

extract patient data from the medical records was asked for all newborns who received resuscitative interventions at birth. If the newborns were already discharged from hospital, parental consent was asked by letter.

During video analysis, the newborn's respiratory effort at placement at the resuscitation cribs was characterised as adequate (eg, crying or showing mild or moderate retractions), inadequate (eg, grunting or severe retractions) or apnoeic. Drying and stimulation was considered adequate if the newborn received tactile truncal stimulation (drying, chest and back rubs) prior to respiratory support.[21] We recorded mode and duration of PPV, indication for intubation and duration of intubation attempts, and duration of chest compressions. If established, type of intravenous access and number of fluid/epinephrine boluses were registered. Cord blood samples were taken immediately after birth. We defined short-term outcomes as either death, survival and returned to parents, or survival and admitted to the NICU. Further, we characterised level of intensive care by: length of stay, therapeutic hypothermia, mechanical ventilation, pneumothorax, hypoxic ischaemic encephalopathy (HIE) and death. As all premature newborns <34 weeks of gestation are routinely admitted to the NICU, and the level of intensive care on admission to NICU is strongly related to their prematurity and difficult to part from consequence of resuscitative interventions, we only described short-term outcomes in newborns ≥34 weeks of

gestation. Characteristics of the newborns were retrieved from the medical records.

Analysis

A single investigator (PAB) reviewed all video recordings using the video management software from XProtect Smart Client (Milestone, Copenhagen, Denmark). Statistical calculations were performed in IBM SPSS Statistics V.24 (SPSS). Comparison between groups was done by Mann-Whitney U test for continuous variables and χ^2 test for categorical variables (Fisher's exact test if expected counts were <5). A p value <0.05 was considered statistically significant, all reported p values are two sided. Results are presented as number (%), median (IQR) and mean (SD).

Ethics, patient safety and patient involvement

The study was evaluated as non-interventional by the regional ethical committee and approved by the hospital data protection officer. Waiver of consent was approved for the completion of the incidence reports, ensuring that the registrations were complete and population based. Parental consent was obtained after a resuscitation was videotaped, but prior to video analysis (deferred consent). Video recording is a method increasingly used in clinical research, and its legal and ethical concerns have been debated.[22 23] The safety of data storage was prioritised, and only the project team members had access to the video recordings. Involved healthcare workers were given the opportunity to demand immediate deletion of the video recording. For privacy purposes, all video recordings were erased after 3 weeks, thus obtaining parental consent and analysing video recordings had to be completed within that period. The local NICU parental user involvement group has been consulted during the project planning regarding ethical aspects, parental information and the process of obtaining parental consent.

RESULTS

Incidence of resuscitative interventions

During the study period, 4610 deliveries took place in our region, resulting in 4697 live born and 13 stillborn newborns. Twenty-six newborns were born outside the hospital (14 home deliveries and 12 deliveries during transport to the hospital, all unplanned). Four newborns were excluded as they were extreme preterm deliveries referred from peripheral hospitals. The remaining 4693 live born newborns were included in the incidence analysis. Of these, 5.6% were born preterm (<37 weeks' GA). There were 85 sets of twins, and one set of triplets. The caesarean section rate was 13.7%; 9.6% was acute and 4.1% elective.

In total, 291 (6.2%) newborns received resuscitative interventions. Respiratory support alone, either by CPAP or PPV, was sufficient in 97% of the resuscitated newborns, whereas the remaining 3% received full cardiopulmonary resuscitation (ie, chest compressions).

Table 3 Level of respiratory support by respiratory effort at arrival on the resuscitation crib

	Airway support		
Respiratory effort	**CPAP**	**PPV**	**Total**
Apnoeic	16	98	114
Inadequate*	34	18	52
Adequate†	24	5	29
Total	74	121	195

*Grunting or severe chest retractions.
†Crying, mild or moderate chest retractions.
CPAP, continuous positive airway pressure; PPV, positive pressure ventilation.

The incidence of different resuscitative interventions for all newborns and in groups by GA is presented in table 1.

The characteristics of the resuscitated newborns for which consent was provided to access further details are shown in table 2.

Characteristics of the resuscitative interventions

We video recorded and analysed 195 of the 291 resuscitations, of which 121 were vaginally delivered newborns and 74 were caesarean sections. The inclusion process and reasons for missed video recordings are shown in figure 1.

On arrival on the resuscitation crib, 160/195 (82%) newborns were adequately dried and stimulated before receiving resuscitative interventions. The respiratory effort of the newborn at arrival at the resuscitation crib, and the level of respiratory support provided, are presented in table 3.

The median duration of CPAP in the group treated with CPAP only was 246 s (113–562). The median duration of PPV was 106 s (54–221), and 87 of 121 (72%) newborns were ventilated for more than 60 s. The T-piece resuscitator was the provider's initial choice in all resuscitations, but in five resuscitations, the provider switched to a self-inflating bag and mask without PEEP during ventilation. Intubation was observed in 10 videos. The intubation was successful at the first (n=4) or second (n=6) attempt. Mean intubation time for each attempt was 47 (21) s. Indications for intubation were failed mask ventilation (n=4), chest compressions (n=3) or need for prolonged respiratory support (n=3).

Eight of the newborns who received chest compressions were video recorded (table 4).

In three of these, chest compressions were provided for less than 1 min, while three newborns underwent resuscitation with chest compressions exceeding 15 min. In one newborn, return of spontaneous circulation did not occur, and the resuscitation attempt was discontinued after 18 min.

Short-term outcome of newborns ≥34 weeks' GA

Resuscitated newborns born ≥34 weeks' GA (n=203) were either immediately returned to their parents

Table 4 Overview of newborns receiving chest compressions after birth

Duration of chest compressions	Duration of PPV prior to chest compressions (s)	Gestational age in weeks	Venous pH/BE*	Arterial pH/BE*	Intubated	Intravenous access	Epinephrine boluses (n)	Fluid bolus	Immediate outcome	Therapeutic hypothermia	MRI signs of hypoxic ischaemic encephalopathy
0 min/17 s	0	40	7.27/–7.99	7.18/–8.31	No	None	–	–	Parental care	–	–
0 min/36 s	120	37	7.38/0.62	7.35/–1.20	No	None	–	–	Parental care	–	–
0 min/46 s	106	40	7.23/–4.11	7.14/–3.79	No	None	–	–	NICU admission	No	No
1 min/51 s	0 s	35	7.25/–2.38	7.20/–1.59	Yes	None	–	–	NICU admission	No	No
3 min/46 s	140	41	7.31/–4.04	7.26/–3.59	Yes	PVC	0	No	NICU admission	No	No
16 min/41 s	140	39	7.28/–5.65	7.18/–5.76	Yes	PVC	2	Yes	NICU admission	Yes	No
18 min/13 s	62	40	–/–	-/-	Yes	IO needle	1	Yes	Discontinued	–	–
19 min/28 s	44	40	6.51/–20.98	6.88/–16.58	Yes	UVC	2	Yes	NICU admission	Yes	Severe

*Blood values from umbilical cord blood gas taken directly after birth.
BE, base excess; IO, intraosseous; NICU, neonatal intensive care unit;PPV, positive pressure ventilation; PVC, peripheral venous catheter; UVC, umbilical venous catheter.

Table 5 Comparison of newborns ≥34 weeks' gestation returned to parental care or admitted to neonatal intensive care unit (NICU)

	Returned to parental care (n=128)	Admitted to NICU (n=75)	P value
General characteristics			
Weight (g)	3629 (3217–3989)	3455 (2865–3870)	0.042*
Gestational age (weeks)	40 (39–41)	40 (38–41)	0.073*
Interventions			
CPAP only	65 (51%)	20 (27%)	0.001†
PPV	63 (49%)	55 (73%)	0.001†
PPV duration (s)	77 (40–112)	202 (90–391)	<0.001*
Intubation	0	8 (11%)	<0.001‡
Chest compressions	2 (2%)	5 (7%)	0.066‡
Intravenous access	0	13 (17%)	<0.001‡
Umbilical blood values			
Arterial pH	7.19 (0.11)	7.17 (0.12)	0.166*
Arterial base excess	−4.6 (3.1)	−5.9 (4.1)	0.073*
Venous pH	7.30 (0.09)	7.26 (0.09)	0.002*
Venous base excess	−5.1 (2.8)	−6.3 (3.5)	0.023*
Apgar scores			
1 min Apgar	6 (6–8)	5 (3–6)	<0.001*
5 min Apgar	9 (8–9)	7 (6–8)	<0.001*
10 min Apgar	9 (9–10)	8 (7–9)	<0.001*

Umbilical cord blood values presented as mean (SD). All others presented as n (%). Weight, gestational age, PPV duration and Apgar presented as median (IQR).
*Mann-Whitney.
†χ^2.
‡Fisher's exact test.
CPAP, continuous positive airway pressure; PPV, positive pressure ventilation.

(n=128/63%) or admitted to the NICU (n=75/37%). Length of stay on the NICU was median 3 days (2–8), with 70% of the newborns discharged home within 1 week. Twelve newborns needed mechanical ventilation for median 3 (2–5) days. Pneumothorax was diagnosed in three of the resuscitated newborns. Therapeutic hypothermia was provided in five resuscitated newborns, of which two had MRI findings compatible with HIE; one mild/moderate and one severe. Two newborns died during the NICU stay, one due to severe HIE and the second due to severe comorbidity. Table 5 compares the characteristics of newborns >34 weeks' GA who were returned to their parents and those admitted to the NICU.

DISCUSSION

In this unselected population in a high-resource setting, newborn resuscitation was still a frequent concern, with more than 6% of all newborns requiring resuscitative

interventions at birth. Most newborns responded to respiratory support alone, and the need for full cardiopulmonary resuscitation (ie, chest compressions and epinephrine boluses) was rare. Term newborns had the lowest incidence of interventions with higher incidences among near-term (34–36 weeks' GA) and post-term (>42 weeks' GA) newborns. All extreme preterm newborns (<28 weeks' GA) received PPV, and the intubation rate was 54%.

We defined CPAP as a resuscitation intervention, as it is suggested in the ILCOR guidelines as a means to augment endogenous respiratory effort.[4] Still, its indication is not clearly defined, and it is not a part of the resuscitation algorithm. In our study, more than 30% of the newborns receiving CPAP were evaluated as adequate breathers by the viewer, highlighting the uncertain necessity of the intervention.

The incidence of PPV in this study was lower than reported in studies conducted in low-resource settings.[7–9 12] In high-resource settings with modern fetal monitoring and comprehensive obstetric care, the reported incidences vary substantially. Whether these differences represent an unwarranted variation in clinical practice, or different patient characteristics, is unknown. Niles *et al* found that 6% of newborns received PPV in a tertiary-level hospital in Philadelphia, however the caesarean section rate was near 30%, and near 50% received PPV for less than 60 s.[13] A study from a tertiary-level hospital in Iran reported that only 2.8% of the newborns received PPV at birth, despite being a referral centre for high-risk deliveries with a study population including more than 20% premature newborns <37 weeks' GA.[15] This was, however, based on medical records alone and could suffer from under-reporting. Our findings are similar to previous findings from Norway by Skåre *et al*, for both incidence and duration of PPV, in a similar setting with a similar caesarean section rate.[14 24] Our intubation rates of extreme premature <28 weeks' GA were in line with nationally reported numbers.[25]

The incidence of full cardiopulmonary resuscitation was low and comparable to findings from other studies.[5 8 15 26] Still, three of the newborns in our study received chest compressions for less than 1 min, suggesting proper airway handling might have been sufficient. When ILCOR revised their guidelines on newborn resuscitation in 2015, the recommended time of PPV before initiating chest compressions was prolonged, recognising that most compromised newborns will respond to adequate ventilatory support alone.[4] Our findings may support this recommendation.

When comparing near-term or term newborns admitted to the NICU with those who were returned to their parents after resuscitation, there was a significant difference in Apgar scores, but no difference in arterial umbilical blood gases. Apgar score is used to evaluate the newborn's condition after birth, and to determine the need for, and evaluate the effectiveness of, resuscitation.[27] The decision on whether or not to admit a newborn to the NICU after resuscitation is commonly based on clinical judgement and therefore likely to correlate with the Apgar scores. Furthermore, umbilical cord blood gas, as a predictive value for outcomes, is inconclusive.[28 29]

The mean umbilical artery base excess (BE) in non-asphyxiated newborns is −4 to −4.8 mmol/L,[30 31] and asphyxial injury does mostly not occur until fetal BE is ≤ −12 mmol/L.[32 33] The reported umbilical blood gas values in our study showed low evidence of fetal distress, and the morbidity and mortality were low. This supports the assumption that the majority of newborns in need of resuscitative interventions primarily represent newborns that are not severely affected. Nevertheless, correct and timely management of these newborns is essential for good outcomes,[7] with a potentially huge impact on socioeconomical perspectives.

This study has some limitations. It is a single-centre study with relatively few births, consequently the estimates for the incidences of low frequency interventions such as intubation, chest compressions and intravenous epinephrine are uncertain. We have no information on stimulation attempts in the delivery room prior to arrival at the resuscitation crib. Video cameras were not available at all resuscitation cribs. In particular, many of the NICU mobile resuscitation cribs were without a camera, resulting in a relatively higher missed video recording rate for premature newborns than for near-term and term newborns. This could potentially lead to an underestimation of the characteristics of the resuscitative interventions. There was a poor response rate when consent was asked by letters. This typically included newborns who were discharged early from hospital, and may represent a group where lesser interventions were required. Importantly, the results regarding incidences of resuscitative interventions were not consent or video dependent and therefore not affected by these potential biases.

CONCLUSION

Our study shows a high incidence of newborn resuscitation even in an unselected population in a high-resource setting and supports the recommendations that an adequately trained team must be available in all delivery centres for immediate assistance in the delivery room. Higher level of awareness is appropriate both in near-term and postmature deliveries.

Acknowledgements We thank all the midwives, nurse assistants and physicians working in the labour units at Stavanger University Hospital, and the parents with their newborns participating in this study.

Contributors All authors are responsible for the reported research and have approved the manuscript as submitted. All authors designed the study protocol. PAB and SIR practically implemented, supervised and carried out the study and the data collection on site. PAB analysed all video materials. All authors participated in the interpretation of the results. PAB drafted the initial manuscript. All authors read and improved the final manuscript.

Funding PAB and SIR received an unconditional PhD grant from Laerdal Foundations.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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II

Neonatology

Original Paper

Neonatology 2020;117:175–181
DOI: 10.1159/000506772

Received: January 21, 2020
Accepted after revision: February 24, 2020
Published online: April 3, 2020

Compliance with Guidelines and Efficacy of Heart Rate Monitoring during Newborn Resuscitation: A Prospective Video Study

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Keywords
Newborn resuscitation · Birth asphyxia · Positive pressure ventilation · Delivery room · Guideline compliance · Heart rate assessment · Pulse oximetry

Abstract
Objective: Newborn resuscitation guidelines recommend initial assessment of heart rate (HR) and initiation of positive pressure ventilation (PPV) within 60 s after birth in non-breathing newborns. Pulse oximeter (PO) and electrocardiogram (ECG) are suggested methods for continuous HR monitoring during resuscitation. Our aim was to evaluate compliance with guidelines and the efficacy of PO versus ECG monitoring in real-life newborn resuscitations. ***Methods:*** In this prospective observational study, we video recorded resuscitations of newborns ≥34 weeks of gestation receiving PPV at birth. ***Results:*** 104 resuscitations were analysed. Median (IQR) time from birth to arrival at the resuscitation bay was 48 (22–68) s ($n = 62$), to initial HR assessment 70 (47–118) s ($n = 61$), and to initiation of PPV 78 (42–118) s ($n = 62$). Initial HR assessment (stethoscope or palpation) and initiation of PPV were achieved within 60 s for 35% of the resuscitated newborns. Time to initial HR assessment and initiating PPV was significantly longer following vaginal deliveries than caesarean sections: 84 (70–139) versus 44 (30–66) s ($p < 0.001$) and 93 (73–139) versus 38 (30–66) s ($p < 0.001$). Time from birth and sensor application to provision of a reliable HR signal from PO versus ECG was 348 (217–524) ($n = 42$) versus 174 (105–277) s ($n = 30$) ($p < 0.001$) and 199 (77–352) ($n = 65$) versus 16 (11–22) s ($n = 52$) ($p < 0.001$). ***Conclusion:*** Initial HR assessment and initiation of PPV were achieved within 60 s after birth in only 1/3 of newborn resuscitations. When applied for continuous HR monitoring, ECG was superior to PO in time to achieve reliable HR signals in real-life resuscitations.

Introduction

Birth asphyxia remains a leading cause of neonatal mortality [1, 2] and is a major cause of long-term neurologic disability and impairment in children [3, 4]. Newborn resuscitation has the potential to reduce morbidity and mortality caused by birth asphyxia [5]. Newborn resuscitation program (NRP) guidelines state that in non-breathing newborns, the heart rate (HR) should be as-

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sessed and positive pressure ventilation (PPV) initiated within the first 60 s after birth [6, 7]. However, compliance with guidelines is challenging even for trained resuscitation teams [8, 9]. Continuous HR monitoring by pulse oximetry (PO) or electrocardiography (ECG) is essential to guide and evaluate the effect of resuscitative interventions. Studies have demonstrated that ECG is faster in achieving a reliable HR monitoring in healthy newborns under controlled settings [6, 10–12]. However, the efficacy of PO versus ECG for HR monitoring in real-life newborn resuscitation remains unclear.

The objectives of this study were, in apnoeic or inadequately breathing late-preterm and term newborns in a high-resource setting, (i) to describe if time from birth to initial assessment of HR and initiation of PPV comply with current guidelines, and (ii) to compare the efficacy of PO versus ECG in providing a reliable HR signal during real-life newborn resuscitation.

Materials and Methods

Setting

This prospective observational study was conducted from October 1, 2016 until September 30, 2017 at Stavanger University Hospital, Norway, with approximately 4,500 deliveries annually. The department of obstetrics includes a midwifery run low-risk delivery unit, a general labour ward, and two operating rooms for elective and emergency caesarean sections. Each site has a centrally placed resuscitation room with a resuscitation bay, where compromised newborns are brought for stabilization and resuscitation. The resuscitation bays are equipped with a patient monitor (Carescape Monitor B450 or B650, GE Healthcare, Chicago, IL, USA) and basic NRP-recommended resuscitation equipment. The distance from the delivery rooms to the resuscitation room varies between 3 and 20 m (mean 12 m). For caesarean sections, the resuscitation room is adjacent to the operating theatre.

Resuscitation Team and Guideline

A resuscitation team is called upon for high-risk deliveries (i.e., shoulder dystocia, pathologic foetal HRs, and emergency caesarean sections), consisting of a paediatric resident and/or a consulting neonatologist and the midwife or nurse assistant responsible for the delivery. A neonatal nurse, an anaesthesiologist, and/or an anaesthetic nurse can be called upon if needed. All staff involved in newborn resuscitation undergo regular simulation-based training with fortnightly in situ simulation sessions and a yearly whole-day simulation training session. National resuscitation guidelines [13] are based on the International Liaison Committee on Resuscitation (ILCOR) [7] and European Resuscitation Council guidelines on newborn resuscitation [6]. Apnoeic or inadequately breathing newborns not responding to drying and stimulation are immediately brought to the resuscitation bay. Assessing the initial HR (by stethoscope or palpation) and initiating PPV should be accomplished within 60 s after birth. Continuous HR monitoring should be established, either by PO (Masimo LNCS Neo wrap-around sensor, Masimo, Irvine, CA, USA) placed around the newborn's right wrist or hand and/or gel electrode ECG (Neonatal ECG electrodes, CareFusion, San Diego, CA, USA) applied to the newborn's chest. The order of HR sensor application, PO, and/or ECG is left to the discretion of the resuscitation teams.

Data Collection

An "observational incidence report form" was completed for every newborn, documenting if a newborn received PPV after birth. Resuscitations were recorded by video cameras with motion detectors mounted on the resuscitation bays. The patient monitor image displaying PO and ECG data was extracted from the video output of the patient monitor and synchronically stored with the camera recordings. To determine the time from birth, the nurse assistants were instructed to start a stopwatch at the time when the whole body was delivered. When newborns were brought to the resuscitation bay, the stopwatch showing the exact time from birth was presented to the camera. Deferred parental consent was obtained prior to video analysis. For patient and personnel safety, all video recordings were erased after 3 weeks.

Inclusion and Exclusion Criteria

All newborns of gestational age ≥34 weeks who received PPV at birth were eligible for this study. Newborns were excluded when perceived to have adequate respiratory effort upon arrival at the resuscitation bay, if the treatment was not video recorded (i.e., due to technical issues), parents or staff declined participation, or consent could not be obtained within 3 weeks after the incident.

Data Analysis

A single investigator (P.A.B.) reviewed all video recordings using video management software from XProtect Smart Client (Milestone, Copenhagen, Denmark). The respiratory effort of the newborn on arrival at the resuscitation bay was categorized as adequate, inadequate (e.g., grunting or severe retractions), or apnoeic [6, 7]. Drying and stimulation were considered adequate if the newborn received tactile truncal stimulation (drying, chest and back rubs) prior to respiratory support as opposed to excessive stimulation for longer than 15 s or none at all [14]. We registered time and mode of initial HR assessment and time to initiation of and duration of PPV. The time to reliable PO signals was defined as the time from when the sensor was placed around the newborn's hand or wrist until the monitor displayed a continuous pulse wave and HR values for at least 3 s. The time to reliable ECG signals was defined as the time from when all three electrodes were placed until the monitor showed regular QRS complexes. These definitions of reliable PO and ECG signals are in accordance with previously published studies [15–17]. The time to reliable HR monitoring was compared between newborns with 5-min Apgar <7 and ≥7 [18]. Patient and birth characteristics were extracted from medical records.

Statistics

Data were analysed using R-studio version 1.2.1335 (R Core Team 2019, Vienna, Austria), and results presented as number (%) or median (IQR). Groups were compared with Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. All reported p values are two sided. $p < 0.05$ was considered statistically significant.

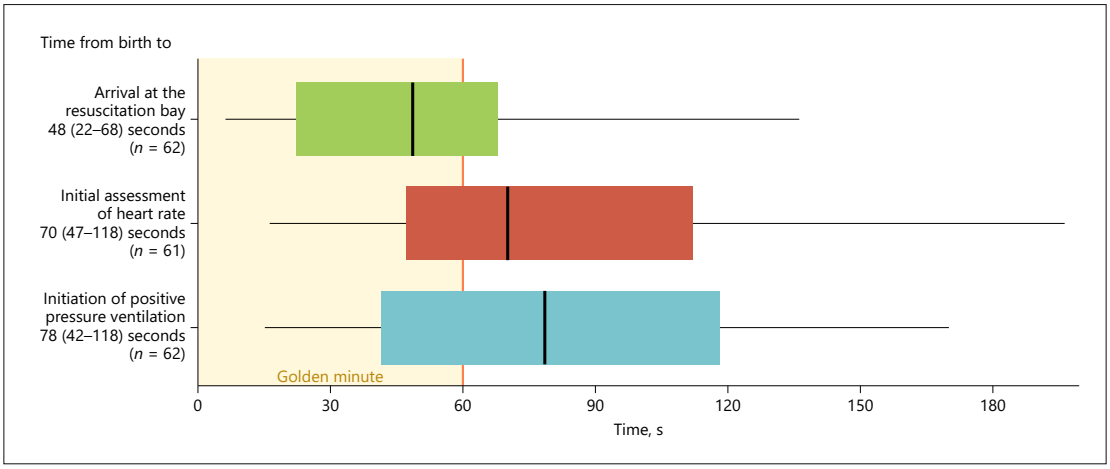

Fig. 1. Timelines from birth to arrival at the resuscitation bay, assessment of initial heart rate, and initiation of positive pressure ventilation for apnoeic or inadequately breathing newborns. The boxes represent the median, first and third quartile and the whiskers represent the range without outliers. Values in headings are shown as median (IQR).

Ethics and Patient Safety

The study was evaluated as non-interventional by the regional ethical committee (2015/1162/REK vest) and approved by the hospital data protection officer. Deferred consent was chosen as only 3% of newborns need PPV at birth in our hospital [19], and obtaining informed consent prior to birth from all parents could evoke unnecessary anxiety. Only the project team members had access to the video recordings. Parents were entitled to view the recording of their newborn, but copies were not provided.

Results

Of 4,619 newborns with gestational age ≥34 weeks born in the study period, 134 (2.9%) were resuscitated with PPV within the first 5 min after birth. Of these, 25 were not included due to missing consent ($n = 9$) or because the resuscitations were not video recorded ($n = 16$). During video analysis, five newborns were excluded for having adequate respiratory effort when arriving at the resuscitation bay. The remaining 104 newborns were included in the further analyses; 89 apnoeic and 15 having inadequate respiratory efforts. The characteristics of the included newborns and deliveries are shown in Table 1.

Initial Assessment and Time to Initiate PPV

Upon arrival at the resuscitation bay, 78/104 (75%) of the newborns were adequately dried and stimulated. The

Table 1. Clinical characteristics and modes of deliveries of 104 apnoeic or inadequately breathing newborns receiving positive pressure ventilation

Characteristics of newborns	
Birth weight, g	3,500 (2,984–3,906)
Male gender	67/104 (64%)
Apgar scores	
1-min Apgar	5 (3–6)
5-min Apgar	7 (6–9)
10-min Apgar	9 (8–10)
Umbilical blood values	
Arterial pH	7.17 (0.12)
Arterial base excess	–5.0 (3.5)
Venous pH	7.27 (0.13)
Venous base excess	–5.7 (3.5)
Characteristics of deliveries	
Delivered by vacuum	32/104 (31%)
Delivered by forceps	6/104 (5.8%)
Induced labour	32/104 (31%)
Mode of delivery	
Vaginal cephalic	55/104 (53%)
Vaginal breech	8/104 (7.7%)
Planned caesarean section	2/104 (1.9%)
Emergency caesarean section	39/104 (38%)

Birth weights and Apgar scores are given as median (IQR). Umbilical blood values are given as mean (SD). All other data presented as *n* (% of included).

Table 2. Time from birth and arrival at the resuscitation bay to initial heart rate assessment and positive pressure ventilation in newborns, either apnoeic or inadequately breathing at birth, by delivery mode

	Total	Vaginal delivery	Caesarean section	*p* value
Time from birth to arrival at the resuscitation bay	48 (22–68) (*n* = 62)	62 (50–116) (*n* = 38)	19 (12–26) (*n* = 24)	<0.001
Time from arrival at the resuscitation bay to				
Initial assessment of heart rate	23 (10–46) (*n* = 99)	32 (12–49) (*n* = 59)	16 (8–40) (*n* = 40)	0.11
Initiation of positive pressure ventilation	22 (12–42) (*n* = 104)	23 (12–40) (*n* = 63)	21 (13–43) (*n* = 41)	0.79
Time from birth to				
Initial assessment of heart rate	70 (47–118) (*n* = 61)	84 (70–139) (*n* = 37)	44 (30–66) (*n* = 24)	<0.001
Initiation of positive pressure ventilation	78 (42–118) (*n* = 62)	93 (73–139) (*n* = 38)	38 (30–66) (*n* = 24)	<0.001

All values are presented as median (IQR) seconds. Groups are compared with Mann-Whitney test (two sided).

initial HR was assessed in 99/104 (95%) newborns, either by stethoscope (*n* = 84) or through palpation (*n* = 15).

The time from birth to arrival at the resuscitation bay was recorded in 62 ventilated newborns. Of these, 22/62 (35%) had the initial HR assessed and 22/62 (35%) PPV initiated within the first 60 s of birth. The timelines from birth to arrival at the resuscitation bay, initial assessment of HR, and initiation of PPV are shown in Figure 1. The time from arrival at the resuscitation bay to the first assessment of HR and initiation of PPV was 23 (10–46) and 22 (12–42) s. PPV was continued for 98 (49–219) s (*n* = 104).

The time from birth and arrival at the resuscitation bay to initial HR assessment and initiation of PPV, by delivery mode, is shown in Table 2. The time to arrival at the resuscitation bay was significantly shorter following caesarean sections than vaginal deliveries, contributing to an earlier initial HR assessment and initiation of PPV.

HR Monitoring

A PO sensor was applied in 98/104 (94%) resuscitations, whereas ECG electrodes were applied in 66/104 (63%). Monitor recordings of PO and ECG were eligible for analysis in 85 and 58 resuscitations. PO failed to provide reliable HR signals in 20/85 (24%) resuscitations whereas ECG failed to provide reliable HR signals in 6/58 (10%) (p = 0.110). There was no difference in time from birth or from arrival at the resuscitation bay to the application of PO and ECG sensors. The time to reliable HR signals was significantly shorter for ECG than for PO (Fig. 2).

The time to PO-based HR signals was 296 (149–393) and 134 (63–291) s in newborns with 5-min Apgar score <7 (*n* = 25) versus ≥7 (*n* = 40) (p = 0.03). There was no significant difference in the time to ECG signals in newborns with 5-min Apgar <7 (*n* = 20) versus ≥7 (*n* = 32); 14 (11–19) and 16 (12–24) s (p = 0.332). The difference between PO and ECG in obtaining reliable HR signals was significant both for newborns with 5-min Apgar score <7 (p < 0.001) and ≥7 (p < 0.001).

Discussion

This prospective study used video recordings to document timelines during 104 real-life resuscitations of apnoeic newborns. We were not able to assess HR or initiate PPV within 60 s after birth in approximately two-thirds of the resuscitations. Similar results were reported by McCarthy et al. [8], having studied high-risk deliveries attended by alerted teams. They did not achieve HR assessment and initiation of PPV within the Golden minute in 2/3 of the resuscitations, despite the newborn arriving at the resuscitation bay at 16 s [8]. The delay in completing tasks in our department was mainly due to a delay from birth to arrival at the centrally placed resuscitation bays following vaginal deliveries. However, Niles et al. [9] reported that only 45% of apnoeic newborns received PPV within 60 s of birth in a setting with resuscitation bays in each delivery room, suggesting that the distance to the resuscitation bay is not decisive. We practise delayed cord clamping, and all vaginally delivered newborns are dried and stimulated on the mother's chest. Birth attendants may hesitate to separate the newborn from the mother, hoping that the newborn will respond to stimulation, thus delaying the transfer of the newborn to the resuscitation bay. Bedside resuscitation units, allowing intact cord resuscitation, could have reduced the time to initiating PPV [20, 21].

Initial HR Assessment and HR Monitoring

Initial HR was mostly assessed by stethoscope, which is the most common method for HR assessment world-

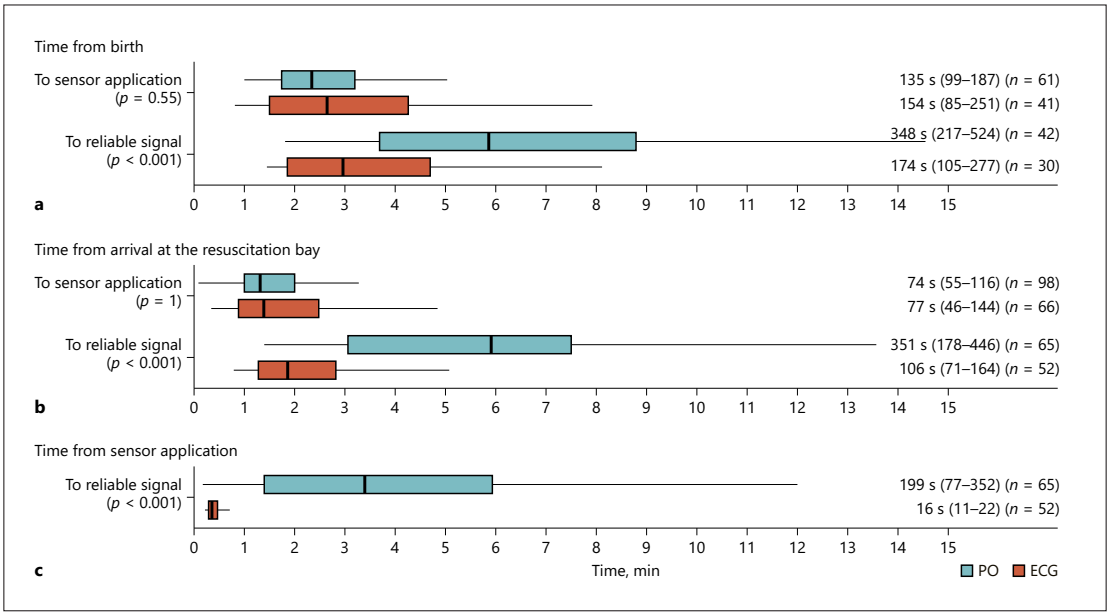

Fig. 2. Efficacy of ECG and PO in achieving a reliable HR monitoring during real-life newborn resuscitation. The boxes represent the median, first and third quartile and the whiskers represent the range without outliers. Values to the right of the boxplots are presented as median seconds (IQR). *p* values are calculated with two-sided Mann-Whitney U test.

wide. However, HR assessment by stethoscope has proven unreliable [22], and more accurate continuous monitoring of HR by PO and ECG during resuscitation is recommended [6, 7].

In our study, reliable HR monitoring through PO was achieved in about 80% of the resuscitations when applied, but only after several minutes' delay. Importantly, the time to reliable HR signals by PO was significantly longer in newborns with 5-min Apgar score <7, possibly due to poor circulation of the extremities in more severely compromised newborns. Consequently, the team must rely on repeated manual HR assessments to guide the resuscitation during the first critical minutes, at the expense of personnel resources and reliable HR feedback [23, 24]. Our findings are not in accordance with earlier studies, which have demonstrated that reliable HR monitoring by PO can be achieved within 12–32 s from sensor application and 68–122 s after birth [16, 17, 25–28]. However, these studies were mainly conducted on healthy newborns or during high-risk deliveries with personnel dedicated to apply PO sensors immediately after birth.

Several studies suggest that ECG is a more effective method for determining HR during the first minutes after birth [17, 25, 26, 29], in agreement with our study. Moreover, ECG was equally effective in newborns with 5-min Apgar scores <7. Our findings support the recommendation of ECG as an alternative to PO for HR monitoring during newborn resuscitation. However, the use of ECG does not replace the need for PO to assess the oxygenation.

Troublesome fixation of ECG leads on wet skin is an issue during newborn resuscitation [10]. We found that this challenge applied to PO sensors as well. The occasional vigorous handling of the newborn during resuscitation, combined with the newborn's wet skin, disrupted or delayed the fixation of both the PO wrap-around sensor and the ECG gel electrodes. Consequently, the sensors had to be reapplied or replaced, further delaying the time to obtain reliable HR. This was not a frequent concern, but has likely contributed to the delay in achieving continuous HR monitoring in our real-life study compared to studies with more con-

trolled settings. Nevertheless, these aspects of real-life resuscitations should be taken into account when comparing the reliability of different methods of continuous HR monitoring in newborns.

Limitations

Our study has limitations. We do not have information about the management of the newborns prior to arrival at the resuscitation bay. Stimulation attempts in the delivery room or events where the newborn collapsed after initial crying are both plausible reasons for a delayed transfer for resuscitation. Due to technical issues, 16 resuscitations were not video recorded, and another 13 newborns did not have HR monitor recordings. However, these incidents occurred randomly and should not bias the results.

Conclusion

In this study with video recordings of newborn resuscitations, initial HR assessment and initiation of PPV were not achieved within the recommended 60 s after birth in the majority of resuscitations, largely due to a delay in transfer to centrally placed resuscitation bays. When PO or ECG was applied for continuous HR monitoring during real-life resuscitations, reliable HR signals were achieved substantially faster by ECG than by PO. The time to reliable HR signals by PO was significantly longer in newborns with 5-min Apgar score <7 versus ≥7, whereas ECG was equally effective in both groups.

Acknowledgement

We thank all the midwives, nurse assistants, and physicians working in the labour units at Stavanger University Hospital, and parents with their newborns participating in this study.

Statement of Ethics

The study was evaluated as non-interventional by the regional ethical committee (2015/1162/REK vest) and approved by the hospital data protection officer. Deferred consent was chosen as only 3% of newborns need PPV at birth in our hospital [19], and obtaining informed consent prior to birth from all parents could evoke unnecessary anxiety.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

P.A.B. and S.I.R. have received unconditional grants from Laerdal Foundations.

Author Contributions

All authors designed the study protocol. P.A.B. and S.I.R. practically implemented, supervised, and carried out the study and the data collection on site. P.A.B. analysed all video material. All authors participated in the interpretation of the results. P.A.B. drafted the initial manuscript. All authors read and improved the final manuscript.

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III

OPEN ACCESS

Changes in heart rate from 5 s to 5 min after birth in vaginally delivered term newborns with delayed cord clamping

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► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/fetalneonatal-2020-320179).

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Received 7 July 2020
Revised 21 October 2020
Accepted 23 October 2020

To cite: Bjorland PA, Ersdal HL, Eilevstjønn J, *et al*. *Arch Dis Child Fetal Neonatal Ed* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2020-320179

ABSTRACT

Objective To determine heart rate centiles during the first 5 min after birth in healthy term newborns delivered vaginally with delayed cord clamping.

Design Single-centre prospective observational study.

Setting Stavanger University Hospital, Norway, March–August 2019.

Patients Term newborns delivered vaginally were eligible for inclusion. Newborns delivered by vacuum or forceps or who received any medical intervention were excluded.

Interventions A novel dry electrode electrocardiography monitor (NeoBeat) was applied to the newborn's chest immediately after birth. The newborns were placed on their mother's chest or abdomen, dried and stimulated, and cord clamping was delayed for at least 1 min.

Main outcome measures Heart rate was recorded at 1 s intervals, and the 3rd, 10th, 25th, 50th, 75th, 90th and 97th centiles were calculated from 5 s to 5 min after birth.

Results 898 newborns with a mean (SD) birth weight 3594 (478) g and gestational age 40 (1) weeks were included. The heart rate increased rapidly from median (IQR) 122 (98–146) to 168 (146–185) beats per minute (bpm) during the first 30 s after birth, peaking at 175 (157–189) bpm at 61 s after birth, and thereafter slowly decreasing. The third centile reached 100 bpm at 34 s, suggesting that heart rates <100 bpm during the first minutes after birth are uncommon in healthy newborns after delayed cord clamping.

Conclusion This report presents normal heart rate centiles from 5 s to 5 min after birth in healthy term newborns delivered vaginally with delayed cord clamping.

What is already known on this topic?

- Heart rate is an important clinical indicator of newborn status immediately after birth.
- Centile charts of newborn heart rate after birth lack data from the first 60 s and were obtained with immediate cord clamping.
- Delayed cord clamping is increasingly implemented as standard of care and may result in a smoother newborn transition with less bradycardia.

What this study adds?

- A heart rate centile chart from 5 s to 5 min after birth in healthy newborns delivered vaginally and with delayed cord clamping.
- The median heart rate increases rapidly and peaks at approximately 1 min after birth, earlier than previously reported.
- Heart rates below 100 beats per minute are uncommon in newborns who do not need intervention and account for less than 5% of newborns at 30 s after birth.

BACKGROUND

The transition from intrauterine to extrauterine life involves a series of rapid cardiopulmonary changes.[1] The heart rate of the newborn infant is one of the most important clinical indicators used to determine the need for and response to resuscitation.[2] A heart rate below 60 beats per minute (bpm) is considered an indication to commence cardiac compressions, and below 100 bpm is a requirement for positive pressure ventilation.[2]

Widely referenced heart rate centiles were published in 2010 by Dawson *et al*.[3] These were obtained from newborns undergoing immediate cord clamping, using a pulse oximeter, and acquiring data from approximately 60 s after birth. Infants had a median (IQR) heart rate of 96 (65–127) bpm at 1 min of life, rising to 139 (110-166) at 2 min. These findings have led to confusion among clinicians, since they suggest that many 'normal' infants meet criteria for intervention.

It has been suggested that pulse oximetry systematically underestimates heart rate at birth compared with three-lead gel electrode electrocardiography (ECG).[4] Furthermore, ECG detects heart rate much earlier compared with pulse oximetry.[5–8] A novel newborn heart rate metre based on dry electrode ECG allows reliable heart rate monitoring at 3–10 s after birth,[9] even earlier than previously achieved by conventional three-lead gel electrode ECG.[4 6]

Delayed cord clamping, defined as that occurring beyond 1 min after birth, is increasingly implemented as standard of care worldwide and might result in a smoother newborn transition at birth and less bradycardia.[10 11] The International Liaison Committee on Resuscitation (ILCOR) recently suggested that ECG can be used to provide a rapid and accurate estimation of the heart rate.[12]

Therefore, due to changes in standard umbilical cord management practices and in the technology to assess heart rate, the pattern of normal heart rate changes during the first minutes of life requires re-evaluation.

The aim of this study was to describe the pattern of heart rate changes during the first minutes after birth in uncompromised term newborns delivered vaginally and undergoing delayed cord clamping, using a dry electrode ECG-based newborn heart rate monitor.

METHODS

Setting

This study was conducted at Stavanger University Hospital, Norway, from March to August 2019. Stavanger University Hospital serves a population of 350 000 with approximately 4500 deliveries annually and is the only hospital in the region with delivery and newborn services. A midwife and a nurse assistant are present at each birth and may call on an obstetrician for assistance whenever needed. Delayed cord clamping is implemented as standard procedure.

Inclusion and exclusion process

All women admitted to the department of obstetrics in labour at term (≥37 weeks of gestation) were asked to participate in the study. Newborns delivered by caesarean section or assisted delivery (ie, vacuum or forceps) and newborns who received any medical interventions (eg, supplementary oxygen or assisted ventilation) at birth were excluded.

Data collection

Laerdal Global Health (Stavanger, Norway) developed a novel neonatal heart rate metre named NeoBeat, incorporating dry electrodes in an abdomen-shaped circlet for rapid application to the newborn. Instead of gel electrodes used in traditional three-lead ECG, NeoBeat uses dry electrodes, and thorough skin cleaning prior to application is unnecessary. The NeoBeat heart rate algorithm is based on a zero-crossing count algorithm[13] that adds a proprietary layer that includes noise detection and noise handling. Motion is the primary source of ECG distortion, and the algorithm uses measured acceleration energy as well as ECG features such as amplitude and rate variability to determine when there is likely too much motion to get a reliable heart rate. A predecessor of NeoBeat, based on the same technology, was used in a study in Tanzania, and heart rate was registered within 3–10 s after birth.[14] NeoBeat displays the newborn's heart rate and can transfer heart rate data via Bluetooth Low Energy to the Liveborn tablet application (Laerdal Global Health, Stavanger, Norway).

During the study period, each delivery room was equipped with a NeoBeat. If prospective parental consent was given, the nurse assistant attending the birth carried a tablet (iPad, Apple, Cupertino California, USA) with the Liveborn application installed. The nurse assistant marked the exact time of birth (ie, time when the whole body was delivered) by starting a counter in the application, and the dry electrodes were applied to the newborn by the midwife without delay (online supplemental figure 1). Midwifes were trained in the use of the NeoBeat and the Liveborn application using manikins, and data collection was trialled during a pilot phase before study commencement. The newborn was managed in accordance with standard guidelines: drying and stimulation, immediate skin-to-skin contact and delayed cord clamping for at least 1 min. The Liveborn application recorded real-time heart rate data from the ECG every second during the data collection period. NeoBeat did not provide heart rate if it detected that the signal was too distorted with noise or motion artefacts. The nurse assistant marked the time of cord clamping in the application. The heart rate was recorded for the first 5 min after birth, or until the cord was clamped if this occurred beyond 5 min. Data collection did not interfere with the routine handling of the newborns after birth. Patient and birth characteristics were extracted from the medical record.

Data analysis

We excluded cases where time of birth or heart rate data were suspected to be erroneous based on the following criteria: (1) if the heart rate was registered by the ECG before the recorded time of birth and (2) less than 30 s of heart rate registered during data collection.

Statistics

Using an SD for the heart rate of 21 bpm, as reported by Linde *et al*,[14] a sample size calculation showed that ≥68 observations were needed at each second to estimate the median heart rate with a margin of error of less than ±5 bpm. To obtain a margin of error of less than ±5 bpm for the estimate of the 10th and 90th centiles, sample size calculations showed that at least 482 observations were required.[15] We planned to include 500–1000 newborns to ensure sufficient good quality data. Heart rate data were extracted using Mathlab 2019a (MathWorks, Natick, Massachusetts, USA). Data were analysed, and charts were drawn in R V.3.6.2 (R Core Team 2019, Vienna, Austria). Continuous variables are presented as mean (SD) when normally distributed, and median (IQR) when non-normally distributed. Centile charts were drawn by calculating centiles empirically and then smoothing them using the local regression method (LOESS).[16]

Ethics

Written parental consent was obtained prior to inclusion.

RESULTS

In total, 1764 newborns were delivered vaginally at term during the study period. Consent was obtained for the inclusion of 1416 newborns in the data collection. Of those, 424 were excluded due to: (1) connectivity/technical issues during data collection (n=231), (2) instrumental delivery (n=142) and (3) medical interventions after birth (n=51). Another 94 newborns were excluded during data analysis because the NeoBeat registered heart rate before the recorded time of birth (n=75) or too few heart rate observations were registered (n=19). The remaining 898 newborns were included in the analysis, and their characteristics are presented in table 1.

Time of cord clamping was recorded in 784 newborns, and umbilical cord blood values were available for 854 newborns. Figure 1 shows an overview of the inclusion and exclusion process.

A total of 227 038 individual heart rate observations were registered, resulting in a median (IQR) of 276 (243–286) heart rate observations for each newborn, and 808 (741–819) individual heart rate observations at each second during the 5 min study period. At least 68 individual heart rate observations were reached at 5 s (n=77) and at least 482 individual heart rate observations were reached at 14 s (n=510) after birth. The numbers of individual heart rate observations recorded at each second after birth are displayed in figure 2. The heart rate centiles from 5 s after birth are shown in table 2 and figure 3.

Table 1 Newborn characteristics

	Total (n=898)
Gestational age (weeks)	40 (1)
Weight (gram)	3594 (478)
Male gender	439 (51)
Apgar scores	
1 min Apgar	9 (9–10)
5 min Apgar	10 (10–10)
10 min Apgar	10 (10–10)
Umbilical cord blood values*	
Arterial pH	7.35 (2.53)
Arterial base deficit (mmol/L)	3.7 (2.4)
Venous pH	7.34 (0.07)
Venous base deficit (mmol/L)	4.1 (2.1)
Time after birth to cord clamp (s)	319 (244–412)
Time after birth to the first heart rate data (s)	13 (9–22)

Male gender presented as n (%); Apgar scores, time to cord clamp and time to the first heart rate data presented as median (IQR); all remaining results presented as mean (SD).
*Available in 854 newborns.
†Available in 784 newborns.

The median (IQR) heart rate was 122 (98–146) bpm at 5 s after birth, after which it increased rapidly to 175 (157–189) bpm at 61 s after birth. During the following minutes, the median (IQR) heart rate slightly decreased to approximately 167 (152–179) bpm at 5 min after birth. Heart rates below 100 bpm were uncommon, and the 10th and 3rd centiles crossed 100 bpm at 22 and 34 s after birth, respectively.

DISCUSSION

In this study, we describe the pattern of normal heart rate changes using centiles during the first 5 min after birth in term newborns delivered vaginally, in a setting with delayed cord clamping as standard of care. A novel ECG application method made it feasible to achieve heart rate measurements from 5 s after birth, filling a gap in the existing literature. The heart rate centiles from Dawson *et al*[3] did not include the first minute after birth. This is of importance, as resuscitation guidelines recommend resuscitative actions during the first 60 s after birth based on the newborn's heart rate as well as breathing. Most guidelines recommend initiation of positive pressure ventilation and oxygen saturation monitoring of infants with heart rates below 100 bpm.[12]

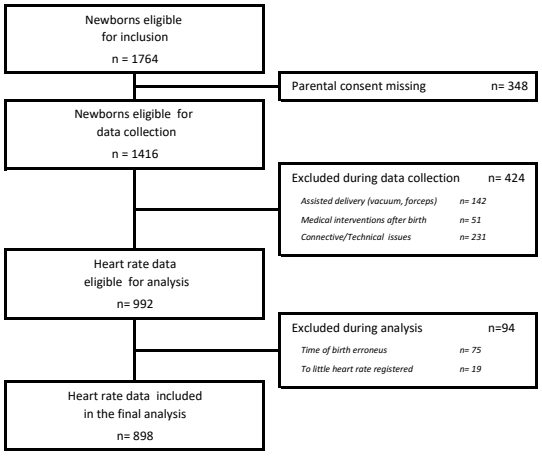

Figure 1 Overview of inclusion and exclusion process.

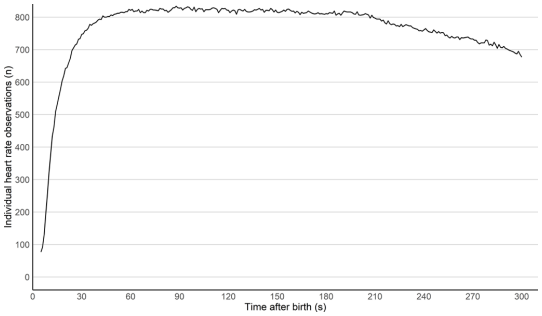

Figure 2 Number of individual heart rate observations at each second after birth.

Our findings differ from the existing centile charts by Dawson *et al*,[3] where heart rates below 100 bpm were commonly observed in healthy newborns during the first minutes after birth. In our study, a heart rate below 100 bpm after 30 s of life was rare. Our results may provide support for the controversial recommendation to provide respiratory support to newborns with heart rates below 100 bpm. Studies of compromised infants requiring assistance are required to progress this question.

Furthermore, Dawson *et al*[3] reported that the 50th centile heart rate reached a plateau of around 160 bpm at 3 min after birth, whereas our results suggest an early peak of approximately 175 bpm within the first minute after birth, thereafter slowly decreasing. The recent study of Padilla-Sánchez *et al*[11] assessed heart rates using pulse oximetry during the first 10 min of life after delayed cord clamping. They found an earlier stabilisation of heart rate compared with Dawson *et al*.[3] They attributed this difference to the haemodynamic effects of delayed cord clamping. However, their results differ from ours in that they

Table 2 Heart rate centiles the first 5 min after birth for term newborns delivered vaginally with delayed cord clamping and no medical intervention

Seconds after birth	Heart rate (bpm) centiles						
	3rd	10th	25th	50th	75th	90th	97th
5	64	78	98	122	146	162	169
10	69	82	102	129	154	172	182
20	81	95	123	155	177	191	202
30	93	111	146	168	185	198	208
40	101	122	152	172	187	199	210
50	104	127	155	174	189	199	209
60	106	131	157	174	189	199	208
90	109	138	157	173	187	197	204
120	112	139	156	171	185	195	203
150	112	136	154	169	183	194	203
180	114	136	153	168	182	192	203
210	117	137	153	167	182	192	202
240	118	138	153	167	181	192	202
270	119	138	152	167	180	192	201
300	120	137	152	167	179	191	199

bpm, beats per minute.

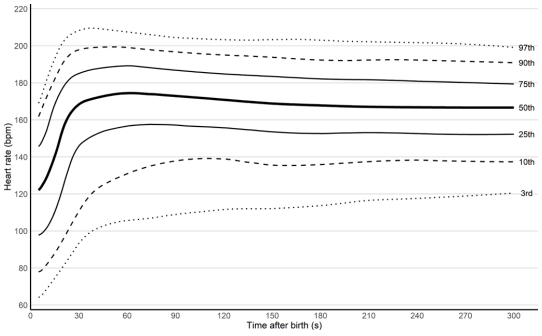

Figure 3 The 3rd, 10th, 25th, 50th, 75th, 90th and 97th heart rate centiles from 5 s after birth for vaginally born term newborns with delayed cord clamping and no medical intervention.

found that heart rates below 100 bpm are to be expected in at least 10% of all healthy newborns the first minute after birth.

In our study, we recorded heart rates by ECG, whereas Dawson *et al*[3] and Padilla-Sánchez C *et al*[11] conducted their studies using a pulse oximeter. Pulse oximetry may underestimate heart rates when compared with ECG, especially during the first minutes of life,[4 7] and might have contributed to the lower heart rates and slower rise in heart rate measured by Dawson and Padilla-Sánchez *et al*. We believe that the different methods of measuring heart rates provide an important explanation for the differences between the centiles of Dawson and ours. ILCOR suggests that in babies requiring resuscitation, ECG can be used to provide a rapid and accurate estimation of heart rate. Hence, a reference range for heart rates obtained using ECG is required.

During labour, the normal baseline fetal heart rate is 110–160 bpm. Brief decelerations to 100–120 are common, attributed to vagal activation in association with uterine contractions.[17 18] The same changes may occur as the newborn descends through the birth canal, and our results suggest a drop in heart rate immediately prior to birth, followed by a rapid increase during the first minute of life.

Delayed cord clamping is considered beneficial for the cardiovascular transition and newborn outcomes.[19] The immediate effect of delayed cord clamping on heart rate is not clear, and randomised controlled studies on ventilated preterm lambs show conflicting results.[10 20] Clinical studies on newborns confirm that delayed cord clamping results in a lower heart rate during the first minutes after birth.[21 22] Importantly, these studies were conducted with a pulse oximeter. Our study did not analyse heart rate in relation to cord clamping and therefore cannot draw conclusions regarding the impact of delayed cord clamping on heart rate.

All newborns in the present study were delivered vaginally. In the study by Dawson *et al*,[3] nearly 50% of the newborns were delivered by caesarean section. They reported a slower rise in heart rate and stabilisation at a lower level around 150 bpm in newborns born by caesarean sections compared with vaginal births (stabilising around 160 bpm). Similar findings were reported by Gonzales and Salirrosas,[23] describing lower heart rate obtained by pulse oximetry in newborns born by caesarean sections compared with vaginal births. Our centile charts are only applicable to term newborns born vaginally, and studies on normal heart rate measured by ECG in newborns born by caesarean sections are required.

Limitations

The time of the first heart rate detection varied between newborns. For half of the included newborns, the heart rate was detected from 13 s, whereas for 75%, the heart rate was detected from 22 s. Even some healthy newborns require stimulation after birth, which will possibly delay the heart rate detection of the NeoBeat due to motion, and these newborns could possibly also have a different heart rate than those without need of stimulation. We have no reason to believe that this has a major impact on the results, but the presented heart rates for the first 15–20 s could be considered more cautiously.

There was a high percentage of missed registrations due to technical issues. This was mostly due to the interruptions in the Bluetooth connection between NeoBeat and the Liveborn application. However, this occurred at random and should not create a bias. To make data collection less intrusive to the parents, we assigned data collection to the attending midwives and nurse assistants. The staff therefore operated the NeoBeat and the application while carrying out other tasks, possibly contributing to the relatively high number of missed cases due to technical issues and erroneous recordings. Dispersing data collection to several individuals may affect validity. However, all personnel involved in data collection were thoroughly instructed in all procedures. Finally, the reference values presented in this study are obtained by ECG and cannot be applied as reference values for heart rates measured by pulse oximetry.

CONCLUSION

Using novel dry electrode ECG technology, this study describes the pattern of normal heart rate changes from 5 s to 5 min after birth in healthy, vaginally delivered term newborns undergoing delayed cord clamping. The median heart rate rapidly increased from 122 bpm at 5 s after birth to a maximum of 175 bpm at approximately 1 min after birth. The third centile crossed 100 bpm at 34 s, suggesting that heart rates <100 bpm during the first minutes after birth are uncommon in healthy newborns after delayed cord clamping.

Acknowledgements We would like to thank all the midwives and nurse assistants in the labour units at Stavanger University Hospital and parents with their newborns participating in this study. We would also like to thank Anastasia Ushakova for statistical counselling.

Contributors PAB, SIR, HLE and KØ designed the study protocol. PAB and SIR practically implemented, supervised and carried out the study and the data collection on site. JE extracted and PAB analysed the heart rate data. All authors participated in the interpretation of the results. PAB drafted the initial manuscript. All authors read, revised and approved the final manuscript.

Funding PAB has an unconditional PhD grant from the Laerdal Foundation (Grant Number 30026) and SR has an unconditional Post Doc grant from the Laerdal Foundation (Grant Number 50007), Stavanger, Norway. NeoBeats were provided by Laerdal Medical.

Disclaimer The external funding sources had no role in study design, data collection, data analysis, data interpretation, writing of the report or in the decision to submit the paper for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Competing interests JE is employed at Laerdal Medical. All other authors had no other financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years or no other relationships or activities that could appear to have influenced the submitted work.

Patient consent for publication Parental/guardian consent obtained.

Ethics approval The study was approved by the regional ethical committee (REKvest 2018/338) and the hospital data protection officer.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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IV

RESUSCITATION 170 (2022) 222–229

Available online at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Tidal volumes and pressures delivered by the NeoPuff T-piece resuscitator during resuscitation of term newborns

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Abstract

Aim: T-piece resuscitators are commonly used for respiratory support during newborn resuscitation. This study aimed to describe delivered pressures and tidal volumes when resuscitating term newborns immediately after birth, using the NeoPuff T-piece resuscitator.

Method: Observational study from June 2019 through March 2021 at Stavanger University Hospital, Norway, including term newborns ventilated with a T-piece resuscitator after birth, with consent to participate. Ventilation parameters of the first 100 inflations from each newborn were recorded by respiration monitors and divided into an early (inflation 1–20) and a late (inflation 21–100) phase.

Results: Of the 7730 newborns born, 232 term newborns received positive pressure ventilation. Of these, 129 newborns were included. In the early and the late phase, the median (interquartile range) peak inflating pressure was 30 (28–31) and 30 (27–31) mbar, and tidal volume was 4.5 (1.6–7.8) and 5.7 (2.2–9.8) ml/kg, respectively. Increased inflation times were associated with an increase in volume before plateauing at an inflation time of 0.41 s in the early phase and 0.50 s in the late phase. Inflation rates exceeding 32 per minute in the early phase and 41 per minute in the late phase were associated with lower tidal volumes.

Conclusion: There was a substantial variation in tidal volumes despite a relatively stable peak inflating pressure. Delivered tidal volumes were at the lower end of the recommended range. Our results indicate that an inflation time of approximately 0.5 s and rates around 30–40 per minute are associated with the highest delivered tidal volumes.

Keywords: Newborn resuscitation, T-piece resuscitator, NeoPuff, Positive pressure ventilation, Tidal volume

Introduction

The transition from foetal to newborn life involves aeration of liquid-filled lungs and onset of air breathing.[1] While most newborns make this transition spontaneously, 4–8% need positive pressure ventilation (PPV) after birth.[2–4] PPV may be administered by a self-inflating bag, a flow-inflating bag, or a flow-driven T-piece resuscitator. Although there has been insufficient evidence to recommend one device over another,[5] flow driven T-piece resuscitators have become increasingly popular in high- and middle resource settings,

Abbreviations: PPV, Positive Pressure Ventilation, PIP, Peak Inflating Pressure, PEEP, Positive End-expiratory Pressure, FRC, Functional Residual Capacity

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https://doi.org/10.1016/j.resuscitation.2021.12.006
Received 22 October 2021; Received in Revised form 2 December 2021; Accepted 7 December 2021

in large part due to their advantage of delivering a steady peak inflating pressure (PIP) and positive end-expiratory pressure (PEEP).[6–8] A recent International Liaison Committee on Resuscitation (ILCOR) summary statement suggests the use of a T-piece resuscitator over the use of a self-inflating bag in newborns receiving PPV at birth.[9] However, while the majority of newborns in need of PPV at birth are term born (gestational age $\geq$ 37 weeks),[3–4,10] the studies supporting this recommendation are mostly limited to premature newborns.[11–14]

The key to successful PPV is to provide sufficient inflation pressures to create functional residual capacity (FRC) and to deliver adequate tidal volumes to ensure gas exchange.[15] When ventilating term newborns, the American Heart Association (AHA) recommends an initial PIP of 20–25 cm H_2O, whereas the European Resuscitation Council (ERC) and the Australian and New Zealand Committee on Resuscitation (ANZCOR) recommend an initial PIP of 30 cm H_2O.[16–18] When using a T-piece resuscitator, the initial PIP is set accordingly. However, airway resistance, lung compliance, the newborn's tone and respiratory effort will vary substantially during the first minutes of PPV. Thus, a single set PIP is unlikely to result in adequate tidal volumes in all neonates. A small study including 20 preterm newborns receiving PPV in the delivery room, showed that a PIP of approximately 30 cmH_2O resulted in tidal volumes between 0 and 30 ml/kg, implying a weak correlation between PIP and delivered tidal volumes.[19] Resuscitation guidelines suggest a target tidal volume between 5 and 8 ml/kg during delivery room resuscitation,[16] although recent studies have suggested that higher tidal volumes may be warranted.[20–21] A recent study from Tanzania, including more than 800 term newborns ventilated with a self-inflating bag without PEEP, suggests that pressures of 37 cmH_2O may sometimes be required in apnoeic newborns to achieve tidal volumes within the target range.[22] In that study, inflation times were approximately 0.45 s. However, longer inflation times and lower inflation rates may ensure tidal volumes within the target range despite a lower PIP.

In this prospective observational study, we placed a flow- and pressure sensor between the facemask and the T-piece resuscitator to measure ventilation parameters during the first minutes of PPV of term newborns. The aim was to assess delivered PIP, PEEP, tidal volume, inflation time and rate, and to study the association between PIP, inflation time, inflation rate, and the achieved tidal volumes.

Methods

Setting

The study was conducted between 1st of June 2019 and 31st of March 2021 at Stavanger University Hospital, Norway. It is the only hospital in the region with delivery and newborn services and has approximately 4300 annual deliveries. Our department practises delayed cord clamping. Depressed newborns who do not respond to drying and stimulation, will have their cord clamped and moved to a centrally placed resuscitation bay for treatment. All resuscitation bays are equipped with a T-piece resuscitator (NeoPuff, Fisher&Paykel Healthcare, Auckland, New Zealand) and self-inflating bag (Upright, Laerdal Medial, Stavanger, Norway).[4] At our hospital, NeoPuff is the primary device for PPV of newborns. The airflow is set at 8 litres per minute, PIP at 30 cmH_20 and PEEP at 5 cmH_2O, in accordance with European guidelines.[16] Settings are checked by midwives once every 8-hour shift, and by the resuscitation team on arrival at the resuscitation bay. The resuscitation team consists of the midwife, nurse assistant, and a paediatric resident. A consultant neonatologist may be called upon in cases of severe asphyxia. All staff involved in newborn resuscitation undergo regular neonatal resuscitation skill and simulation training, including PPV using NeoPuff.

Inclusion- and exclusion criteria

Women were invited to consent to their newborn's participation in the study at routine ultrasound screening in pregnancy week 20 or when admitted for labour. Only newborns born at term who received PPV by NeoPuff within the first 5 min after birth were eligible for inclusion. Newborns ventilated with a self-inflating bag and newborns with congenital malformations were excluded.

Data collection and analysis

Video cameras with motion sensors were mounted on the resuscitation bays, recording all newborn resuscitations. The video recordings were used to assess the newborn's respiratory effort at initiation of PPV (apnoeic, gasping or severe retractions). A respiratory function monitor (Laerdal Global Health, Stavanger, Norway) with a hot-wire anemometer flow sensor (MIM Gmbh, Krugzell, Germany) and a piezo resistive pressure sensor (MPXV5010, Freescale Semiconductor Inc, Austin, TX) was connected between the T-piece and the facemask. The respiratory function monitor has a lever formed to hold the T-piece and mask when not in use, and lifting up the T-piece would initiate recording. For each inflation, the respiratory function monitor measured and recorded PIP and PEEP (in mbar; 1 mbar equals 1.02 cmH_20), tidal volume (defined as expiratory volume in ml), leak (defined as difference between inflated and expiratory volume divided by inflated volume, presented as a percentage), dynamic lung compliance (ml/mbar), inflation time, and instant inflation rate (60 divided by the time interval between current and previous inflation). No visual feedback on ventilation parameters was displayed to the healthcare providers. Patient characteristics were extracted from the electronic medical records. To prevent overrepresentation of data from newborns who were ventilated for a longer period, only the first 100 inflations from each newborn were

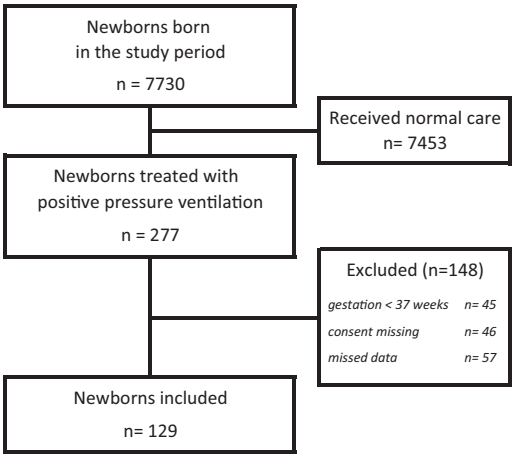

Fig. 1 – Flow diagram of inclusion.

Table 1 – Clinical characteristics of 129 included term newborns receiving positive pressure ventilation at birth.

	n = 129
Male gender	74 (57%)
Weight (g)	3647 (609)
Gestational age (weeks)	40 (1)
Mode of Delivery	
Vaginal delivery	86 (67%)
Caesarean section	43 (33%)
Apgar score at	
1 min	4 (3–6)
5 min	8 (6–9)
10 min	9 (7–10)
Umbilical cord blood values*	
arterial pH	7.19 (7.11–7.25)
arterial base deficit	5.4 (3.9–6.3)
venous pH	7.32 (7.25–7.36)
venous base deficit	4.8 (3.4–6.1)

Gender and mode of delivery presented as n (%), weight and gestational age as mean (SD), Apgar scores and umbilical cord blood values as median (IQR).
* n = 114.

included. We defined the first 20 inflations as the early phase of liquid clearance and establishment of FRC, and the following 80 inflations as the late phase of lung gas exchange with predominantly established FRC.[15,22]

Statistics

Data were analysed, and charts drawn, using R (Version 4.1.1., R Development Core Team, Vienna, Austria). Mann-Whitney U-test was used to compare continuous variables between the early and late phases.

Generalized Estimation Equations (GEE) (R-package: geepack v.1.3–2) were applied to model dynamics of PIP, PEEP, mask leak, lung compliance and tidal volume. Inflation number was included as the only predictor variable. First-order autoregressive covariance structure (AR(1)) was chosen to represent the within-subject dependencies for all models.

Further, we applied GEE to study the relationships between the tidal volume as the outcome variable and inflation rate, inflation time and PIP measured at the same inflation as predictors. We included inflation rates between 20 and 90 per minute, inflation times between 0.2 and 1.4 s, and inflation pressures between 18 and 34 mbar, thus excluding inflations incompatible with ventilation techniques appropriate in this setting. Visual inspection of the smoothing estimates of all models suggested a linear relationship with a sudden change in slope. Thus, for each GEE models we applied segmented regression (breakpoint) analysis, searching for a single breakpoint using quasi-likelihood information criterion (QIC),[23] the estimated breakpoints were presented together with the regression coefficients before and after.

P-values < 0.05 were considered statistically significant. Continuous variables are presented as median (Interquartile range (IQR)) unless otherwise stated.

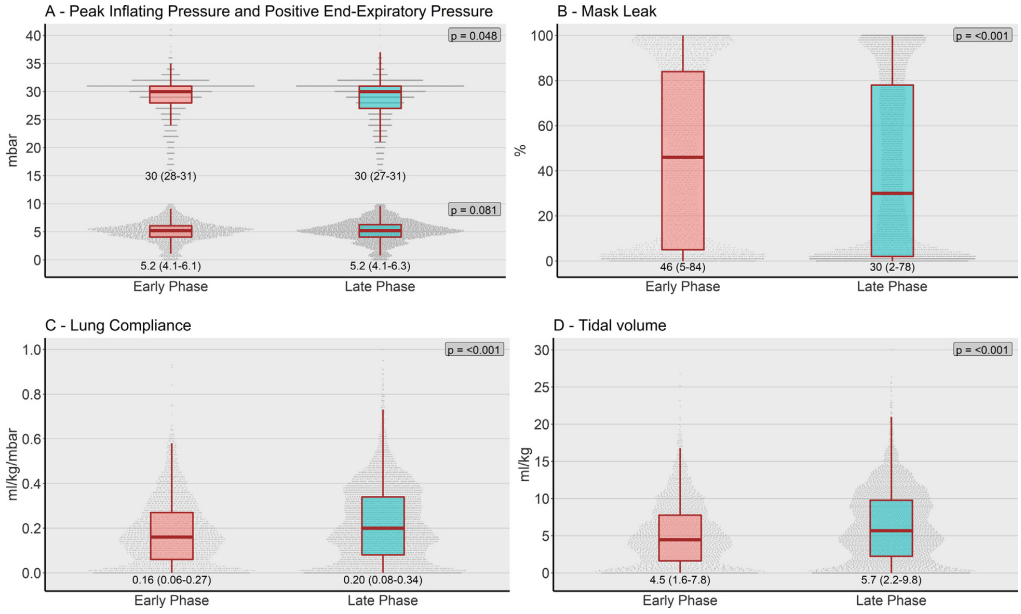

Fig. 2 – Swarmplots and boxplots of A) Peak inflating pressures and Positive End-Expiratory pressures, (B) Mask leak, (C) Lung compliance, and (D) Tidal volumes of the first 100 inflations during positive pressure ventilation of 129 term newborns after birth, and divided into an early phase (first 20 inflations, n = 2393) and a late phase (inflation 21–100, n = 4148). The swarmplots displays the distribution of individual observations on the y-scale. The boxes extend from the 25th to the 75th percentile; the horizontal line within the box denote median values; vertical extending lines denote range excluding outliers. Mann-Whitney U-test was used to compare variables between the early and late phase.

Results

Of 7730 newborns delivered during the study period, 277 (3.6%) received PPV after birth. Of these, 232 were born ≥ 37 weeks of gestation and were eligible for inclusion. We excluded 103 newborns due to missing parental consent (n = 46) or missing ventilation data (n = 57). The remaining 129 newborns were included in the study (Fig. 1), resulting in a total of 6541 inflations for analysis, 2393 in the early phase and 4148 in the late phase. The clinical characteristics of the 129 included newborns are presented in Table 1.

Five resuscitations were not video recorded due to technical issues. In the other 124 resuscitations, 109 (88%) of the newborns were apnoeic upon arrival at the resuscitation table whereas 15 (12%) newborns had insufficient respiratory efforts (i.e. gasping or severe retractions) prior to initiation of PPV. The median (IQR) ventilation time was 86 (49–130) s, and each newborn received 47 (25–72) inflations. The inflation rate was 43 (34–53) per minute and the inflation time was 0.58 (0.45–0.74) s.

Graphical representation of distributions of the tidal volume, mask leak, dynamic lung compliance, PIP and PEEP for the early and late phases are shown in Fig. 2. There was a substantial variation in tidal volumes, despite a relatively stable PIP. Median tidal volume did not reach the recommended range in the early phase and was in the lower end of the recommended range in the late phase. Mask leak decreased and the lung compliance increased from the early to the late phase.

The tidal volumes, mask leak, dynamic lung compliance, PIP and PEEP of the first 20 inflations are shown in Fig. 3. Throughout the early phase, the delivered PIP and PEEP were stable, the lung compliance and tidal volumes slowly increased, and the mask leak decreased.

The impact of PIP, inflation times and inflation rates on delivered tidal volumes are shown in Fig. 4 and Table 2. The tidal volumes increased with increasing PIP up to 30 mbar in both phases and decreased with higher PIP. Increased inflation times were associated with a rapid increase in volume before plateauing at an inflation time of 0.41 s in the early phase and 0.50 s in the late phase. Inflation rates exceeding 32 per minute in the early phase and 41 per minute in the late phase were associated with lower tidal volumes.

Discussion

This single centre study is the first to describe delivered tidal volumes and applied pressures from a flow-driven T-piece resuscitator during ventilation of term newborns. We found substantial variation in delivered tidal volumes despite a relatively stable delivery of PIP. The mask leak was high, and the lung compliance was generally low.

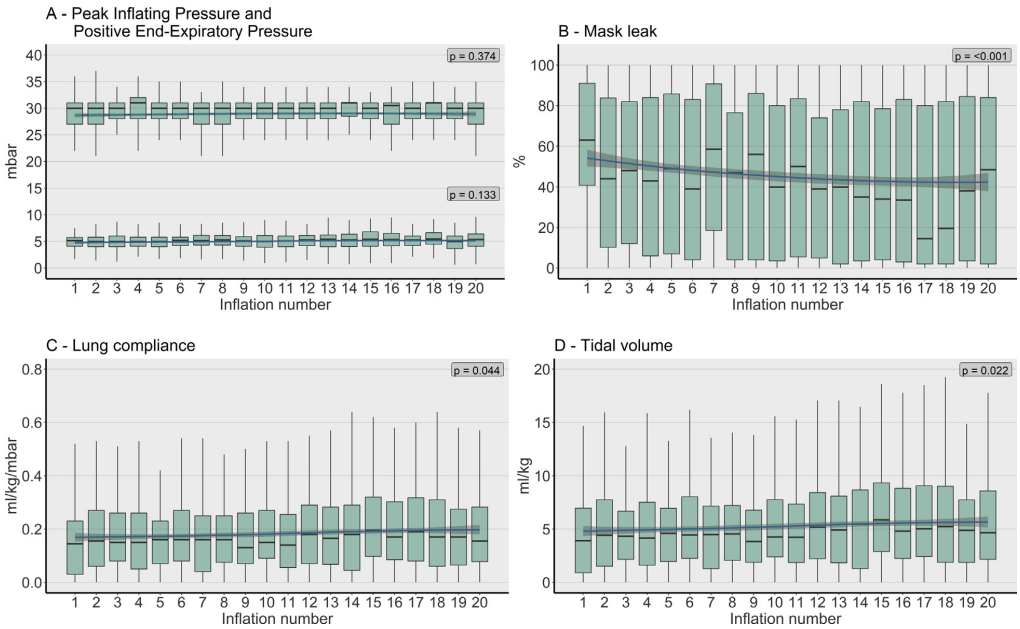

Fig. 3 – Boxplots of (A) Peak inflating pressures and Positive End-Expiratory pressures, (B) Mask leak, (C) Lung compliance, and (D) Tidal volumes for the 20 first inflations during positive pressure ventilation of 129 term newborns after birth. The boxes extend from the 25th to the 75th percentile; the horizontal line within the box denote median values; vertical extending lines denote range excluding outliers. The blue line represents the mean value throughout all 20 inflations, smoothed through local regression (Local Estimated Scatterplot Smoothing) with the grey band representing a 95% confidence interval. P-values are calculated using generalized estimation equations.

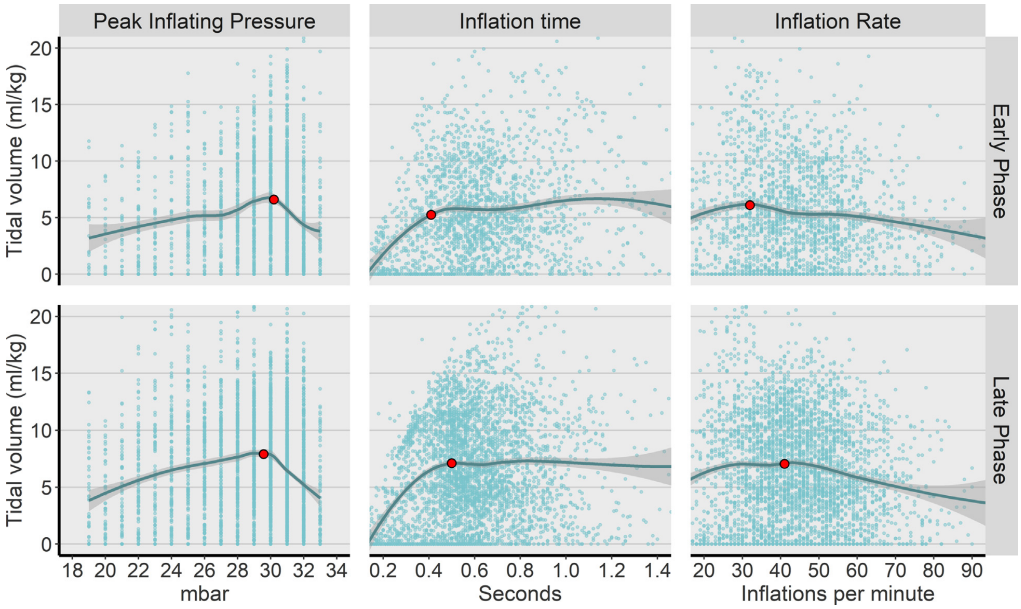

Fig. 4 – Scatterplots illustrating the association between peak inflating pressure, inflation time, and inflation rate on delivered tidal volumes from positive pressure ventilation of 129 term newborns after birth. The blue line represents the mean value smoothed through local regression (Local Estimated Scatterplot Smoothing) with the grey band representing 95% confidence intervals. The red dots represent breakpoints from the segmented regression analysis (Table 2).

Table 2 – Breakpoint- and generalized estimating equations (GEE) analyses of the relationship between tidal volume and different variables when ventilating newborns at term using a T-piece resuscitator in the early (first 20 inflations) and late (inflation 21–100) phases.

Variable	Break point	Before Breakpoint		After Breakpoint	
		Regression coefficient	p-value	Regression coefficient	p-value
Early Phase					
Peak Inflating Pressure (mbar)	30.20	0.27 (0.15; 0.40)	**<0.001**	−1.03 (−1.71; −0.34)	**0.03**
Inflation time (s)	0.41	12.76 (3.50; 22.02)	**0.007**	3.65 (2.12; 5.18)	**<0.001**
Inflation rate (inflations/min)	32.00	0.03 (−0.16; 0.21)	0.77	−0.04 (−0.06; −0.01)	**<0.001**
Late Phase					
Peak Inflating Pressure (mbar)	29.58	0.39 (0.31; 0.48)	**<0.001**	−0.96 (−1.38; −0.54)	**<0.001**
Inflation time (s)	0.50	11.00 (7.26; 14.74)	**<0.001**	2.30 (0.51; 4.09)	**0.01**
Inflation rate (inflations/min)	41.00	−0.03 (−0.08; 0.03)	0.36	−0.04 (−0.06; −0.02)	**<0.001**

The tidal volumes achieved when ventilating compromised newborns with a T-piece resuscitator at the recommended settings of 30/5 cmH_2O did not reach target tidal volumes during the early phase. However, this is a phase where a proportion of the inflated air will remain in the lungs generating FRC. This is visualized by the gradual increase in tidal volumes throughout the early phase (Fig. 3). Hence, the measured (expired) tidal volumes are likely to underestimate delivered tidal volumes. In this phase, the provision of a sufficient and steady pressure may be more important than reaching a target volume.

In the following (late) phase, gas exchange is the primary aim of PPV, as well as maintaining FRC by preventing liquid from re-entering the alveoli. Spontaneously breathing term newborns are reported to achieve a tidal volume between 4–6 ml/kg in the first minutes after birth.[24–25] In apneic newborns, higher tidal volumes may be required to establish and maintain FRC.[26] A study of 215 near-term and term newborns receiving PPV in the delivery room found that tidal volumes above 6 ml/kg were necessary to increase heart rate, and that tidal volumes between 9 and 10 ml/kg ensured the largest increase in heart rate, as a marker of successful lung

aeriation.[20] Another more recent study of 434 late preterm and term newborns found that an inflation rate of 30 per minute and tidal volumes of 10–14 ml/kg were associated with the highest CO_2 clearance.[21] However, high tidal volumes are associated with brain damage in preterm newborns,[27] and animal studies have shown that tidal volumes between 8 and 15 ml/kg may induce lung damage.[28–29] Thus, optimal tidal volumes during PPV in the delivery room remain unknown. Guidelines suggest a target tidal volume between 5–8 ml/kg during newborn resuscitation.[16] In our study, the set PIP of 30 cmH2O resulted in tidal volumes at the lower end of this range.

Of some concern is the substantial variation in delivered tidal volumes and the large proportion of inflations falling outside the recommended target range (Fig. 2). This variety probably has several explanations. Although there was an evident variation in mask leak, the T-piece resuscitator managed to maintain a stable PIP, which should reduce the impact from mask leak on delivered tidal volumes. Hence, we speculate that variation in airway resistance and lung compliance, due to the dynamic course of establishing FRC, may have a greater impact on delivered volume. In addition, maintaining an open airway during repetitive stimulation and handling of the newborns in the time of ventilation is challenging. Finally, as the newborn responds to interventions, the tone and spontaneous respiratory effort will increase. In this aspect, a fixed inflation pressure seems less appropriate. Our findings are consistent with previous studies of mask ventilation at birth.[11,19,21–22,30–35] This illustrates the challenge of estimating delivered tidal volumes, and more importantly, detecting if the newborn receives any tidal volume at all.

Our results clearly demonstrate that steady PIP is no guarantee of adequate ventilation, weakening one of the assumed advantages of T-piece resuscitators. Modern newborn ventilation strategies endorse volume-targeted ventilation,[36] and we see no reason why this should not apply to delivery room resuscitation. Chest rise is an inaccurate method of assessing tidal volume.[19,30] The use of respiratory monitors to provide immediate feedback may improve the quality of PPV in the delivery room.[31,35,37]

As air enters the lungs during inflation, intrathoracic pressure increases until it reaches the inflating pressure, and airflow ceases. The breakpoint analysis (Table 2 and Fig. 4) implies that this equilibrium is reached at an inflation time of approximately 0.5 s, and that longer inflation times will not affect tidal volumes notably. Breakpoint analysis also suggests that tidal volumes start to decrease with inflation rates higher than 30–40 per minute, probably due to reduced inflation times. The recommended inflation times and rates differ between guidelines. ERC and AHA recommend inflation times < 1 second, whereas ANZCOR recommend 0.3–0.5 s.[16–18] ERC suggests inflation rates of 30 per minute, whereas AHA and ANZCOR recommend 40–60 per minute. Our results suggest that when FRC is established (late phase), an inflation time of approximately 0.5 s and inflation rates between 30 and 40 per minute ensure the highest tidal volumes at current set-PIP of 30 cmH_20 (Fig. 4).

Tidal volumes increase with increasing PIP up to 30 mbar (Table 2 and Fig. 3). This breakpoint at 30 mbar is probably reflecting the T-piece resuscitators' set value of 30 cm H_20. We occasionally recorded PIPs clearly exceeding the set-PIP (Fig. 2). These recordings typically corresponded to a negative flow (Supplemental material: Extract of a ventilation monitor report), indicating manipulation of the mask or a newborn respiratory effort. Hence, we would expect a different breakpoint with a different set-PIP, and the association between tidal volumes and PIP for pressures exceeding 30 mbar must be interpreted with caution.

Limitations

There was a high rate of missing ventilation data due to failed recordings and lack of consent. If the T-piece was not placed on the monitors' lever prior to resuscitation, recordings would not be triggered. This occurred often, but randomly, and should not in our opinion create any bias. Parental consent was primarily obtained at routine ultrasound screening in pregnancy week 20, and missing consent should not result in any important bias. During periods of high mask leakage, some of the exhaled air likely bypassed the flowmeter, leading to an underestimation of tidal volumes and lung compliance. Although apnoeic at initiation of PPV, some newborns may have initiated spontaneous breathing gradually during resuscitation, probably affecting the delivered tidal volumes. This study did not include measurements of heart rate, SpO_2 or CO2, nor did it investigate the newborns response to applied PPV, and therefore cannot conclude on the effectiveness of delivered tidal volumes.

Conclusion

During real newborn resuscitation with a T-piece resuscitator at standard settings of 30/5 cmH2O, the delivered tidal volumes were at the lower end of the recommended range. Our results indicate that with a set-PIP of 30 cmH_20, and when FRC is established, highest tidal volumes are achieved with an inflation time of approximately 0.5 s and inflation rates around 30–40 per minute. There was a substantial variation in tidal volumes, indicating that a steady PIP is no guarantee for adequate ventilation.

Conflicts of Interest

None.

CRediT authorship contribution statement

Peder Aleksander Bjorland: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Hege Langli Ersdal:** Conceptualization, Methodology, Writing – review & editing. **Joanna Haynes:** Methodology, Writing – review & editing. **Anastasia Ushakova:** Formal analysis, Writing – review & editing. **Knut Øymar:** Conceptualization, Methodology, Writing – review & editing. **Siren Irene Rettedal:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Acknowledgements

We thank all involved health care personnel at Stavanger University Hospital, and parents with their newborns participating in this study. We also thank Joar Eilevstjønn, Laerdal Medical, for help with the processing of respiration monitor data.

Funding

PAB and JH have an unconditional PhD grant from the Laerdal Foundation (PAB: Bjørn Lind Grant no 30026 and JH Safer Healthcare 2017-2021 grant no 5007), and SR has an unconditional Post Doc

grant from the Laerdal Foundation (Safer Healthcare 2017-2021 grant no 5007). Laerdal Medical (Stavanger, Norway) provided respiration monitors.

The external funding sources had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the paper for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethics and Patient Consent

The study was approved by the regional ethical committee (REKvest 2018/338), and the hospital data protection officer. Written parental consent was obtained prior to inclusion.

Author contribution

PAB, SR, HE and KØ designed the study protocol. PAB and SR practically implemented, supervised and carried out the study and the data collection on site. PAB and AU analysed the ventilation data. All authors participated in the interpretation of the results. PAB drafted the initial manuscript. All authors read, revised and approved the final manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.12.006.

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Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

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ISBN: 9788230841518 (print)
9788230853870 (PDF)