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Neuromonitoring During Newborn Transition

By

Dr. Daragh Finn

MB BCh BAO, MRCPI



A thesis presented to University College Cork in fulfillment of the requirements

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Department of Paediatrics and Child Health and Neonatal Intensive Care Unit

University College Cork

Ireland

Supervisors: Professor Eugene M Dempsey, MD

Professor Geraldine Boylan, PhD

Head of Department: Professor Jonathan Hourihane, MD

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Declaration

The scientific research was performed under the supervision of Professor Eugene Dempsey and Professor Geraldine Boylan. It was performed in the Delivery Room and Neonatal Intensive Care Unit of Cork University Maternity Hospital and as part of the Irish Centre for Fetal and Neonatal Translational Research, University College Cork. The data acquisition was performed between July 2015 and January 2017.

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.

Acknowledgements

I would like to thank Maeve, Maria and Ger for their constant encouragement, support and understanding at all times. Professor Dempsey and Professor Boylan for their leadership, enthusiasm and advice throughout. Ita Herlihy, INFANT research nurse was an invaluable colleague and friend throughout each study. I would also like to thank all of the INFANT team, especially Prof Ryan, Prof Kenny, John, Vicki, Mairéad, Andreea, Aisling, Deirdre, Elena, Rhodri, Liudmilla, and Caroline.

Lastly, and most importantly, I would to thank all of the babies and their parents for trusting in the importance of this research.

Abbreviations

aEEG- amplitude integrated electroencephalography

bpm- breaths per minute

BSI- brain symmetry index

CBF- cerebral blood flow

CBV- cerebral blood volume

CC- connectivity correlation

CO_2- carbon dioxide

CUMH- Cork University Maternity Hospital

DCC- delayed cord clamping

DR- delivery room

ECG- electrocardiography

ECS- elective caesarean section

EEG-electroencephalography

ET- endotracheal

$EtCO_2$ – end tidal carbon dioxide

FD- fractal dimension

FRC- functional residual capacity

GA- gestational age

HI- hypoxic ischaemic

HIE- hypoxic ischemic encephalopathy

HR- heart rate

ICC- immediate cord clamping

IVH- intraventricular haemorrhage

LVO- left ventricular output

NICOM- non-invasive continuous cardiac output monitoring

NICU- Neonatal intensive care unit

NIRS- near infrared spectroscopy

PPV- positive pressure ventilation

RCOG- Royal College of Obstetrics and Gynaecology

$rcSO_2$- regional cerebral saturations

RFM- respiratory function monitor

StO_2- cerebral tissue oxygenation

RCT- randomized controlled trial

RFM- respiratory function monitor

RR- respiratory rate

RVO- right ventricular output

SEF- spectral edge frequency

SpO_{2-} oxygen saturation

SVC- superior vena cava

TH-therapeutic hypothermia

TTN- transient tachypnea of the newborn

TV- tidal volume

UCM- umbilical cord milking

Abstract

Background: Newborn infant neurological function can be measured by monitoring electrical activity (electroencephalography) or cerebral oxygenation via NIRS (near infrared spectroscopy). In practice the clinical applications of electroencephalography (EEG) are limited to monitoring infants following moderate to severe hypoxic ischemic injury (HIE), and for the detection of seizures in at risk infants. NIRS monitoring has been the focus of a number of research trials but has no clinical applications in the immediate newborn period to date, and is not routinely performed in neonatal units.

Aim: To assess the feasibility of infant neuromonitoring in the immediate period in two important clinical scenarios. Firstly, to assess the feasibility of monitoring brain activity during the first minutes of life in healthy term infants. Secondly, to assess the feasibility and utility of monitoring newborn preterm infants' brain activity and cerebral oxygenation in the context of an interventional randomized controlled trial.

Methods:

1. Healthy term newborn infants had EEG monitoring performed for the first ten minutes of life. EEG was assessed both qualitatively and quantitatively. All infants had respiratory function monitoring performed simultaneously.

2. Forty-five infants (< 32 weeks gestation) were randomly assigned to different methods of newborn infant cord clamping. All infants had EEG and NIRS monitoring for the first 72 hours of life. Quantitative features of EEG and median NIRS values were compared between groups at 6 and 12 hours of life as a primary outcome measure.

Results:

1. Forty-nine infants had EEG recordings. Median (IQR) age at time of initial EEG recording was 3.0 (2·5 to 3·8) minutes. End tidal CO_2 and tidal volumes increased over the first 3 minutes of life and then stabilized. Good quality EEG, with continuous mixed frequency activity with a range of 25-50μV, was observed in all infants. The majority of EEG spectral power was within the delta band.

2. There were 45 infants included. One infant died in the delivery room. Median time (IQR) from birth until EEG application was 3.05 (1.85 to 5.38) hrs. For primary outcome measures, data was available for 42/44 (95%) at 6 hrs and 44/44 (100%) at 12 hours. There was no significant difference between groups for measures for EEG values or cerebral NIRS.

Conclusion: Infant neuromonitoring in the immediate newborn period is feasible in the first minutes of life in healthy term infants and within the first hours of life in preterm infants. Normative quantitative data for electrical activity in healthy newborn term infants during the first minutes of life is described for the first time. Neuromonitoring during the first day of life as an outcome measure for preterm interventional trials is possible and the outcomes from this research is promising for further trials.

Aims and Objectives

The primary aim of this thesis is to assess infant neuromonitoring in the immediate newborn period. A real time objective measure of brain function is currently not readily available in the immediate newborn period. The potential benefits of having real time information on infant brain function for clinicians will be explored.

In this thesis, I will describe the research performed which aimed to assess the feasibility of acquiring very early EEG data in term infants, assessing the quality of data acquired, and producing normative EEG data in the immediate newborn period. I will also describe respiratory physiological parameters in the immediate newborn period to clarify the physiological stage of newborn transition that the EEG data acquired represented.

Furthermore, a major objective of this research was to perform neuromonitoring in preterm infants as early as possible, in the context of a randomized controlled trial, and to utilize measures of brain activity and cerebral oxygenation as outcome measures. It had been reported in a large Cochrane review that the incidence of intraventricular haemorrhage was lower in preterm infants following delayed cord clamping, or umbilical cord milking compared to infants who received immediate cord clamping(1, 2). The physiological basis for an increased incidence has been supported by work with animal models (3). However, a reduced incidence of intraventricular haemorrhage following DCC or UCM has not translated into improved neurodevelopmental outcomes to date (1). The objective within this thesis was to assess whether different patterns of cerebral function could be identified following different cord clamping strategies.

In summary the aims were:

1. To assess the feasibility of EEG monitoring in term infants in the immediate newborn period
2. To produce normative EEG data ranges for term infants in the first 10 minutes of life, and assess whether these values correlate with newborn transitioning
3. To assess the value of preterm infant neuromonitoring (EEG & NIRS) in the immediate newborn period in a randomised controlled preterm infant study on different cord clamping strategies

Chapter Summary

Chapter 1: Current modalities for monitoring infants in the immediate newborn period and the rationale for neuromonitoring

Current modalities for physiological monitoring of newborn infants are described. Current international guidelines and ongoing research topics are explored. The current methods and published research on neuromonitoring in the immediate newborn period is described, and a systematic review on EEG monitoring in the delivery room is presented. The rationale for investigating the feasibility and utility of EEG monitoring in the immediate newborn period for term and preterm infants is discussed.

Chapter 2: General methodology

The setting for each study, the subjects and recruitment process, interventions and monitoring techniques, principal outcomes measured, ethics, and the type of statistical analysis applied are described.

Chapter 3: Respiratory Adaptation in Term Infants following Elective Cesarean Section

The timeframe for respiratory adaptation in healthy term infants following elective cesarean section has not been described in detail previously. Prior to the study reported in Chapter 4 members of our research team had recruited fifty term infants in a study where respiratory function monitoring was performed following elective caesarean section. It was decided to continue the recruitment for this study in parallel with the recruitment process described in Chapter 4. This allowed for accurate documentation of respiratory adaptation in a larger cohort of infants. Therefore the understanding of the EEG recordings obtained in Chapter 4 was enriched as it could be clearly seen that our cohort of infants had achieved respiratory adaptation by the time EEG recordings were obtained.

Chapter 4: EEG for the Assessment of Neurological Function of Term Infants in the Immediate Newborn Period

The first objective of this research was to assess the feasibility of obtaining EEG recordings during the immediate newborn period. This was a prospective study where fifty term infants born by elective caesarean section were antenatally recruited and had EEG monitoring for the first ten minutes of life. This is the first study to describe quantitative features of brain activity in healthy term infants in the immediate newborn period.

Chapter 5: Neuromonitoring in the immediate newborn period in a preterm infant randomized controlled trial: Clamping the Umbilical cord in Premature Deliveries (CUPiD)

The second objective of this research was to assess the feasibility of monitoring newborn preterm infants' brain activity and cerebral oxygenation in the context of an interventional randomized controlled trial. In this chapter we describe a prospective, registered randomized controlled trial in preterm infants designed to incorporate measures of EEG and NIRS as primary outcome measures. Different umbilical cord clamping interventions was chosen as a study topic as there is currently much debate regarding neurological outcomes following different interventions. International guidelines advocate performing trials to further assess which approach is superior.

Chapter 6: Conclusion and future directions

The results of this research are evaluated and future directions based on the results are discussed.

Output, Publications, Conference paper presentations

Below is a list of International and National Scientific meetings where this work was presented, In addition, published work is referenced below. The full published manuscripts are attached at the end of this Thesis**.**

Publications

Clamping the Umbilical cord in Premature Deliveries (CUPiD): Neuromonitoring in the immediate newborn period in a randomized controlled trial of preterm infants less than 32 weeks

Finn D, Hayes Ryan D, Pavel A, O' Toole JM, Livingstone V, Boylan GB, Kenny LC, Dempsey EM

J Pediatr. 2019 doi: 10.1016/j.jpeds.2018.12.039

EEG for the assessment of neurological function in newborn infants immediately after birth

Finn D, O'Toole JM, Dempsey EM, Boylan GB

Arch Dis Child Fetal Neonatal Ed. 2018 doi: 10.1136/archdischild-2018-315231

Respiratory adaptation in term infants following elective caesarean section

Finn D, De Meulemeester J, Dann L, Herlihy I, Livingstone V, Boylan GB, Ryan CA, Dempsey EM

Arch Dis Child Fetal Neonatal Ed. 2017 doi: 10.1136/archdischild-2017-312908.

Lost in Transition: A Systematic Review of Neonatal Electroencephalography in the Delivery Room—Are We Forgetting an Important Biomarker for Newborn Brain Health?

Finn D, Dempsey EM, Boylan GB.

Frontiers Pediatrics 2017 doi: 10.3389/fped.2017.00173

Optimising Intravenous Volume Resuscitation of the Newborn in the Delivery Room: Practical Considerations and Gaps in Knowledge

Finn D, Roehr CC, Ryan CA, Dempsey EM

Neonatology 2017 doi: 10.1159/000475456.

Response: Commentary: Enhanced Monitoring of the Preterm Infant during Stabilization in the Delivery Room.

Finn D, Boylan GB, Ryan CA, Dempsey EM.

Frontiers Pediatrics. 2016 doi: 10.3389/fped.2016.00073

Enhanced monitoring of the preterm infant during stabilization in the delivery room.

Finn D, Boylan GB, Ryan CA, Dempsey EM

Frontiers Pediatrics 2016 doi: 4:30.10.3389/fped.2016.00030

First author conference presentations

"Brain activity in the first ten minutes of life"

- *Irish Paediatric Association, Dublin, 2016*[1]
- *European Paediatric Society, Geneva, 2016* [2]
- *Irish Neonatal Research Symposium, Dublin, 2016*[2]

"Defining the reference ranges for respiratory rates, tidal volume and end- tidal CO_2 in healthy term infants following elective caesarean delivery"

- *Paediatric American Society, Baltimore, 2016* [1]
- *Irish Paediatric Association, Dublin, 2016*[1]
- *European Paediatric Society, Geneva, 2016*[2]

- *Irish Neonatal Research Symposium, Dublin, 2016*[2]

"Clamping the Umbilical cord in Premature Deliveries (CUPiD): A Randomized Controlled Pilot Trial"

- *Paediatric American Society, San Francisco, 2017*[1]

"A Brief History of Umbilical Cord Clamping: and Clamping the Umbilical cord in Premature Deliveries (CUPiD): A Randomized Controlled Pilot Trial"

- *Reason Neonatal Conference, University of Warwick, 2016*[2]
- *Irish Paediatric Autumn Conference, Royal College of Physicians, Dublin, 2016* [2]

"Pigs are Superheros. The story of surfactant."

- *Famelab Ireland, Science Foundation Ireland and British Council, Dublin, 2016 (Third Place)*[1]

"Why do babies cry at birth?"

- *Famelab Munster, Science Foundation Ireland and British Council, Cork, 2016 (First Place)*[1]

[1]Poster presentation

[2]Oral presentation

Chapter 1

Current modalities for monitoring infants in the immediate newborn period and the rationale for neuromonitoring

1.1 Introduction

In recent decades, we have witnessed a significant increase in the number of monitoring options for newborn infants. Examples include cardiac (electrocardiography (ECG), echocardiography and non-invasive cardiac output monitoring), respiratory (capnography and respiratory function monitoring), and neurological monitoring (electroencephalography and near infrared spectroscopy). However, at present, routine monitoring of preterm and term infants requiring advanced stabilisation in the immediate newborn period has changed very little over time.

As adjuncts to clinical monitoring during initial infant stabilisation in the delivery room (DR), the recent 2015 ILCOR recommendations advise the use of two objective assessment tools as routine for preterm, and term deliveries where advanced stabilisation measures are expected: 1) pulse oximetry (with or without ECG) to regulate oxygen delivery, and 2) exhaled carbon dioxide (CO_2) detectors for confirmation of correct endotracheal (ET) tube placement (4). These two devices generate real-time accurate physiological data and, if recorded, document changing observations over time. The information provided assists in clinical decision-making

in real-time and has the potential to improve both short and long-term outcomes for newborn infants.

The relative lack of monitoring options in the DR is both a reflection of the difficulties in acquiring the information, and interpreting this data for decision making in real-time. As Bradley and Field reflected, “not all that is measurable is of value, and not all that is of value can be measured” (5). Monitoring techniques encompass simple clinical evaluation to the potential role of newer monitoring devices, including monitoring cerebral activity and cerebral oxygenation during the first minutes of life. It is important to understand the historical perspective and current available methods for monitoring newborn infants in order to understand the rationale for infant neuromonitoring in the immediate newborn period. A summary of current newborn infant monitoring techniques and newer proposed methods can be seen in Table 1.1.

1.2 Review of non- neurological infant monitoring in the immediate newborn period

1.2.1 Historical context and the Apgar score

Dr. Virginia Apgar, in 1953, was the first to describe newborn monitoring in the immediate newborn period in a methodical manner. The Apgar score is the sum of values based on the newborn respiratory (respirations, skin colour), cardiovascular (heart rate, skin colour) and neurological (muscle tone, reflex irritability) systems (6). With the exception of heart rate (HR), all of the variables are based on visual inspection of the infant and as such are somewhat subjective. Large cohort studies identified that 5 minute Apgar scores of < 7 were associated with increased risk of

neonatal death and cerebral palsy in both term and preterm infants, indicating that early clinical assessments may be reliable and meaningful for newborn infants (7-9). On addressing the inter rater variability of the score, Apgar reported that, "When two or more people decide independently, we find a range of one value above or below a decided score to be the widest variation" (10, 11). Currently, Apgar scores remain central to our interpretation of a newborn's condition at birth. They are routinely assigned to all infants in the immediate postnatal period and are usually collected as part of research trials both to assess baseline characteristics of study participants and in some cases as outcome measures. Newborn resuscitation guidelines advise initiating support during infants' transition based on assessment of respirations, tone and heart rate, which are all components of the Apgar score (12-14).

However, more recent studies have shown poor inter and intra rater reliability with regard to Apgar score assignment, especially when the infant is preterm or ventilated (15, 16). The ability of the five minute Apgar score to predict outcome seem less likely than previously thought. Singh et al has shown that in very preterm infant delivery there is no Apgar score cutoff below which "a burdensome outcome was assured or above which an unscathed outcome was likely". Five minute Apgar score and HR values also displayed poor sensitivity and specificity for either survival or survival without disability (17). Manley and colleagues asked clinicians to predict the outcome of preterm infants (<26 weeks gestation) based on their clinical appearance in the DR, at pre-specified time points of 20 seconds, 2 minutes and 5 minutes. This study was based on video recordings of the preterm infants, and monitors displaying HR and oxygen saturation (SpO_2) values were visible. Trainees and staff neonatologists predicted infant survival poorly at each time point. The authors

concluded that neonatologists' "reliance on initial appearance and early response to resuscitation in predicting survival for extremely premature infants is misplaced" (18).

Updated Apgar scoring systems have been proposed and allow for more appropriate descriptions of the condition of the preterm infant at birth. The Combined-Apgar score reports the infants' score in each of the five components of the Apgar score (specified Apgar score), and the interventions required to achieve this score (expanded Apgar score) (19, 20). This Combined-Apgar score has been shown to be superior in predicting outcome in preterm infants when compared to the conventional-Apgar score (21). However, this updated scoring system has yet to be universally adopted and the relevance of conventional Apgar scores in term ventilated, and preterm infants remains limited. Therefore, we can conclude that clinical assessments of newborn infants are important but limited, and enhanced monitoring of infants is required for improved real time information, which is not subject to inter rater variability. Clinical parameters such as oxygen saturation, heart rate, peripheral perfusion and respiratory status have received much attention recently.

1.2.2 Oxygen saturation monitoring

Clinically, infants transition from blue (cyanotic) to pink (normal oxygen saturations) in colour during uncomplicated newborn transition. O' Donnell and colleagues assessed clinical perceptions of newborn infant colour in the DR (22). They found wide variation in observations and concluded that, "clinical assessment of a newborn infant's colour may be unreliable". Assessment of arterial oxygen saturation by pulse oximetry is based on the Beere-Lambert law that relates the attenuation of light to the

properties of the materials through which the light is travelling; and photo-plethysmography, a non-invasive optical technique used to detect blood volume changes in the microvascular bed of the tissue (23). Aoyagi and Kishi, who realized that oxygenated hemoglobin absorbs more light at infrared wavelengths and deoxygenated hemoglobin absorbs more light at red wavelengths, developed arterial oxygen saturation monitoring by pulse oximetry in 1972. The changes during systole and diastole in the ratio of red and infrared light energy absorption is used to produce the pulse oxygen saturation (24).

The device was first commercialized in 1981, and the use of pulse oximetry for continuous oxygen monitoring in newborns was first described in 1986 (25). The clinical benefits of pulse oximetry were quickly recognised, and it has become the mainstay of non-invasive, continuous SpO_2 monitoring in newborns (26). Oxygen saturation monitoring of preterm and compromised term infants is now standard in the DR and these values serve as a guide to stabilisation (25, 26). The titration of oxygen therapy in preterm newborn stabilisation is now routine to achieve targeted saturations by 10 minutes of age (27, 28). Dawson and colleagues have published oxygen saturation percentile charts for the first 10 minutes of life (27). In their study of over 450 infants, they observed the SpO_2 values of preterm infants increased at a slower pace than term infants. At 5 minutes, the median (interquartile range) SpO_2 was 86% (80-92) in preterm and 92% (83-96) in term infants. They have published 3 sets of percentile charts based on gestation (>37 weeks, 32-37 weeks, and < 32 weeks), which may guide neonatal teams in titrating oxygen therapy in the DR. However, these ranges were developed in a cohort of infants born when immediate cord

clamping was frequently practiced following delivery. These ranges may not be as relevant where delayed clamping is practiced.

Pulse oximetry has gained widespread acceptance in neonatal care over the past three decades because of its reliability, ease of use and lack of heat-related complications. The main physiological limitation of pulse oximetry is the inability to detect hyperoxemia in the higher SpO_2 range (>90%) because of the shape of the oxygen-hemoglobin dissociation curve. Thus, relatively small increases in SpO_2 can be associated with a large increase in PaO_2 (29-31). This is particularly important for preterm infants receiving supplemental oxygen because of their vulnerability to oxygen toxicity and oxidative stress (32). Despite this limitation, pulse oximetry is the gold standard for monitoring oxygen saturation during preterm infant stabilisation, and should be used following all preterm and compromised term deliveries.

1.2.3 Heart rate monitoring

Monitoring HR helps to guide newborn transition and the need for intervention in the immediate newborn period. Current recommendations advise that HR should be assessed clinically, and if positive pressure ventilation is commenced HR should be monitored by pulse oximetry, with the option of additional ECG monitoring (4).

Whilst clinical assessment of HR by auscultation at the apex is more accurate than assessment by palpation of the umbilicus, all clinical assessments may misrepresent the actual HR (33). Kamlin et al. compared palpation and auscultation of HR to ECG determined HR in term newborns in the DR. They found that clinical assessments were inaccurate, and infant HR was underestimated when compared with ECG HRs

(34). Hawkes et al. studied healthcare professionals as they palpated a simulated pulsating umbilicus, listened to a tapping heart rate, or auscultated a simulated HR. They found that while study participants performed well at identifying HR > 100 beats per minute (bpm), almost two thirds of participants failed to recognize a HR less than 60 bpm for all methods of assessment (35). These findings emphasize the importance of early accurate objective HR monitoring during preterm infant transition for identification of infants who may require support or active resuscitation (HR less than 60 bpm).

Pulse oximetry provides real time accurate information about the HR of infants (36). However, pulse oximetry values are not available immediately as the sensor takes time to apply correctly and once applied, there is a delay before the monitor provides a reading. Limb perfusion will affect the time taken to achieve a pulse oximeter heart rate (36). Studies that have assessed the feasibility of obtaining prompt and reliable pulse oximetry readings have reported times to signal acquisition of between 1 and 2 minutes after delivery (28, 37). There is conflicting evidence as to whether quicker signal acquisitions are obtained by applying the sensor cable to the oximeter prior to applying the sensor to the infant, or after. Observational studies reported that the quickest method involved turning on the pulse oximeter prior to delivery, applying the sensor to the infant's right hand and then connecting the cable of the sensor to the oximeter. This results in mean readings within 25 seconds of reaching the resuscitation table in a research setting (37, 38). A recent randomized controlled trial (RCT) in the DR contradicted these findings and found significantly faster signal acquisition times in infants who had the sensor connected to the oximeter first (39). A limitation of pulse oximetry HR monitoring is that HRs < 100 bpm are not

consistently detected, and in a study by Kamlin et al were only reported 89% of the time (36).

ECG monitoring can provide accurate HR values sooner than pulse oximetry following delivery (36, 40). The electrodes can be applied quickly and there is little lapse in time waiting for monitor readings to appear. Katheria and colleagues reported that median times to acquire a signal from ECG and pulse oximetry were 4 seconds and 32 seconds respectively (40). A limitation of ECG monitoring is the risk of pulseless electrical activity being misinterpreted as HR on ECG (41). Doppler ultrasound blood flow HR assessments in the DR are accurate compared with clinical and pulse oximetry assessments (42). Measurements can be taken through a polyethylene bag. However, clinical experience is required for accurate assessments and continuous measurements are not practical.

ECG monitoring cannot replace the need for pulse oximetry, which is necessary for SpO_2 monitoring. However, given that ECG monitoring is more accurate than clinical estimations, ECG may prevent unnecessary interventions secondary to false clinical estimations of low HR. Alternatively, it could increase interventions, which may or may not be appropriate, as a result of earlier accurate bradycardia detection. Whilst awaiting further evidence, there are a few important points to be made: initiation of ECG monitoring in the DR is easily achievable, is more accurate than clinical assessment and provides HR values more expediently than pulse oximetry. Clinical trials are required to assess whether ECG monitoring affects the frequency of stabilisation interventions, and ultimately whether its use affects stabilisation outcomes.

1.2.4 Peripheral perfusion monitoring

Peripheral perfusion is determined by cardiac output and the caliber of the vessels transporting blood to the peripheries. Current clinical methodologies for non-invasive monitoring of peripheral perfusion include assessments of capillary refill time, peripheral temperatures, and palpation of peripheral pulses. Each method relies on subjective assessments and continuous measurements are impractical. Blood pressure monitoring by Doppler and oscillometric methods are feasible in the DR and measurements for term infants have been reported (43). However, non- invasive measurements are not reliably consistent in preterm neonates and invasive BP monitoring is not practical within the DR setting. Interpretation of and intervention based on non-invasive blood pressure measurements in the immediate newborn period is currently not recommended.

A recent review by Baik et al. identified four studies of echocardiographic monitoring during newborn stabilisation in term infants (44-48). Left ventricular output and stroke volume increased over the first 15 minutes of life and one study reported an increase in left to right shunting across the ductus (46-48). The studies did not assess echocardiographic measurements of HR. The authors of the review concluded that echocardiographic monitoring in the DR would enhance our knowledge about "cardiac function changes" (44). However, it does not add useful clinical information during newborn stabilisation, and routine monitoring is not advised.

Non-invasive continuous cardiac output monitoring (NICOM) is now feasible in neonates (49). This technology is based on the assumption that changes in the resistance to electrical currents captured by electrodes on the thorax are directly

related to changes in aortic volume during different stages of the cardiac cycle (32). NICOM measurements correlate well with timed echocardiographic measurements (49, 50). However, NICOM may underestimate the actual cardiac output value (49). Song and colleagues performed 108 paired NICOM and echocardiography studies in 40 preterm infants (51). Right and left ventricular output had a high level of correlation between the two modalities, even in the presence of a significant ductus arteriosus. The level of agreement decreased if the infant was on high frequency ventilation. The authors noted that while NICOM was a feasible tool to monitor trends in cardiac output, absolute values are not reliable, and they do not support routine monitoring.

Perfusion index (PI) monitoring is a non-invasive method of assessing real-time peripheral perfusion, derived from, and displayed by the pulse oximeter. Pulse oximetry values are derived from red (660nm) and infrared wavelengths (910-940nm) (52). By using a third wavelength (800 nm), the overall hemoglobin content can be calculated and the pulsatile component of arterial blood can be distinguished from the non-pulsatile component (53). Perfusion index has been utilized to monitor preterm infants in a number of clinical areas (54). These include screening for congenital cardiac disease (55, 56), predicting low systemic blood flow (57), and assessing perfusion following blood transfusion (58). However, while PI values are easily obtained in the DR, and normative values for preterm infants in the first day of life have been published (59, 60), they are highly variable in the immediate newborn period, for both term and preterm infants (61). There are no trials comparing PI and clinical assessments of peripheral perfusion in preterm care, nor trials assessing

whether PI monitoring affects preterm outcomes. Therefore, evidence in favour or against PI monitoring in the immediate newborn period is lacking.

1.2.5 Respiratory support monitoring

Lung aeration is a critical point in newborn transition from fetal life. Newborn infants are at an increased risk of needing respiratory support following delivery. Inadequate ventilation may result in hypoxia and resultant bradycardia. International guidelines advise a stepwise approach to achieving optimal ventilation following delivery and prior to escalating cardiovascular support; therefore positive pressure ventilation is the cornerstone of neonatal resuscitation (62, 63). It is provided either by mask ventilation, single or double nasal prongs or via an endotracheal (ET) tube. Adequate airway ventilation is assessed clinically by chest rise, an increase in HR, and auscultation for air entry on both sides of the lung fields during DR stabilisation. Visual assessments of chest rise are not reliable (64). After initiating mask ventilation and if the clinical response is suboptimal, guidelines advise repositioning of the mask to optimize the seal and reduce leak, and airway opening manoeuvers to combat airway obstruction. If there is no clinical improvement after such interventions a definitive airway, in the form of ET intubation is advised (4). The mnemonic MRSOPA identifies these methods; improve Mask seal, Re- position the airway, Suction and/or Open the mouth, increase the inflation Pressure, and consider an Alternative airway.

Monitoring stabilisation efficacy in infants in the NNU is achieved by monitoring CO_2 levels, which can be achieved by measuring either transcutaneous or exhaled CO_2 levels. There is very little information on CO_2 assessment at birth. Studies in the

DR have focused on exhaled CO_2 detection, either by qualitative or semi quantitative disposable colormetric CO_2 detectors that change color upon contact with CO_2, or quantitative capnography that provides a breath by breath end tidal CO_2 measurement (65). Quantitative capnography is achieved either by mainstream capnography that utilises an infrared absorption technique, or side stream capnography that continuously transports a sample of gas to a sampling cell within a monitor. Both capnography methods provide a continuous visual display of CO_2 values (capnometry) (65).

CO_2 detectors are routinely used to aid in the assessment of correct ET tube placement (12). The use of CO_2 detectors reduces the time to confirmation of ET tube placement and has been endorsed in resuscitation guidelines (12, 66). Their use may be limited by false negative readings, during cardiopulmonary arrest and severe airway obstruction (67, 68). Employing quantitative capnography following ET tube placement also results in quicker and more accurate confirmation of correct placement when compared with clinical assessments (69, 70).

The use of CO_2 detectors during face mask ventilation has been shown to help determine airway patency on an almost breath-to-breath basis, and can aid resuscitation teams in recognizing airway obstruction and leak during DR positive pressure ventilation (71-74). However, CO_2 monitoring is not routine during mask ventilation. Van Os and colleagues displayed the benefits of CO_2 detectors in helping resuscitation teams to recognize airway obstruction in 24 very low birth weight infants during positive pressure support in the DR (71). Quantitative capnography during mask ventilation has been shown to improve CO_2 elimination with the onset of

an infant's respiratory efforts; however, other authors have not found that it reduces the occurrence of hypocapnia or hypercapnia (75, 76). In a recent mannequin study quantitative capnography was superior to CO_2 detectors in improving efficacy of face mask ventilation (77). A recent randomized controlled trial found no significant difference in the incidence of normocarbia in the first two hours of life between quantitative and qualitative CO_2 detection (78).

During newborn stabilisations, the user controls ventilation pressures delivered to the infants' lungs. The lungs of newborn infants are susceptible to injury if exposed to high airway pressures. Immature animal models have shown that lung injury can occur after a few manual inflations at high pressure (79). On the other hand, face mask ventilation can be inadequate secondary to leak, even if the user is highly experienced (80, 81). In NNUs ventilation adequacy can be assessed by respiratory function monitors (RFMs) which are incorporated into modern ventilators (82). They provide information not only on airway pressures, but also on delivered tidal volumes. The monitor displays breathing pattern, tidal volumes, flow and pressure waves and percentages of gas leak. RFMs have also been used to guide positive pressure ventilation in newborn resuscitations (83, 84). Schmolzer and colleagues found that RFM use during mask ventilation of preterm infants results in significantly less leak, more mask adjustments and a lower rate of excessive tidal volume given (84). RFMs have also been used in a RCT, which displayed improved ventilation with masks compared with nasal tubes during stabilisation of preterm infants (85). However, the use and interpretation of a RFM can be technically challenging for many inexperienced users. Milner and colleagues recently surveyed 51 neonatal trainees who had used RFMs during preterm stabilisation (86). They found that the usefulness

of respiratory function monitoring was dependent on the trainee's level of experience, and that appropriate responses to the RFM data were more frequent in the hands of senior clinicians compared with their junior colleagues. Therefore, although beneficial, respiratory function monitoring during facemask ventilation is limited by user dependency, and further trials are warranted.

1.2.6 Conclusion

Objective real time physiological monitors are essential in the care of preterm, and term infants requiring advanced stabilisation during the immediate newborn period. The monitoring tools described thus far do not provide clinicians with information on infant brain health during infant transition, the most vulnerable time for brain injury in infancy. Assessing brain health in the immediate newborn period has not been prioritized historically nor in current international guidelines for monitoring newborn infants. The current methods under investigation for assessing brain health in the immediate newborn period are described in the next chapter.

Table 1.1 Variables and monitoring tools in the immediate newborn period

Variable	Monitor	Data acquisition feasible	Normative Values Established[1]	Comments	Strength of recommendation
SpO2	Pulse Oximeter	+	+	Accurate but unable to detect hyperoxaemia	Class I
HR	Pulse Oximeter	+	+	Accurate but time delay in data acquisition	Class I
	ECG	+	+	Rapid accurate data acquisition	Class I
Peripheral perfusion	Echocardiography	+	-	Not assessed in preterm infants	Class III
	Perfusion Index	+	+	Normative values highly variable in newborns	Class III
ETT position	CO_2 Detector	+	n/a	Reduces time to confirmation of correct placement	Class I
Facemask ventilation effectiveness	CO_2 Detector	+	n/a	Reduces mask leak and obstruction Further RCTs required	Class IIa
	Capnography	+	_	Reduces mask leak and obstruction Further RCTs required	Class IIa
	Respiratory Function Monitor	+	_	Reduces mask leak and obstruction Further RCTs required	Class IIa

[1] For preterm infants < 32 weeks gestation in the immediate newborn period

1.3 Neuromonitoring in the immediate newborn period

1.3.1 Introduction

As survival rates continue to improve for term infants following hypoxic ischaemic injury (HIE) and preterm infants delivered at the cusp of viability, focus has shifted on neuroprotection strategies. The recent Safeboosc trial suggests that brain oxygenation monitoring in the NICU results in a reduction in the percentage of cerebral hypoxia sustained by preterm infants (87). At present, assessment of neurological wellbeing in the immediate newborn period is based on clinical assessment alone. As previously described, assessments of muscle tone and reflex irritability are incorporated into the Apgar score (6). The brain is the most vulnerable organ in newborn infants. As survival of the most immature infants increase, concerns have been raised about increased risks of adverse neurodevelopmental outcomes (88, 89). Resuscitative measures should aim for the best possible neurological outcomes and a non-invasive, continuous measurement of cerebral oxygenation and cerebral activity would be ideal, but these currently are not routine and their role in this setting has yet to be evaluated. The current and proposed methods for assessing brain health are summarised in Table 1.2.

Table 1.2 Methods for assessing neonatal brain health

	Method	Strengths	Limitations
Clinical assessment	Muscle tone and reflex irritability as part of the APGAR score	Immediate score	Subject to inter and intra rater variability
Cerebral blood flow	Ultrasound Doppler of cerebral or carotid artery	Immediate assessment of cerebral blood flow	Technically challenging and continuous data acquisition not feasible
NIRS	Non-invasive monitoring of cerebral tissue oxygenation by application of NIRS pad to frontal area	Feasible to obtain continuous reliable data in the DR Normative values established	Wide range for normative values
Fetal EEG	Application of > 1 EEG electrodes to fetal scalp during labour	Would allow for real time assessment of fetal brain health	Technically challenging Can only be applied during late stages of labour Not established as method for assessing fetal health Paucity of normative data
EEG	Application of > 1 EEG electrodes to neonatal scalp after delivery	Would allow for real time assessment of neonatal brain health Established method for monitoring neonatal brain health in neonatal	Technically challenging Paucity of normative data

1.3.2 Cerebral blood flow

Studies that sought to introduce neurological monitoring into the DR initially focused on cerebral blood flow using doppler measurements of cerebral or carotid arteries (46, 90-94). Monitoring was found to be technically difficult and did not provide continuous data (95). Furthermore, there is conflicting evidence on the role of cerebral Doppler in identifying impaired cerebral autoregulation and resultant abnormal cranial ultrasound findings (96, 97).

1.3.3.1 Cerebral oxygenation- Background

More recently, researchers have concentrated on near infrared spectroscopy (98). NIRS provides non-invasive monitoring of regional cerebral tissue oxygenation ($rcSO_2$) (99-112). NIRS was first described in 1977 by Jobsis as a technology that was capable of non-invasive monitoring of oxygenation in tissues, and its first use in neonates as a cerebral oximeter was described by Brazy et al in 1985 (113).

Since its development and introduction into clinical practice, there has been progressive device and probe development resulting in a range of readily available and easy to apply machines (114). Currently most available devices are Food and Drug Authority approved for use in neonates (115).

NIRS utilizes the transparency of biological tissue to light in the near infrared spectrum to measure tissue oxygenation (116). Light in the near infra-red range (700-1000nm) penetrates the soft tissues and bones, in particular thin tissues which includes the thin neonatal cranium (117). Circulating haemoglobin (Hb) absorbs this near infrared light and absorption of the transmitted light will differ depending on the

HB's oxygenation state (118). Changes in tissue concentration of oxyhaemoglobin (O_2Hb) and deoxyhaemoglobin (HHb) can be measured in real time (118). Total haemoglobin [tHb = O_2Hb+HHb] and haemoglobin oxygen saturation [StO_2 =O_2Hb/tHb] can also be calculated (34). With these values a regional cerebral oxygenation concentration $rcSO_2$ or haemoglobin difference [HbD=O_2Hb-HHb] can be calculated. The $rcSO_2$ reflects a regional balance between oxygen supply and demand for the underlying tissue (31). In addition cerebral blood volume [CBV], cerebral blood flow [CBF] and cerebral fractionated tissue oxygen extraction can be estimated [cFTOE = ($pSaO_2$-$rcSO_2$)/$pSaO_2$](43). Increased cFTOE reflects higher oxygen consumption in relation to oxygen delivery to the brain and decreased cFTOE suggest less utilization of oxygen by the brain tissue (119). Naulaers and colleagues showed a positive correlation between tissue oxygenation index (TOI- vascular haemoglobin oxygen saturation) and cFTOE during a validation study in piglets (120) (121).

NIRS monitoring allows neonatologists to monitor regional cerebral oxygenation (rcSO2) in real time, and for indirect assessments of cerebral blood flow (CBF) and cerebral tissue oxygen extraction (cTOE) (31). These NIRS indices can also be utilised in combination with continuous blood pressure measurements to monitor cerebral autoregulation. However, despite the impressive evolution of this device over time, its use in neonates is currently predominantly limited to clinical research, with very few centres using NIRS as a bedside tool to manage preterm infants (117).

A disadvantage for many clinicians is the wide range of normative $rcSO_2$ values. Although the use of NIRS technology as a cerebral monitor has been available for

over 30 years establishing reference normative values for cerebral oxygenation in neonates has taken time (32, 33). Values of 55% and 85% are currently being used for the INVOS device(119)(Table 1.3). The rcSO2 values below 55% represent cerebral hypoxia and above 85% represent cerebral hyperoxia. These values of 55% and 85% were determined from an INVOS device, with the adult NIRS probes, but reference ranges obtained from the newer small neonatal probes, which tends to overestimate rcSO2 values measured by the adult probe, may be more appropriate (122).

Table 1.3 NIRS Reference Values

High (Hyperoxia)	Normal	Low (Hypoxia)	Critically low (hypoxia) Avoid if possible
>85% (> +2SD)	≤ 85% ≥ 55 (± 2SD)	<55% >45% (<-2 SD)	<45 %

Initial research which established normative $rcSO_2$ values concentrated on animal studies. Hou et al, studied the effects of varying cerebral oxygenation on newborn pigs (123). NIRS was used to monitor the $rcSO_2$ of 27 newborn pigs. After mechanical ventilation and inhalation of 3-11% oxygen for 30 minutes by the newborn pigs, the pigs were grouped according to the $rcSO_2$ in the brain caused by inhalation of different concentrations of oxygen. There were six animals each in $rcSO_2$< 30%, 30-35%, 35-40%, 40-50% groups and three animals in the $rcSO_2$ > 60% group (normal control). This study found that under varying degrees of hypoxia, when the $rcSO_2$ is between 30% and 40%, brain injury occurs and the functional zones of

the mitochondria are injured. When the rSO_2 is less than 30%, there was significant impairment in physiologic parameters; the oxygen saturation and pH of blood were lower than those of the control group, and the blood lactic acid level was higher than that of the control group. Also the mean arterial blood pressure (MAP) of the newborn pigs was significantly lower than that of the animals in the control group.

Cerebral hyperoxia on the other hand has also been shown to cause damage to the immature brain. Yis et al exposed rat pups from birth until day five to 21% or 80% oxygen (124). The neuronal density and apoptosis in CA1 and dentate gyrus of hippocampus, prefrontal cortex, parietal cortex, and retro-splenial cortex were assessed by immunohistochemistry and ELISA cell death assay. DNA fragmentation was detected by an ELISA that is specific for nucleosome-associated cytosolic DNA. Neuronal density of the investigated brain areas were significantly decreased in the hyperoxia group. Furthermore, using ELISA cell death and TUNEL assays, they observed an increased cell death in the developing brain in the hyperoxia group (124).

Gerstner et al investigated pathways of maturation-dependent oligodendrocyte death induced by hyperoxia in vitro and in vivo. In this study, developing and mature oligodendrocytes in vitro were exposed to 80% oxygen from 0 to 24 hours (125). Lactate dehydrogenase assay was used to assess cell viability. Furthermore, rat pups were subjected to 80% oxygen, and their brains were processed for myelin basic protein staining. Significant cell death was detected after 6 to 24 hour incubation in 80% oxygen in pre- oligodendrocytes but not in mature oligodendrocytes. Cell death was executed by a caspase-dependent apoptotic pathway. Accumulation of superoxide and generation of reactive oxygen species were detected after two hours of oxygen

exposure. The group also extended these studies by testing the effects of hyperoxia on neonatal white matter. Postnatal day 3 and day 6 rats showed bilateral reduction in myelin basic protein expression with 24 hours exposure to 80% oxygen (125). Hyperoxia causes oxidative stress and triggers maturation-dependent apoptosis in pre-oligodendrocytes, which involves the generation of reactive oxygen species and caspase activation, and leads to white matter injury in the neonatal rat brain. These observations may be relevant to white matter injury observed in preterm infants (125).

1.3.3.2 Cerebral oxygenation in the immediate newborn period

Cerebral NIRS in the immediate newborn period remains limited to research studies, but emerging data suggest that it may have a significant role in preterm stabilisation in the future (113). Cerebral tissue oxygen saturations in preterm infants have been shown to correlate well with superior vena cava flow and left ventricular output in the first days of life (126, 127). A number of studies have displayed the feasibility of obtaining cerebral oxygenation values using NIRS during newborn transition (95). Normative values for infants (predominantly term) not requiring resuscitation in the DR have been published recently (106).

NIRS measurements are readily obtained and in a recent study conducted by this group, the NIRS values were obtained within seconds of application of the device in the DR, in contrast to the variable time for pulse oximetry saturation readings (128). Binder et al performed NIRS on 49 preterm infants in the immediate newborn period (103). They reported different $rcSO_2$ transition time courses for infants requiring respiratory support and those with normal transitions. Infants requiring respiratory support had lower $rcSO_2$ values over the first 10 minutes of life before reaching

similar steady state levels as their counterparts. Fuchs et al. reported $rcSO_2$ values for 51 infants weighing less than 1500g (111). Low median $rcSO_2$ values (37%) were reported at 1 minute of life, which continuously rose to steady state levels (61-84%) at 7 minutes of age. $rcSO_2$ values did not differ in relation to the degree of resuscitation required in the DR, but it was noted that 2 infants with subsequent IVHs had $rcSO_2$ values that were < 10^{th} centile for their cohort. Kenosi et al evaluated transitional cerebral NIRS values in preterm infants less than 32 weeks and found that preterm infants requiring greater than 30 % oxygen to maintain peripheral saturations had a significantly higher degree of cerebral hypoxia (128). All infants initially received a FiO_2 of 0.3 and oxygen was titrated according to standard resuscitation guidelines. There were no differences in cerebral hyperoxia between the two groups. These findings suggest that some preterm infants may require a more rapid increase in oxygen titration in the DR. At present, NIRS remains in the realm of research for infant monitoring in the immediate newborn period, but as more studies emerge, we believe that it will have a future role in monitoring preterm infants and guiding oxygen titration during DR stabilisations.

Pichler and colleagues recently performed a pilot RCT, in which infants < 34 weeks were randomized in the DR either to cerebral NIRS and SpO_2 monitoring, or SpO_2 monitoring alone to guide titration of oxygen therapy (129). They found that additional NIRS monitoring significantly reduced the time that infants' $rcSO_2$ was <10th centile in the first 15 minutes of life. There was no difference in rates of intraventricular haemorrhage (IVH) or abnormal neurological assessments at discharge. The clinical trials where NIRS was performed in the immediate newborn period are summarized in Table 1.4. Further trials are required to ascertain how

oxygen therapy should be guided when $rcSO_2$ and SpO_2 values are both available in the DR.

Cerebral NIRS monitoring may also have a future in providing outcome measures for neonatal studies. A recent RCT randomized infants (28 – 33+6 weeks gestation) to receive either 1-3 sustained lung inflations (30 cm H_2O for 15 seconds) followed by standard respiratory care, or standard respiratory care only (130). Cerebral tissue oxygenation values were similar for both groups over the first 15 minutes of life. However, cerebral blood volume patterns differed between groups. Cerebral blood volume decreased in the control group over time, but remained static in the intervention group who received sustained lung inflations. The authors hypothesized that differences may have been caused by impaired venous return secondary to increased thoracic pressures during sustained lung inflations, with resultant cerebral venous stasis. These findings highlight the importance of assessing cerebral haemodynamics during interventional neonatal studies.

Guidelines for the use of NIRS monitoring and EEG in NICUs overlap, and it is advised that they should be used simultaneously (131). However, EEG in the immediate newborn period has received little attention in the literature.

Table 1.4 A summary of neonatal studies assessing cerebral oxygenation in the immediate newborn period

Reference	Neonates	Number (*N*)	Design	Resuscitation group included	Observation
Fuchs et al. (109)	Preterm VLBW (<1500 g)	24	Observational	Yes All infants had SLI followed by CPAP	Increases in cerebral StO_2 and HR preceded increases in SpO_2 following SLI
Fuchs et al. (108)	Preterm VLBW (<1500 g)	51	Observational	Yes	Increases in cerebral StO_2 values from 1 to 7 min of life before steady-state values reached Percentile charts produced
Binder et al. (100)	Late preterm 30 + 0 to 36 + 6 weeks	42	Observational	Yes	StO_2 values were consistently higher in normal transitional group compared with stabilization group
Pichler et al. (103)	Term and preterm	*N* = 381 Preterm *n* = 27	Observational	No	Preterm infants post cesarean delivery had higher StO_2 than term infants Percentile charts produced
Kenosi et al. (114)	Preterm <32 weeks	47	Observational	Yes	Infants requiring FiO_2 > 3.0 had increased cerebral hypoxia, but no increase in cerebral hyperoxia compared to infants requiring FiO_2 < 3.0
Pichler et al. (115)	Preterm <34 weeks	60	RCT	Yes	Reduction in cerebral hypoxia burden in group with NIRS and SpO_2 monitoring in the DR

1.3.4.1 Electroencephalography- Background

Electroencephalography (EEG) was first discovered in 1875, by an English physician Richard Caton, who observed the EEG from the exposed brains of rabbits and monkeys. In 1924, Hans Berger, a German neurologist made the first EEG recording from the human scalp, by using radio equipment to amplify the electrical activity of the brain, and obtained a written output on paper. He claimed that brain activity that is observed through the use of EEG can change in a consistent, reliable and recognizable fashion when the state of the patient changes, such as going from relaxation to alertness, sleep, and lack of oxygen (132). This breakthrough gave rise to further research and the varied applications of EEG in use today.

EEG consists of the summed electrical activities of populations of neurons. The neurons are excitable cells with characteristic intrinsic electrical properties, and their activity produces electrical and magnetic fields. These fields may be recorded by means of electrodes.

There are two main types of neuronal activity, action potentials and postsynaptic potentials (133):

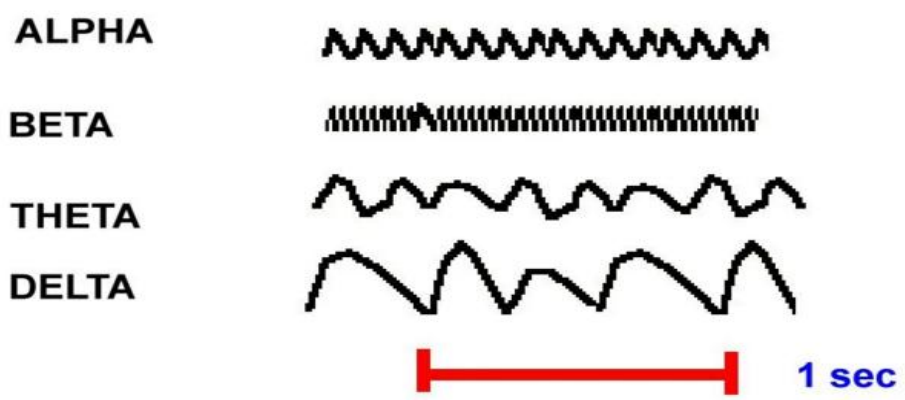
1. Action potentials are the result of the very rapid depolarization of a neuron mediated mainly by changes in permeability of the membrane to sodium and potassium ions. They occur when the cell depolarizes to a certain degree from its negative resting state potential. Once the threshold is reached, there is a rapid firing of the action potential (about 1 ms) from the beginning of the axon at the cell body down to the axon terminals. Due to action potentials being

very rapid and brief, the electrodes placed on the scalp simply cannot detect them, and it is not possible to monitor by EEG.

2. Postsynaptic potentials are voltages produced when the neurotransmitters bind to the receptors on the membrane of the postsynaptic cell, making ion channels open or close. They are mediated by a number of neurotransmitter systems and generally entail slower changes in membrane potentials. The change in electrical charge outside the membrane lasts in the extra-cellular space for up to 200 ms. The extra-cellular electrical charge, positive or negative, is what is measured with electrodes placed on the scalp. Therefore, EEG is a measure of summated postsynaptic neuronal activity in the cortex and represents a sum of excitatory and inhibitory postsynaptic potentials.

EEG exhibits a rich variety of frequencies, amplitudes and waveform morphologies from all monitored brain regions. The most familiar classification uses EEG waveform frequency (Alpha waves - 8-13 Hz, Beta waves - >13 Hz, Theta waves - 3.5-7.5 Hz, Delta waves - <3 Hz)(134)(Figure 1.1). Neonatal EEG can be assessed qualitatively and quantitatively. The neonatal EEG contains complex spatiotemporal information and interpretation is more complex than the interpretation of other vital sign signals such as heart rate or respiratory rate. Qualitative EEG analysis is mainly used for clinical purposes. It is based on visual interpretation of the EEG signal and describes such background features as amplitude, frequency, continuity of the EEG and sleep–wake cycling (SWC). Quantitative EEG analysis is a method predominantly used in research and includes time and frequency domain analysis.

Figure 1.1: EEG waveforms of varying frequencies



1.3.4.2 Electroencephalography applications

EEG has a range of clinical and research applications (135):

1. Monitor human brain development
2. Investigate epilepsy, locate seizure origin, and assess response to anti-epileptic treatment
3. Monitor alertness, coma, and brain death
4. Locate areas of damage following head injury, or pathological processes
5. Investigate sleep patterns and disorders

All of the above are relevant to neonatal care and EEG has become more common in NICUs over the past two decades in both clinical and research domains. In contrast to cerebral blood flow and NIRS, EEG has well documented applications in the clinical management of newborn infants (6). Its usefulness includes monitoring infants with perinatal asphyxia (7-10), the diagnosis of seizures (11-13), and more recently in assessing the long-term prognosis of premature infants (14).

1.3.4.3 EEG in the immediate newborn period- term infants

The immediate postnatal period is the time when EEG is often performed on critically ill term neonates. In infants with hypoxic ischaemic encephalopathy (HIE), multi-channel and amplitude integrated EEG are increasingly being used to decide eligibility for therapeutic hypothermia (136). The EEG is exquisitely sensitive to any impairment in oxygen delivery to the brain. EEG is of the order of microvolts and has a temporal resolution that is much higher than functional MRI and can display brain activity on a millisecond scale. A reduction in oxygen leads to an immediate suppression of synaptic transmission with a reduction (often complete suppression) in EEG amplitude (137, 138). This adaptive response, believed to be mediated by multiple inhibitory neuromodulators including adenosine, to hypoxia may be protective by decreasing energy consumed by the generation of synaptic potentials (139). If cerebral hypoxia is sustained however, EEG amplitudes remain severely reduced and membrane failure will eventually occur accompanied by energy depletion and cell damage (140) . Thus, sustained suppression in the EEG signals a risk of impending brain injury.

Decisions regarding long-term prognosis following neonatal HIE are made based on qualitative EEG analysis. Low background amplitude and discontinuity of EEG activity (burst suppression) occur following significant hypoxic-ischaemic injury, and are associated with a poor prognosis (141). Disruption of sleep wake cycling has been described in neonatal post-asphyxial injury, and its absence soon after birth has been associated with a poor neurodevelopmental outcome (142). In neonates with hypoxic ischaemic encephalopathy (HIE), an EEG showing sustained suppression for hours after birth has long been associated with a very poor outcome (143-146). Neonatal

EEG monitoring is recommended for all infants with moderate and severe HIE, and neonatal teams are now familiar with its application in NICUs.

Previous studies have shown that the EEG of fetal sheep can be recorded during labour (137, 147, 148). Thaler and colleagues performed intrapartum EEG on fourteen women with uncomplicated pregnancies (149). A clinical trial of EEG monitoring during labour is also currently underway (https://clinicaltrials.gov/ct2/show/NCT03013569). During normal labour, the fetus is exposed to brief but repeated episodes of hypoxia which are balanced by the fetus's striking ability to adapt to these episodes (150). Fetal EEG monitoring in both human and animal studies during labour has shown that these episodes are associated with rapid EEG amplitude reduction and also with fast amplitude recovery as soon as the uterine contraction ends (137, 140). Fetal EEG monitoring has clear benefits for the early recognition of hypoxic ischaemic (HI) injury but requires considerable research before it is adopted as a routine tool for fetal surveillance. Neontal EEG acquisition in the immediate newborn period on the other hand is much more feasible and may quickly identify those neonates that have not tolerated labour and delivery very well, which will be seen as suppression or disrupted patterning on the EEG.

An early EEG in the DR of an infant requiring advanced stabilisation will indicate if EEG activity is present or not or if EEG activity returns following this stabilisation process. We know that EEG activity should recover immediately following restoration of oxygen delivery to the brain. If EEG activity does not return immediately post resuscitation or activity is severely disrupted, this may indicate that the infant is at risk of HI brain injury. This could provide a clear indication for immediate passive cooling prior to transfer to the NICU. This early indication of

cerebral function is very important as Thoresen et al have shown that infants cooled within 3 hours of birth have better neurodevelopmental outcomes when compared to infants whose cooling commenced between 3 hours and 6 hours (151). Further improvements in outcome are highly likely to arise from earlier improved identification of affected infants that would allow earlier initiation of treatment after resuscitation.

1.3.4.4 EEG in the immediate newborn period- Preterm Infants

EEG is also the gold standard for the accurate detection seizures in preterm infants (131, 152). However, electrographic seizures are infrequent within the first few days of birth in very preterm infants (153). The EEG can also provide real-time markers of cerebral dysfunction, even when it is secondary to systemic disease and macroscopic cerebral lesions are not evident (154). EEG monitoring of preterm infants in the immediate newborn period may have a role in predicting outcomes and furthering our understanding of the multiple factors affecting outcome in the immediate newborn period. Prediction of outcome following preterm delivery is more complicated than following term asphyxia, but investigations are ongoing (155). We now understand how brain activity changes over time in preterm infants, and can develop into mature healthy EEG patterns over time following preterm delivery (156). Therefore, a knowledge of the gestational age of the infant is essential as the EEG varies dramatically with maturity (157).

Accurate neonatal EEG interpretation requires a thorough appreciation of the appropriate maturational features for neonates of all gestational ages (GA) as baseline EEG patterns evolve in line with the rapid maturational changes taking place in the

brain (158). The EEG develops in the most immature neonates at 23/ 24 weeks GA through to full-term age with four major trends (156):

1. Increasing continuity, with defined periods of EEG quiescence for specific GAs:

Early preterm EEG exhibits an intermittent or discontinuous pattern (tracé discontinu) consisting of low-voltage activity, known as inter-bursts, followed by short-duration higher-voltage activity, known as bursts or spontaneous activity transients (159). This pattern differs to the burst-suppression pattern found in the EEG of full-term infants following severe brain injury (160). From a physiological perspective, this feature can be explained from animal experiments that have shown that the cortex produces spontaneous, intermittent activity that is a crucial endogenous driver for the development of brain connectivity before cortical networks are modulated by external sensory input (161-163). Furthermore, early in development, GABAergic transmission is not effectively inhibitory and may allow the generation of these endogenous events (164). With the maturation of normal inhibitory GABAergic transmission, spontaneous events are gradually abolished and 'continuous' oscillations emerge at different frequencies due to the increasing influence of exogenous sensory driven input (165). Consequently, the overall amount of discontinuity decreases and continuity increases with GA.

Analysis of this discontinuous pattern includes measurements of interburst interval (IBI) duration which decrease with increasing GA (166) (Figure 1.2). Normative values for different GAs have been now reported as follows:

23- 27 weeks GA: <60 seconds

28–29 weeks GA: ≤30 seconds (40 seconds accepted if occasional)

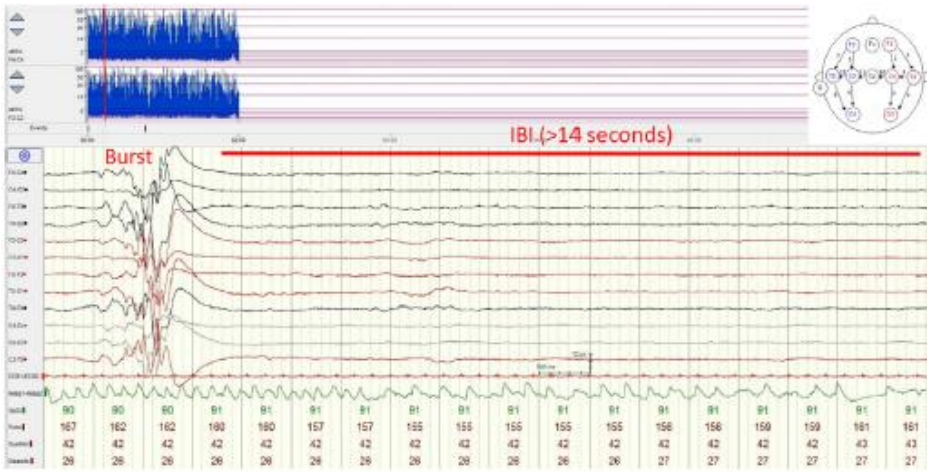
30–31 weeks GA: ≤20 seconds

32–34 weeks GA : ≤10–15 seconds

35–36 weeks GA: <10 seconds

Aside from the duration of IBIs, their amplitude also changes over time, becoming less suppressed with increasing GA (167).

Figure 1.2 Example of Interburst Interval in infant 26/40 weeks gestation



2. The appearance of sleep cycling

Differentiation of sleep is detectable in preterm infants <30 weeks GA (168-170). Sleep-wake cycling relies on the maturation of interconnected neural networks located throughout the cortex, diencephalon and brainstem and is recognisable in younger preterm infants because of the influence of deeper brain structures, before proper thalamo-cortical connectivity has developed (171-173). In the normal preterm EEG, different sleep states and cyclicity are increasingly evident overtime and at 35 weeks all sleep stages are clearly recognisable (Figures 1.3 and 1.4).

Figure 1.3 Example of active sleep with continuous activity in infant 31 weeks gestation

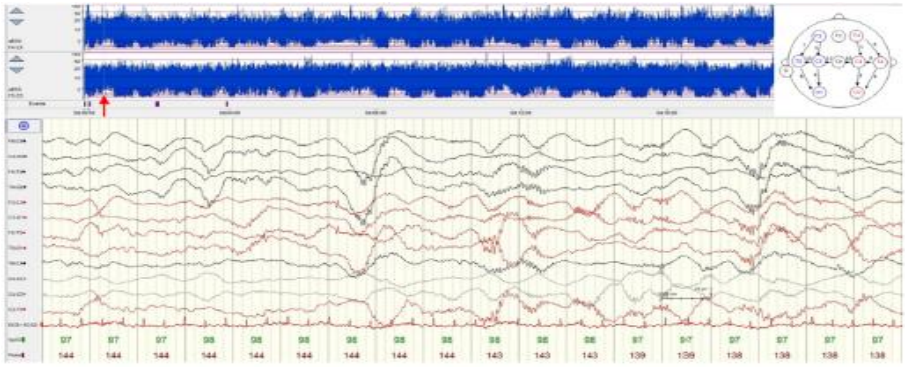
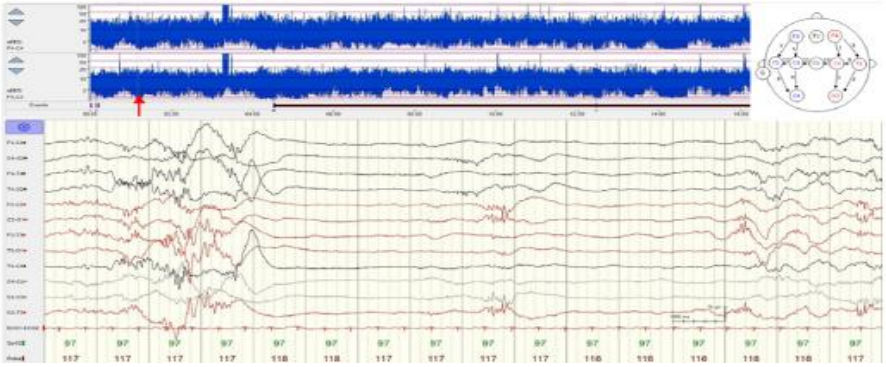


Figure 1.4 Example of quiet sleep with discontinuous activity in infant 31 weeks gestation



3. Changes in synchrony between hemispheres

Synchrony in the EEG is present when all EEG features occur simultaneously in homologous areas over both hemispheres. Although interhemispheric synchrony has been shown to increase with increasing GA, synchronous bursts/IBI activity between the two hemispheres is present in preterm infants <30 weeks GA (174, 175). Synchrony is an important feature of EEG maturation and reflects the development of the corpus callosum and, therefore, the interconnections between the two hemispheres (175). Asynchrony decreases with increased maturity, disappearing at term age (175).

4. The appearance of several transient waveforms of prematurity.

Delta activity (0–3.5 HZ), a common background feature < 28 weeks gestation is high amplitude, low frequency (0.3–1 Hz) smooth activity organised as unilateral or bilateral bursts in centro-occipital or temporal regions, or as short sequences (<80 seconds) mainly in the occipital regions bilaterally (167). Delta brushes are one of the most important features of the preterm EEG. Delta brushes consist of a slow delta wave with fast rhythms superimposed (in the alpha-beta range) mainly on the ascending slope of the slow wave. They have been reported in all GAs but have a peak between 32 and 35 weeks and tend to disappear between 38 and 42 weeks (167). Theta activity (4–7.5 HZ), 'Sharp theta on the occipitals of premature infants' occur at earlier GAs, with a peak at 25 weeks (176).

Analysis of preterm EEG at a given GA allows for real time monitoring of cerebral function and brain health. Several studies have shown that early background EEG suppression correlates with severity of periventricular haemorrhage (177-179). The most common EEG biomarkers associated with poor outcomes are seizures, positive rolandic sharp waves, EEG suppression/increased interburst intervals, mechanical delta brush activity, and other deformed EEG waveforms, asymmetries, and asynchronies (154). A continuous display of inter-burst interval duration has been cited as a useful prognostic measure in preterm infants in the near future (171, 180).

Accurate and early prediction of neurodevelopmental outcome in the preterm infant provides important clinical information that can be used to guide early intervention, assist clinical management, and ensure appropriate long-term needs are identified. Predicting outcome at 2 years or more, in the first few days after birth is ambitious

however, as preterm infants are vulnerable to brain injury during their entire stay in the NICU (181).

Many studies have attempted to predict short-term outcome. Early clinical information, including Apgar scores, gender, birthweight, GA, and illness severity scores, such as SNAP-II and SNAPPE-II have been used to predict short-term outcome (182-184). Quantitative analysis of multiple risk factors combined in a multivariate model can improve outcome prediction (185). Saria *et al.* showed that a combination of quantitative features of early physiological measurements, including HR, RR, and SpO2, could predict short-term outcome with a high level of accuracy (sensitivity of 86% and specificity of 96%) (186). Medlock *et al.* found that multivariate models of early clinical information predicted mortality in preterm infants better than birthweight or GA alone. Studies implementing the commonly used SNAP-II and SNAPPE-II scores showed a range of AUC values for the prediction of neonatal mortality, from 0.66 to 0.78 in SNAP-II studies and 0.60 to 0.91 in SNAPPE-II studies (185). The absence of a reliable measure of neurological function, however, may limit the ability of these approaches to predict neurodevelopment in the longer term, beyond the early intensive care stage.

Previous studies have shown that early measurements of EEG can predict long-term neurodevelopmental outcome, with high specificity and low sensitivity ranging from 88 to 96% and 25 to 61%, respectively (187-190). Other studies have shown that the amplitude integrated EEG (aEEG) can predict long-term outcome, with specificity ranging from 73 to 89% and sensitivity ranging from 56 to 87% (190-192).

Multimodal prediction models, which include EEG, have shown promise in predicting outcome. A recent study which utilized quantitative analysis of physiological signals,

combined with GA and graded EEG, displayed potential for predicting mortality or delayed neurodevelopment at 2 years of age (193). In this study infants <32 weeks gestation had simultaneous multichannel EEG, peripheral SpO2, and HR monitoring. EEG grades were combined with GA and quantitative features of HR and SpO2 in a logistic regression model to predict outcome. Bayley Scales of Infant Development-III assessed 2 year neurodevelopmental outcome. A clinical course score, grading infants at discharge as high or low morbidity risk, was used to compare performance with the model. While performance of the model was similar to the clinical course score graded at discharge, with an AUC of 0.83 (95% confidence intervals (CI): 0.69–0.95) vs. 0.79 (0.66–0.90) (P = 0.633), the model was able to predict 2 year outcome days after birth. Early EEG grade alone demonstrated low sensitivity (50%) and high specificity (89%), compared to clinical course score sensitivity (88%) and specificity (70%). The multimodal model which included EEG provided a more balanced sensitivity–specificity result (75–74%) (193).

1.3.4.5 The rationale for EEG in the immediate newborn period

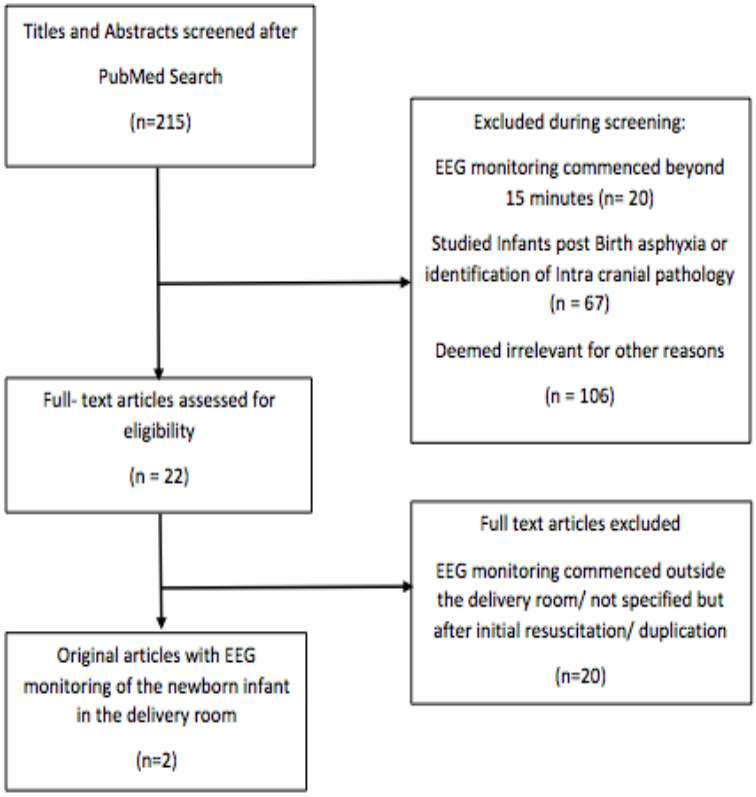
EEG is not a new technique but its application in neonatology in the past has been hampered by a lack of appropriate technology for recording and analysis. This has changed dramatically in the last decade and there are now high quality digital amplifiers available that can record excellent EEG signals even in very noisy environments. The time is now right to re-explore the use of EEG as a valuable biomarker of neurological function in the delivery room; an environment where previously, it was just not possible.

EEG monitoring in the immediate newborn period, for term and preterm infants, could provide neonatal teams with valuable, much needed, information about the neurological status of the newborn infant, immediately after birth. Following preterm delivery EEG monitoring could also enhance our understanding of preterm infant outcomes. Thus, a systematic review was performed to assess whether any studies had already attempted to measure the human EEG in the immediate newborn period.

1.3.4.6 Results of a systematic review of EEG in the immediate newborn period

The initial search identified 215 articles (methodology available section 2.9). After assessment of these articles, two original studies were identified that described EEG monitoring of the newborn infant within the delivery room (Fig 1.5). One study also contributed to a review article identified by our search, which was excluded from our study to avoid duplication (95). Table 1.5 summarises the 2 studies identified.

Figure 1.5 Flow Diagram of Literature Search



Pichler et al. performed a prospective observational study of infants born by elective cesarean section over 34 weeks gestational age (105). Infants at lower gestational ages were excluded due to concerns about their small head size, and the feasibility in applying EEG leads and NIRS to a small surface area. Four gold electrodes (2 frontal and 2 parietal) were applied with contact gel, along with a NIRS pad to the left forehead, and overlying elastic bandages for support. Amplitude integrated EEG (aEEG), a rectified, filtered and compressed form of EEG was acquired and stored. Overall they found that aEEG monitoring of the newborn infant in the DR is feasible, but it is difficult to obtain continuous reliable data. Of a total number of 63 infants, 17 (27%) were excluded due to unreliable data. Of the remaining 46 infants, no data was

recorded prior to 3 minutes of delivery, 25% had data available at 3 minutes, and just over 50% were available at 5 minutes. aEEG data was analyzed for mean minimum and mean maximum voltages every minute, and then correlated with cerebral oxygenation, heart rate and pre-ductal oxygen saturations. Findings were then compared between infants who were uncompromised at birth (n= 47) and infants who required neonatal resuscitation (n=16).

Different cerebral activity patterns were identified between uncompromised newborns and those requiring resuscitation. They reported that infants in the uncompromised transition group started with initially high voltages on aEEG, followed by a significant decrease to baseline voltages at 4-5 minutes. In contrast, infants in the group requiring respiratory support did not show this pattern. However, there were no significant differences between minimum and maximum voltages when the 2 groups were compared, which the authors attribute to low numbers in the respiratory support group.

Tamussino et al. recorded simultaneous aEEG and NIRS in 244 term neonates during the first 15 minutes after delivery (194). Similar to the study of Pichler et al. aEEG data was analyzed for mean minimum and mean maximum voltages every minute, and then correlated with cerebral oxygenation, heart rate and pre-ductal oxygen saturations. Neonates with initial low voltages, which normalized during transition, were compared to neonates with normal aEEG values throughout the monitoring period. Nine neonates had low initial aEEG voltages and were compared to 50

neonates with normal aEEG voltages throughout. Therefore, of 244 infants recruited, 59 aEEG recordings were included in the analysis. Neonates with initially low cerebral activity during immediate transition after birth displayed lower cerebral saturations (<10th percentile) on NIRS, but increased cerebral oxygen extraction (cFTOE > 90th percentile). The authors concluded that neuro-monitoring with aEEG and NIRS might provide useful information on the neonates' condition during immediate transition.

Table 1.5 Summary of neonatal EEG studies in the immediate newborn period

Author/year	Neonates	Number recruited and monitored	Design	Number included in analysis	Observation
Pichler, 2013	>34 weeks	46	Observational aEEG analysed for minimum and maximum voltages NIRS	N=46 31 uncompromised 15 required respiratory support	No significant differences between minimum and maximum voltages when the 2 groups Uncompromised infants had higher V max in minute 3 and 4 compared with minute 10
Tamussino, 2016	Term	244	Observational aEEG analysed for minimum and maximum voltages Infants with initial low voltages which normalised were compared to infants with normal voltages throughout NIRS	N=59 9 met inclusion criteria 50 control studies	Neonates with initially low cerebral activity during immediate transition after birth displayed lower cerebral saturations (<10th percentile) on NIRS, but increased cerebral oxygen extraction (cFTOE > 90th percentile).

1.3.5 Summary

The brain is the most vulnerable organ in newborn infants. Birth asphyxia and preterm brain injury account for the vast majority of neonatal brain injuries, and are a major cause of disability. A non-invasive, continuous method to measure cerebral activity (EEG) is already available but it has not progressed to the immediate newborn period. As the importance of the early instigation of neuroprotective strategies for term newborns with perinatal asphyxia has become evident, EEG monitoring (usually aEEG) has become more common in NICUs (195, 196). In contrast to cerebral blood flow and NIRS, EEG has well documented applications in the clinical management of newborn infants. It is the gold standard method for the accurate detection of all neonatal seizures in term and preterm infants (131, 152). It has well proven efficacy in predicting outcomes following perinatal asphyxia, based on patterns of poor background activity and the timing of sleep wake cycling reestablishment (143, 197-199). Prediction of outcome following preterm delivery is more complicated but investigations are ongoing (155). This is important as assessing preterm infant neurological outcomes is challenging.

Despite its importance in monitoring the newborn brain in the NICU, EEG monitoring in the immediate newborn period is currently not recommended. Stabilisation of newborn infants in the delivery room occurs without any objective measure of brain activity and we found only two studies that have assessed the feasibility of obtaining a newborn EEG recording in the DR. Both studies used the aEEG trend and both found it possible to obtain aEEG tracings within 3 minutes in some cases, but obtaining continuous reliable data was generally difficult (105). The studies did not include infants less than 34 weeks due to technical challenges. Within these limitations the

authors describe different patterns in brain activity for infants that required respiratory support and infants that transitioned independently. Also, aEEG was correlated with different cerebral oxygenation patterns.

Both studies analyzed brain activity by interrogating the aEEG mean minimum and mean maximum voltages. However, the aEEG trend alone is a high level summary measure of the EEG with poor time resolution due to compression in the aEEG algorithm and it does not display the second by second activity of the brain; as a result, it is not optimal for application in the DR. Digital aEEG machines obtain one or two channels of EEG signal, which is then amplified and passed through an asymmetric band-pass filter that strongly attenuates activity less than 2 Hz and more than 15 Hz, to minimize artifacts. Additional processing includes semilogarithmic amplitude compression, rectification, and time compression (200). Heavy signal processing used in the aEEG algorithm eliminates much of the detail (e.g. frequency band content) available in the EEG and many clinically important features are lost. Furthermore, there is no clear definition for aEEG and most EEG machines implement different versions of the aEEG algorithm (201). The mean and maximum of the aEEG voltage needs to be plotted and displayed for a number of minutes before any assessment of the overall baseline EEG activity can be made. In addition, it is well known that interpretation of the background aEEG pattern can be problematic due to baseline drift and other artefacts (202, 203). This is not optimal for DR EEG recording when real-time second by second information would be advantageous. For example, a recording of approximately 30 seconds duration alone using standard EEG would be enough to establish the presence of continuous EEG activity in a term

newborn. This information would be hugely beneficial in the DR to help guide resuscitation and to determine the need for immediate passive cooling. Thoresen et al coined the phrase ‘time is brain’ in relation to the timing of cooling for neuroprotection (151).

EEG in its raw format (not a modified aEEG) can be assessed both qualitatively and quantitatively. Qualitative EEG analysis is mainly used for clinical purposes. It is based on visual interpretation of the EEG signal and describes background features such as amplitude, frequency, and continuity of the EEG, symmetry, synchrony, and sleep–wake cycling. Quantitative EEG analysis is a method predominantly used in research and includes time and frequency domain analysis. Neither study identified in our review analyzed the EEG in its raw format, either for qualitative or quantitative purposes.

EEG has long been considered just too difficult to deploy in environments like the DR and NICU. There have been major recent advances to the adoption of EEG in the NICU primarily due to advances in technology (204). The application of EEG in preterm infants has also progressed, and many technical barriers overcome (205). Modern machine learning techniques are also advancing rapidly and will soon be able to provide non-EEG experts with the help needed to assist in the interpretation of EEG patterns on a 24/7/365 basis. These difficulties should no longer be a barrier to the adoption of EEG in the immediate newborn period.

In conclusion, the time is now right to advance the objective monitoring of neurological function of newborn infants in the immediate newborn period, and specifically brain activity, measured by EEG.

Chapter 2

General methodology

2.1 Introduction

This chapter provides an outline of the general methods used in the studies described in this thesis. The chapter describes how and where the patients were recruited, the devices used, data collection and storage, and the statistical methods used to analyze the data. Other specific methods used in certain studies presented in this thesis are outlined in the relevant chapters.

2.2 Subjects and Settings

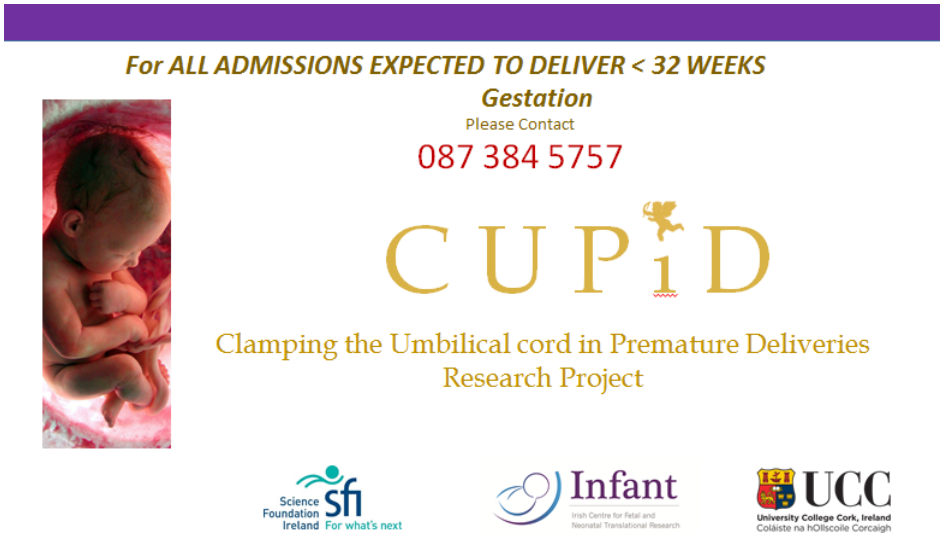
This research was performed in the delivery room and neonatal unit of the Cork University Maternity Hospital (CUMH). This is a level three maternity unit with up to 8500 deliveries per annum. Infant cohorts were recruited between July 2015 and January 2017.

2.3 Patient Recruitment

Antenatal recruitment was used for all studies. For studies in term infants (Chapters 3 and 4), recruitment occurred during daytime working hours as all infants included were delivered by elective caesarean delivery. Recruitment for preterm infants (Chapter 5) was more challenging as they are by nature emergency deliveries. Therefore, a number of measures were taken to optimize patient recruitment. Firstly, the medical and nursing staff of the neonatal unit and the obstetric and midwifery staff in the labour ward were informed of the study, its aims and recruitment criteria.

Laminated posters stating the recruitment criteria were placed in the NICU, the labour ward, antenatal ward, and medical staff on- call rooms (Figure 2.1). All staff were encouraged to contact me if there was a possibility of a preterm infant being delivered < 32 weeks gestation. There was a dedicated research phone which could be contacted 24/7. This phone was carried by me or by one my research colleagues, AP and DHR. AP and DHR were Clinical Research Fellows in the INFANT Research Centre in CUMH and were both ethically approved to consent and randomize infants for this trial.

Figure 2.1 Poster for Preterm Infant Trial



Despite these measures a number of challenges to recruitment persisted. The time period prior to delivery is a stressful time for parents. It is difficult to find an appropriate time where a sensitive and thorough antenatal consent consult can be performed. The clinical needs of the mother always took precedence, and parents were only approached if there was adequate time for consultation, and parents were happy to proceed. It was a priority that all parents were fully informed and had read the appropriate parent information leaflet before consenting. Many deliveries during

the study period occurred under emergency circumstances and it was not possible for a researcher to attend in a timely fashion. Flow diagrams detailing patient recruitment are available in the relevant chapters.

2.4 The Consent Process

For trials in term infants parents were approached on the day of admission prior to elective caesarean delivery. For trials in preterm infants parents were approached where possible on the antenatal ward or in the case of imminent delivery on the labour ward.

The reasons, the risks and the benefits for the study were explained to both parents. Any concerns relating to the study were also discussed with the parents. It was emphasized that the current study might not be of any benefit to their infant but that the data collected could be an important source of information in our quest to improve care and survival of infants in the future.

A written detailed information leaflet explaining each study and outlining the rationale for doing such research was provided to the parents. The information leaflet also mentioned any potential risks and benefits. The information leaflet was for parents to keep and to read in their own time if they needed time to make up their mind on whether to participate or not. Along with the information leaflet, parents were given a consent form that they could sign if they agreed to participate in our study. Both documents are included in the Appendices.

Parents were given an opportunity to think about the information provided, and opt in or out of participation in the study as they wish and at any stage of the study. It was

also made clear that they could opt out of the study at any later time and that any data that had been collected would be deleted. Parents who agreed to participate in the study were given a copy of the signed consent form as evidence of the agreement to participate in the study.

2.5 Ethics

Ethical permission to carry out all studies was obtained from the Clinical Research Ethics Committee (CREC) of the Cork University Hospital Teaching Hospitals prior to study commencement. The ethics acceptance letter and consent forms and parent information leaflet are provided in the Appendices.

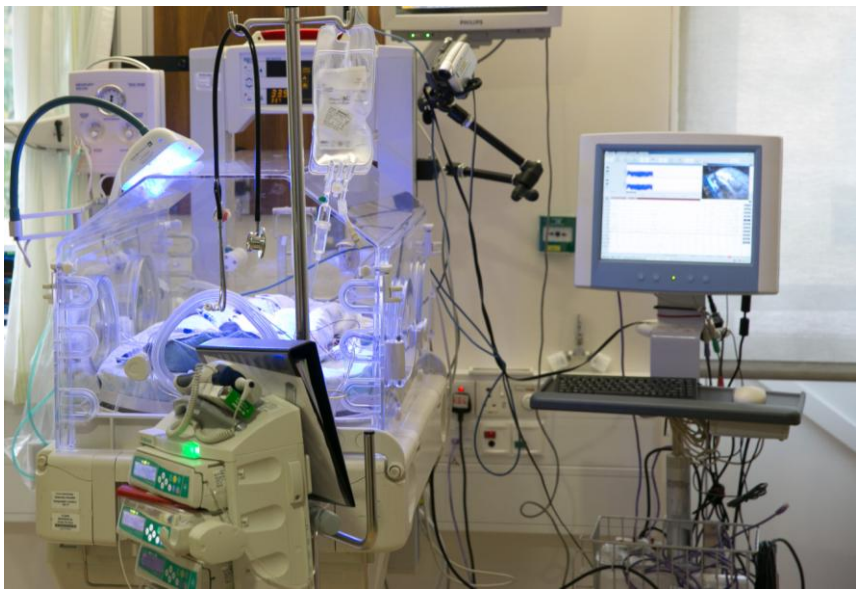
2.6 Infant monitoring

2.6.1 EEG monitoring

2.6.1.1 EEG devices

For term infants included in this thesis, all recordings were performed and stored using the Unique EEG system (Inspiration Healthcare, Leicester, UK). For preterm infants, recordings were obtained either with the NicoletOne (CareFusion Co., San Diego, USA)(Figure 2.2) or Moberg (Moberg Research Inc., PA, USA) EEG systems.

Figure 2.2 Nicolet 1 EEG operating system



2.6.1.2 EEG application

A member of the research team performed all EEG studies following a standardized protocol. For term infants the aim was to capture brain activity as soon as possible after birth. All EEG recordings were obtained in the DR as soon as possible after birth. For preterm EEG was applied in the DR or in the NICU. When EEG was applied in the DR, recordings were commenced at that time, were discontinued during transfer to NICU and commenced again on arrival to NICU.

For term infants the infants' scalp was first cleaned using an alcohol wipe. As per usual clinical practice previously described in our NICU, the hair was then parted at EEG sensor sites, and the skin gently abraded three to four times using a sterile cotton bud and skin preparation gel (Nuprep)(205). Six sterile disposable flat surfaced EEG electrodes were then attached to the infants' scalp over frontal and central regions (F4, C4, F3, C3, ground, and reference) bilaterally using the 10-20 system of electrode placement and the EEG was recorded for up to ten minutes. Two channels of a bipolar recording were displayed (F4-C4, F3-C3) on the monitor. The study was designed to obtain 2 channels as applying more electrodes would have delayed the onset of recordings.

The method for electrode placement in preterm infants in our unit has previously been described (205). Depending on infant size, 4- 11 electrodes were positioned according to the international 10–20 system of electrode configuration over the frontal, central, temporal, and occipital regions, a reference electrode at Fz, and a ground electrode behind the left ear (Figure 2.3). Although the aim was to obtain as many channels of EEG as possible, infant stability and the length of time to apply extra electrodes was taken into account at all times.

Figure 2.3 Example of EEG electrode placement in a preterm infant



2.6.1.3 EEG data collection and analyses

EEG data was sampled at 256 Hz and stored on computer hard disk for off-line anlysis. Firstly, the recordings were assessed for quality and periods of artefact-free EEG were identified for analysis. All EEG recordings for term infants were initially anotated for 3 minute artefact free segments. All EEG recordings for preterm infants had one hour segments at 6 and 12 hours annotated. They were then visually analyzed by GBB for quality, overall voltage, continuity and frequeny (206). Annotated segments of EEG were then analysed for quatitative measures. Different quantitative measures for term and preterm recordings were applied and are described in the relevant chapters.

All quantitative measures were performed using the software package NEURAL, a neonatal EEG feature set in matlab (v0.3·0), which runs within the Matlab environment (The MathWorks, Inc., Natick, Massachusetts, United States). NEURAL

was developed to standardize quantitative analysis of newborn EEG by including full implementation details(206).

Quantitative EEG analysis provides an alternative to visual interpretation, and provides consistency without the varying degrees of inter-rate agreement associated with visual interpretation. Quantitative analysis can also uncover attributes not accessible with visual analysis alone, and can facilitate reproducible research for clinical and scientific studies.

2.6.2 NIRS monitoring

The INVOS 5100 near infrared spectrometer (Somanetics Corporation, Troy, MI, USA)(Figure 2.4) was used to measure $rcSO_2$. A NIRS neonatal probe, OxyAlertTM NIRSensor (Covidien IIc, Mansfield, MA, USA) was applied in a fronto temporal location (Figure 2.5). The INVOS machine recorded and stored $rcSO_2$ throughout the DR and NICU periods with a sampling period of five and six seconds. This device's $rcSO_2$ measurements are limited to a specific lower and upper limit of 15% and 95% respectively, therefore no measurements below 15% and above 95% can be measured (207).

Figure 2.4 INVOS NIRS System



Figure 2.5 OxyAlert TM NIRS sensor



2.6.3 Respiratory function monitoring

A Respironics NM3 Monitor (Philips, Amsterdam, Netherlands)(Figure 2.6) was used, which is a non-invasive respiratory function monitor with combined mainstream

capnography and flow monitoring (Capnostat 5 sensor, Philips, Amsterdam, Netherlands). The dead space volume as reported by the manufacturer is ~ 1 ml. The CO_2 / flow sensor was attached to a facemask (Laerdal infant mask; Stavanger, Norway) and placed over the infants' mouth and nose on arrival to the resuscitator. End tidal CO_2 was measured by infrared absorption spectroscopy, while RR, TVs, and airway pressures were measured by a gas flow sensor (Capnostat 5 sensor).

Figure 2.6 Respironics NM3 Monitor



2.6.4 Echocardiography

Echocardiographic measurements were performed using the GE Vivid I ultrasound machine (KPI Healthcare, CA, USA). Measurements were taken to assess systemic blood flow, by superior vena cava (SVC) flow (ml/kg/min), right ventricular output (208) (ml/kg/min), and left ventricular output (LVO)(ml/kg/min). All measurements were performed by a member of the research team following a standardized protocol previously described (209).

2.7 Delayed cord clamping with bedside resuscitation

Delayed cord clamping with bedside resuscitation was the experimental interventional arm in the preterm infant trial which will be described in detail in chapter 5. A mobile resuscitation trolley (Lifestart, Inspiration Healthcare, UK)(Figure 2.7) designed specifically to facilitate newborn bedside resuscitation, with an intact cord was introduced to CUMH.

A key element in the design is flexibility to allow the baby to be placed on the trolley while the umbilical cord is still intact. This required the trolley platform to be easily manoeuvrable. Thermal support is provided by the CosyTherm electric heated mattress. Fixed around the central pillar are two universal Medirails which accommodated a Tom Thumb Infant Resuscitator (Viamed, Keighley, UK), oxygen blender (Inspiration Health Care Ltd., Leicestershire, UK), a suction bottle driven by the wall-supplied air supply (Oxylitre Ltd., Manchester, UK) and the control unit for the CosyTherm heated mattress (Inditherm, Rotherham, UK). It was connected with hoses to the air and oxygen wall supply. Infants were placed on a mobile resuscitation trolley with the cord intact, and at or below the level of the placenta. Routine neonatal care was provided and the cord clamped at 60 seconds following delivery.

Figure 2.7 Lifestart bedside resuscitation trolley



2.8 Statistical analysis

SPSS version 22, and PROC MIXED in SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) were used along with the Matlab programming environment to perform statistical tests. Patient characteristics were compared using the t-test or Mann-Whitney U test, as appropriate. A p-value <0.05 was considered to be statistically significant. Specific statistical models are described in detail in the relevant chapters.

2.9 Search Strategy and Study selection for Systematic review- EEG in the Immediate Newborn Period

A systematic stepwise search of PubMed was performed as per the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) (210). Articles up to and including February 2017 were included. Studies had to involve EEG monitoring in the DR. Search terms included: infant, newborns, neonate, delivery room, afterbirth, transition and electroencephalography. Only human studies were included and this was incorporated into the initial search. Additional published reports identified in review articles, or referenced in articles screened were also included.

Articles identified by our search strategy were screened for inclusion by one author (211). Titles and abstracts were initially screened. Articles had to pertain to EEG monitoring immediately after birth. Studies that focused on infants post birth asphyxiation or infants who had intra cranial pathology were excluded as the subjects were, by nature, recruited post-delivery and not relevant to our search. Studies that specified a time frame for initial EEG monitoring outside of the first fifteen minutes

of life, or initial recruitment outside of the delivery room were also excluded. Where uncertainty remained regarding eligibility for inclusion the full text was reviewed. Studies that were not available in English were excluded.

2.10 Work undertaken for this MD

I was the lead clinical research fellow on all studies included in this thesis. I worked with my supervisors, EMD and GBB, in designing each study. I obtained ethical approval from University College Cork for the studies described in Chapters 3 and 5, and designed the consent and parent information leaflets. I registered the randomized controlled trial CUPID which is described in Chapter 5 with an international registry. I led the recruitment phase for each study and obtained the majority of informed ethical consents for all studies, and when I was not available members of the INFANT research team (EMD, DRH, AP, JDM) obtained consent.

I performed data collection in all studies:

Chapter 2: I performed the systematic review of EEG in the immediate newborn period.

Chapter 3: I performed all EEG studies.

Chapter 4: I performed 50/100 respiratory function monitoring. Fifty patients recruited had monitoring performed by research team members JDM and LD.

Chapter 5: I introduced delayed cord clamping with bedside resuscitation to CUMH. This involved liaising with obstetricians, neonatologists, theatre nurses, midwives, neonatal nurses, infection control and clinical engineering. I designed standard operating procedures for the use and maintenance of the resuscitation trolley. I trained all necessary staff in the use of the mobile resuscitation trolley. I performed bedside resuscitation in the majority of infants randomized to delayed cord clamping.

I performed the EEG, NIRS and echocardiography in the majority of patients. When I was not available EEG and NIRS was performed by research team members (AP, RL, CA, EP, LK) and echocardiography by EMD.
IH research nurse aided in the recruitment and data collection for all studies.

I collected the data for each study and performed initial data analysis. I was aided in the analysis of data. JOT performed quantitative analysis of EEG and NIRS data for all studies. GBB performed visual analysis of EEG data. VL aided with all statistical analysis. I interpreted the data for all studies, and drafted the initial manuscripts for each study. The manuscript for each study was reviewed by all authors who are listed on pages 18-20. I drafted the manuscript for this thesis which has been reviewed, edited and approved for submission by GBB, and EMD.

Chapter 3

Respiratory Adaptation in Term Infants following Elective Cesarean Section

3.1 Introduction

In the next chapter brain activity in the first minutes of life will be discussed. However, it is important to first explore newborn respiratory adaptation. Our understanding of newborn respiratory adaptation is the result of many innovative clinical trials and collaborative efforts over the past 60 years (212-219). Lung aeration and the establishment of functional residual capacity (FRC) is critical in newborn transition from fetal life (212).

In recent years, technological advances in neonatal monitoring have facilitated real time monitoring of physiological parameters during newborn transition (220, 221). As previously described, Dawson and colleagues produced centile charts detailing the normalisation of oxygen saturations over time during newborn adaptation (27). More recently Schmolzer and colleagues utilized respiratory function monitors (RFM) to document exhaled CO_2, and tidal volumes (TV) for term infants immediately after vaginal deliveries (222).

However, gaps in our understanding of newborn adaptation remain. Respiratory function monitoring values in infants born by ECS and thus not exposed to the mechanical and hormonal adjustments that occur during labour and vaginal delivery have not been reported. The aim of this study is to define newborn physiological

ventilation parameters (RR, TV, $EtCO_2$) over the first minutes of life in healthy term infants following ECS, and also to assess the time at which these parameters stabilise.

3.2 Methods

3.2.1 Study participants

Infants > 37 weeks' gestational age, born by ECS, were eligible for inclusion in the study. Infants with major congenital abnormalities affecting newborn respiratory adaptation were excluded. Infants requiring intervention to support stabilisation beyond being warmed, dried, and stimulated, or Apgar scores < 7 at 1 minute were also excluded from the study.

3.2.2 Data acquisition

Following delivery, infants were brought immediately to a Panda Resuscitator (GE Healthcare, Laurel, MD, USA) which has a continuous-flow, pressure-limited, T-piece device with a built-in manometer and a PEEP valve. A Respironics NM3 Monitor (Philips, Amsterdam, Netherlands) was used, which is a non-invasive respiratory function monitor with combined mainstream capnography and flow monitoring (Capnostat 5 sensor, Philips, Amsterdam, Netherlands). The dead space volume as reported by the manufacturer is ~ 1 ml. The CO_2 / flow sensor was attached to a facemask (Laerdal infant mask; Stavanger, Norway) and placed over the infants' mouth and nose on arrival to the resuscitator. Each infant was monitored for up to 10 minutes. End tidal CO_2 was measured by infrared absorption spectroscopy, while RR, TVs, and airway pressures were measured by a gas flow sensor (Capnostat 5 sensor). All infants included in the study were breathing spontaneously without additional flow or oxygen. As all infants were born by cesarean section, monitoring did not

interfere with skin-to-skin time or initiation of breastfeeding. Follow up RFM was performed, where appropriate, for 2 minutes at 2 hours of age using the same RFM. All measurements were performed by one of the research team following a standardized protocol. Each infant was video recorded during study measurements. Recordings were commenced once an infant's whole body was delivered and captured infants once they were placed on the resuscitaire. This allowed for future accurate documentation of the age (in seconds) when monitoring commenced. There is no hospital protocol on the timing of umbilical cord clamping following ECS, and timing of clamping was not influenced by this research study. The time of cord clamping was not recorded. Maternal and infant demographics were recorded.

3.2.3 Data Collection and Statistical analyses

For the duration of each recording a breath-by-breath analysis was exported from the Respironics NM3 Monitor (Philips, Amsterdam, Netherlands) to SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). Respiratory rates, TV, inflation time, and $EtCO_2$ means were calculated for each minute of the recording, starting from time of birth. In the initial study design the aim was to record all infants for the first ten minutes of life. However, the practical needs requiring infants to be weighed, dressed and brought to their parents within the time constraints of a busy obstetric theatre led to many recordings being terminated early. Breaths were excluded if mask leak was >30%. At each minute time point, the data for the features were summarized descriptively using the number of observations (n), mean and standard deviation (223).

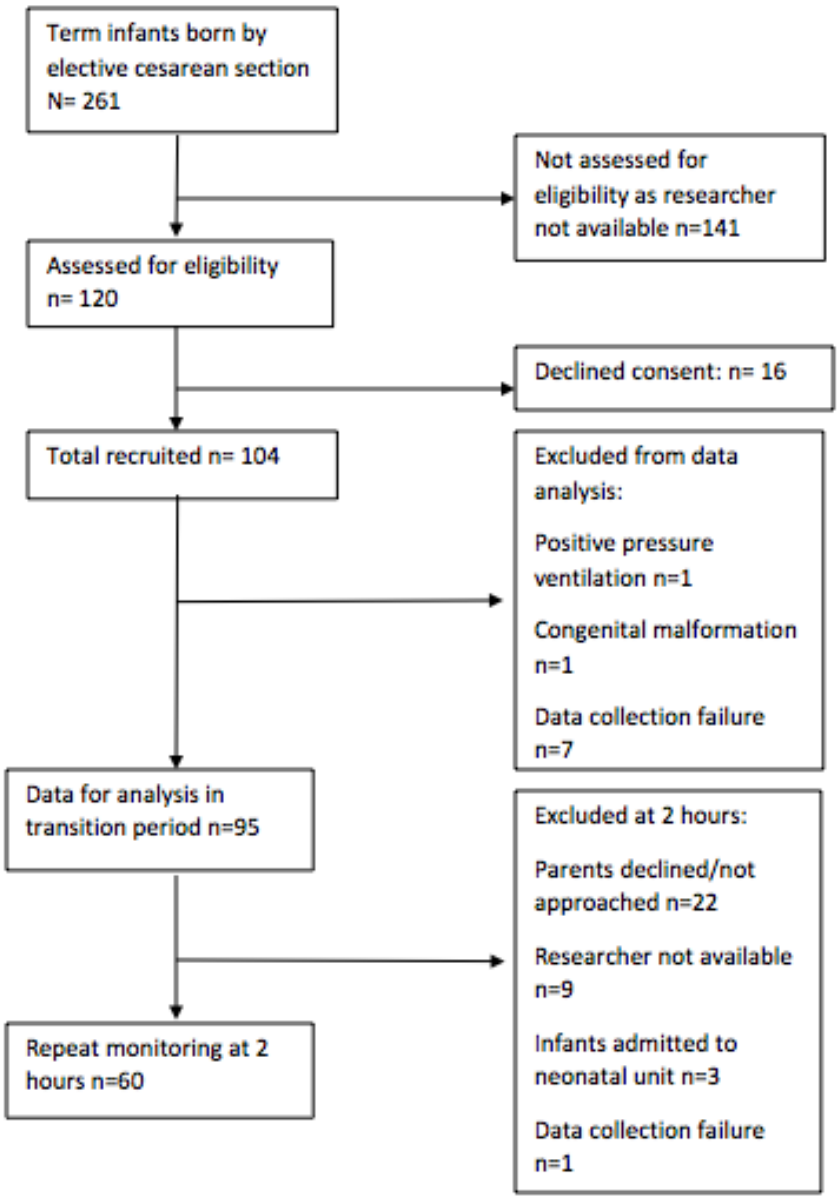
To investigate how each feature (RR, TV and $EtCO_2$) changed over time, a mixed modeling approach was used. The optimal functional form of the trajectory over time was identified by considering the family of polynomial functions (a straight line, a quadratic curve and a cubic curve), and identifying the best fitting model (224). A bottom-up strategy was used, beginning with an empty random intercepts model (no fixed effects and individual as a random effect) and then adding each fixed time effect (linear, quadratic, cubic), followed by its corresponding random time effect (linear, quadratic, cubic), in turn (225). Likelihood ratio tests were used to compare the difference between the deviance statistics across consecutive models to test the impact of each new term. Model fit was evaluated using the deviance statistic (-2 log likelihood) and the Akaike Information Criterion (AIC). For each feature, the predicted values from the best-fitting mixed model and their corresponding standard errors were used to construct a 95% reference range, assuming a normal distribution. For all analysis, time was centred at one minute (start of study). To investigate if changes over time differed by admission group (admitted/not admitted), the fixed effects of admission group and the interactions of admission group by time (linear, quadratic and cubic, as appropriate) were added to the mixed model. Pearson's correlation coefficient was calculated between RR, TV and $EtCO_2$ for each time point and between the first minutes of $EtCO_2$ and the 2-hour values. All statistical analysis was performed using PROC MIXED in SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). All tests were two-sided and a p-value <0.05 was considered to be statistically significant.

3.3 Results

3.3.1 Study Participants

One hundred and four infants born by ECS at term were recruited. Ninety-five infants were included in the analysis (Figure 3.1). One infant was excluded due to unexpected congenital malformation noted following delivery, and one infant due to the need for positive pressure ventilation (PPV) during newborn stabilisation. The Respironics RFM stored measurements sequentially for each infant breath. However, for seven infants, measurements were not automatically saved from the beginning of the recording and the timing of subsequent values recorded could not be fully ascertained. Therefore, these infants were excluded from the data analysis. The median (IQR) gestation was 39 weeks (38.2- 39.1) and median (IQR) birth weight was 3420g (3155-3740). Forty-seven (49%) infants were male. Indication for ECS were; prior caesarean section n=81 (85%), breech presentation n= 8 (8%), prior traumatic vaginal delivery n=5 (5%), IVF pregnancy n=1 (1%). Median time from birth until initiation of monitoring was 26.5 (range: 20-39) seconds. Nine infants were admitted to the NICU. The discharge diagnosis for all nine infants was transient tachypnea of the newborn (226).

Figure 3.1 Flow Diagram



3.3.2 Measures of TV, RR and $EtCO_2$

It was intended for measurements to be performed on all infants (n=95) for the first10 minutes of life. However, for practical reasons many recordings were terminated early and values are not reported beyond the first seven minutes of life. The mask was

removed and replaced on a number of occasions for each baby due to loss of seal, movement of newborn and/or presence of secretions. These values (12% of all breaths) were omitted from the analysis and the mixed model effect analysis was utilised to account for these over time.

Descriptive statistics for RR, TV and $EtCO_2$ at each time point are presented in Table 3.1. Mean RR increased for each time point between 1 minute (44.31) and 7 minutes (61.62) of life. Mean TV increased over the first 3 minutes (5.18mls/kg- 6.44mls/kg) and then decreased over time (5.07mls/kg at 7 minutes). Mean $EtCO_2$ measurements also increased over the first 3 minutes (4.32kPa-5.64kPa) and then stabilised (5.74kPa at 7 minutes). The mixed modelling approach found that the trajectories for mean RR, TV and $EtCO_2$ changed significantly over the first minutes of life. The best fitting models included fixed cubic time effects and random cubic time effects for TV and $EtCO_2$ and a fixed quadratic time effect and a random quadratic time effect for RR. Trends over time can be appreciated in Figures 3.2, 3.3, and 3.4.

Table 3.1 Descriptive statistics of features at each time point

Minutes after birth	RR		TV		$EtCO_2$	
	n	mean (SD)	n	mean (SD)	n	mean (SD)
1	88	44.307 (14.538)	87	17.708 (8.125)	84	4.315 (1.151)
2	86	48.209 (11.831)	87	19.462 (7.496)	85	5.303 (1.138)
3	90	53.006 (15.000)	91	22.000 (7.315)	89	5.635 (1.224)
4	89	57.109 (15.091)	90	21.416 (8.403)	88	5.631 (1.265)
5	94	57.686 (16.710)	93	20.682 (8.465)	93	5.481 (1.363)
6	87	61.554 (16.284)	86	20.261 (8.885)	83	5.516 (1.321)
7	68	61.618 (18.294)	67	19.842 (8.923)	65	5.741 (1.376)

Figure 3.2 Respiratory Rate (breaths per minute) between 1 and 7 minutes after birth

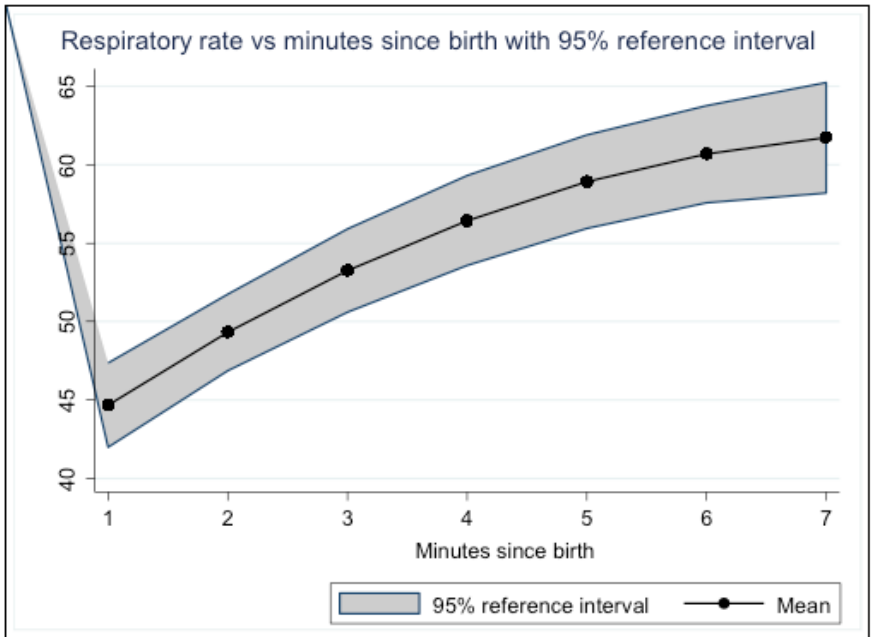


Figure 3.3 Tidal volume (mls/kg) between 1 and 7 minutes after birth

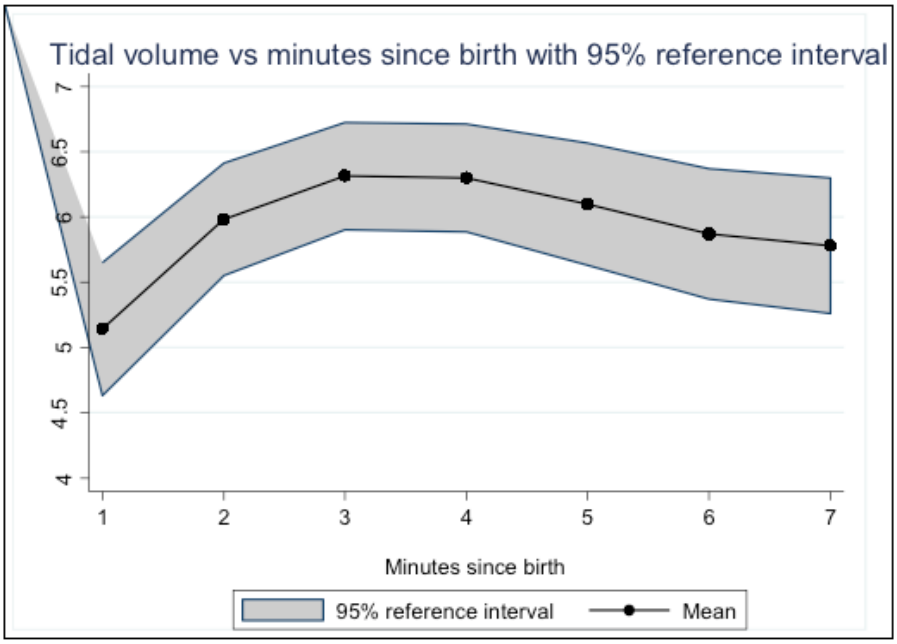
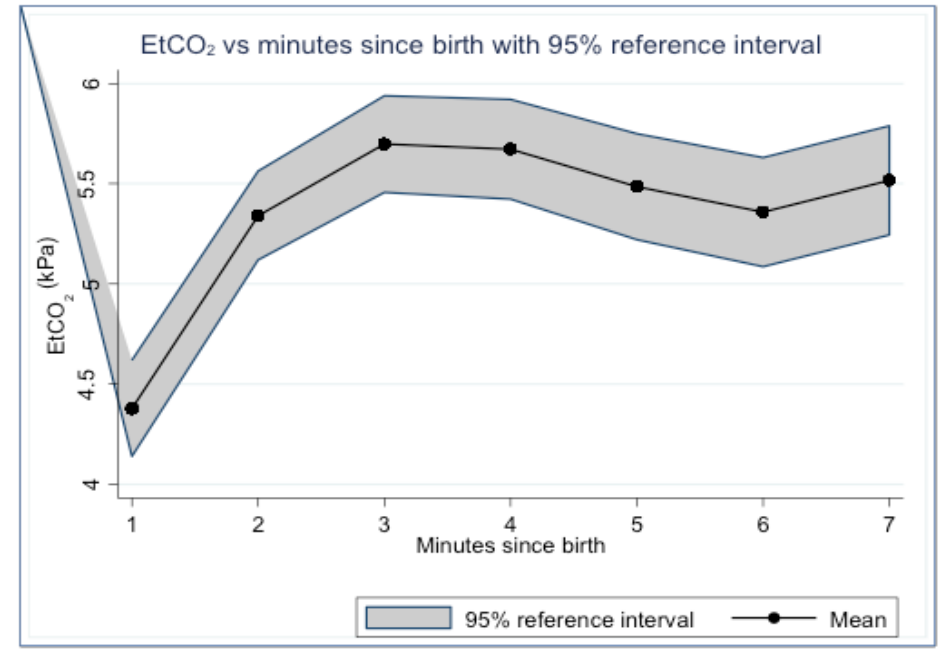


Figure 3.4 $EtCO_2$ (kPa) between1 and 7 minutes after birth



3.3.3 Correlations between RR, TV and $EtCO_2$

Pearson's correlation coefficients between pairs of features were calculated for each time point (minutes 1-7 separately). TV and $EtCO_2$ are positively correlated, whilst no correlation between TV/RR nor $EtCO_2$/RR exist.

3.4 Discussion

This study describes changes in RR, TV and $EtCO_2$ over the first minutes following elective cesarean section in a large number of healthy term infants. Following delivery, the trajectories of TV and $EtCO_2$ correlated, with both increasing over the first 3 minutes before stabilizing. This is important, as median (IQR) age at time of initial EEG recordings in Chapter 3 was 3.0 (2·5 to 3·8) minutes. This implies that functional residual capacity had been established for the majority of infants when brain activity was measured, and that the values reported represent brain activity at a time when respiratory adaptation has been achieved. It was also noted that respiratory rates increased continuously from birth until recordings ceased.

Over the past 50 years a number of novel studies have informed our understanding of how newborn infants' clear fluid from their lungs and establish FRC to facilitate gas exchange (213, 216, 218, 227, 228). Schmolzer et al performed RFM in 20 term infants during the first 2 minutes of life following vaginal delivery (222). They found that FRC is partially established soon after delivery and exhaled CO_2 can be detected within 1-8 breaths after birth. Similar to our findings, CO_2 levels were closely associated with TVs and increased as FRC was established over the first few minutes. Similar absolute values for TV and $EtCO_2$ are also reported in their study, but peak levels were reached earlier in their cohort of infants following vaginal delivery. End tidal CO_2 peaked at 3 minutes in our cohort at mean values of 5.69kPa, whilst Schmolzer et al reported exhaled CO_2 values of 5.73kPa at 2 minutes. Tidal volumes of 6.3ml/kg were reached at 2 minutes in Schmolzer's cohort. Similar volumes (when corrected for mean weights) were reached at 3 minutes in our infant cohort. These

findings are not surprising, as previous studies have described variations in transition between infants born by cesarean section and vaginal delivery (215, 219).

Newborn transition begins prior to delivery for infants born following spontaneous vaginal labour (229)(230). Functional residual capacity was established later in infants following cesarean section compared with vaginally delivered infants in studies using plethysysmography (215). Our findings in infants born by cesarean section support this work. Increased interstitial pulmonary fluid in these infants may delay the establishment of FRC and time to reach optimum gas exchange levels. However, our cohort had peak levels of $EtCO_2$ at 3 minutes whilst Palme-Kilanders' cohort of infants born by caesarean section had increasing levels of CO_2 over the first 5 minutes, which is delayed compared to our findings. Comparisons between historical studies may not be appropriate as they all had small study numbers, high levels of intervention in the DR, and relied on chart based analog equipment compared to current digital RFM. It also highlights the importance of having documented respiratory adaptation in a cohort of infants following ECS in order to interpret newborn brain activity following ECS.

RRs increased continuously over time during our study and plateau levels were not captured during the first 7 minutes. However, respiratory patterns were not studied, and may be more important than the actual rate. Different respiratory patterns such as expiratory braking, which is common in newborn infants occurs when expiratory flow is followed by a period of low or absent flow and results in short or multiple expiratory flow peaks (212).

This study has a number of limitations. The Respironics RFM recorded values on a breath-by-breath basis, which allowed for accurate documentation of values and to monitor the progression of physiological parameters over time. However, an intrinsic error within the monitoring system resulted in the monitor failing to record all measurements, with up to 3% of breaths being missed in an individual baby. A mixed model analysis was performed to allow for missing data entries. The mixed model has the advantage over other statistical tests (such as a repeated one way ANOVA) as it uses all available data, and infants are not excluded from the analysis if they are missing data at some of the time points. However, seven infants were excluded as initial breaths were not recorded and the timing of the values that were recorded could not be ascertained. Also, many recordings were terminated early for practical reasons and we were unable to report findings beyond the first seven minutes of life. These limitations highlight the challenges in performing such studies in the immediate newborn period. It must also be noted that monitoring is associated with additional dead space, which may theoretically increase the work of breathing and confound results.

In conclusion, this study documents for the first time values for RR, TV and $EtCO_2$ during newborn transition following elective cesarean section in a large cohort of healthy term infants. These findings provide valuable information pertaining to physiological respiratory parameters during newborn transition to extrauterine life following elective cesarean section.

Chapter 4

EEG for the Assessment of Neurological Function of Term Infants in the Immediate Newborn Period

4.1 Introduction

Neonatal electroencephalography (EEG) monitoring has well documented applications in the management of infants with hypoxic ischemic encephalopathy (HIE) (131, 231-234). EEG is essential for the diagnosis of neonatal seizures (200, 235, 236). Hypoxic ischemic encephalopathy is a leading cause of neonatal death and long-term neurological disability, with an estimated incidence of 1·5 per 1000 live births (237). Therapeutic hypothermia (TH) is now the standard treatment for infants with moderate or severe HIE, and results in a significant reduction in mortality, without an increase in major disability amongst survivors (238). The optimal timing to commence TH is within 6 hours of birth and thus eligibility for TH should be decided as soon as possible (239, 240).

Information about newborn electrocortical activity to date is almost exclusively based on EEG recordings performed after six hours of age, or occasionally from around three hours in infants that are unwell (241, 242). Infants are stabilised in the delivery room following potentially severe hypoxic ischemic events without objective information about brain activity. Clinical assessments of newborn wellbeing are limited and liable to inter and intra rater variability (15, 16). Therefore, the introduction of EEG monitoring in the immediate newborn period may be a useful

adjunct in certain circumstances. The first step in evaluating its use is to assess whether it is feasible to perform, and if so, to establish normative reference values.

This study assesses qualitative and quantitative features of the EEG during newborn transition and aimed to produce reference values for healthy term infants during this vulnerable time period.

4.2 Methods

4.2.1 Study participants

Infants born in Cork University Maternity Hospital, Ireland were recruited over two months between September- October 2015. Infants > 37 weeks' gestational age, born by elective caesarean section (ECS), were eligible for inclusion in the study. Infants with major congenital abnormalities were excluded. Infants requiring intervention to support stabilisation beyond being warmed, dried, and stimulated, or with Apgar scores < 7 at one minute were also excluded from the study.

4.2.2 EEG acquisition

Following delivery, infants were brought immediately to a Panda Resuscitator (GE Healthcare, Laurel, MD, USA). All EEG studies were performed by DF following a standardized protocol. The infants' scalp was first cleaned using an alcohol wipe. As per usual clinical practice previously described in our NICU, the hair was then parted at EEG sensor sites, and the skin gently abraded three to four times using a sterile cotton bud and skin preparation gel (Nuprep)(205). Six sterile disposable flat surfaced EEG electrodes were then attached to the infants' scalp over frontal and central

regions (F4, C4, F3, C3, ground, and reference) bilaterally using the 10-20 system of electrode placement and the EEG was recorded for up to ten minutes. Two channels of a bipolar recording were displayed (F4-C4, F3-C3) on the monitor. All recordings were performed and stored using the Unique EEG system (Inspiration Healthcare, Leicester, UK). Each EEG study was video recorded and recordings commenced after delivery of the infant. This allowed for future accurate documentation of infant age (in seconds) when monitoring commenced, and to correlate recordings with infant movements and newborn care. As all infants were born by caesarean section, monitoring did not interfere with skin-to-skin time or initiation of breastfeeding. Maternal and infant demographics were recorded, including type of anaesthesia used and Apgar scores. Newborn admissions to the NICU, and discharge diagnosis on chart review were also documented.

4.2.3 Data Collection and analyses

EEG data was sampled at 256 Hz and stored on computer hard disk for off-line analysis. All EEG recordings were visually analyzed. Firstly, the recordings were assessed for quality and periods of artefact-free EEG were identified for analysis. The EEG was then assessed for overall voltage, continuity, frequency, and maturity. Three minutes of artefact-free continuous EEG segments were then selected from each infant's recording for quantitative analysis. All quantitative measures were performed using the software package NEURAL, a neonatal EEG feature set in matlab (v0.3·0), which runs within the Matlab environment (The MathWorks, Inc., Natick, Massachusetts, United States). NEURAL was developed to standardize quantitative analysis of newborn EEG by including full implementation details (206), and is freely available as open-source software

(https://github.com/otoolej/qEEG_feature_set). Quantitative measures that capture amplitude and frequency characteristics were used. Features of spectral power were calculated within 4 frequency bands, to quantify specific activity at delta (0·5-4 Hz), theta (4-7 Hz), alpha (7-13 Hz), and beta (13-30 Hz) bands.

Features reported are:

- Total and relative spectral power for the four frequency bands.
- Range-EEG (rEEG): median, lower and upper margins, and asymmetry(243).
- Spectral edge frequency and fractal dimension over the total 0·5-30 Hz frequency band.

A comprehensive description of each measure, including implementation details, is available in reference (206). Spectral power and rEEG features capture amplitude characteristics of the EEG; spectral edge frequency and fractal dimension features capture the spectral characteristics. The edge frequency estimates the extent of spectral spread: higher values indicating a more disperse spectrum and lower values indicating a more condensed spectrum around the lower frequencies. Fractal dimension captures the shape of the spectrum. Within a frequency band, typically 0·5-30 Hz, neonatal EEG is known to follow a spectral power law, with a linear log-log spectral relation defined as $P(f) \propto 1/f^{\alpha}$, where α represents the slope of spectrum (244). The fractal dimension estimate D provides an estimate of this slope, as $\alpha = 5 - 2D$ (245).

Range-EEG (rEEG) gives a measure of peak-to-peak voltage (243). rEEG was proposed as an alternative to amplitude-integrated EEG (aEEG) as there is no clear definition of aEEG and most EEG machines implement different versions of the

aEEG algorithm (246). A 1-20 Hz bandpass filter was applied to the EEG before generating the rEEG.

All features, except for the rEEG, are computed on a 32 second epoch of EEG with a 50% overlap. The median value over all epochs is used to summarize the feature. The median value is also used to summarize across the two channels.

Mean values, standard deviation, minimum, and maximum values were used to describe symmetrical data. Median, interquartile range, minimum and maximum values were reported on non-Gaussian data.

4.3 Results

4.3.1 Study Participants

Fifty- two infants born by ECS at term were recruited. Forty-nine infants were included in the analysis. Three infants were excluded: one infant due to unexpected congenital malformation noted following delivery, one infant due to the need for positive pressure ventilation during newborn stabilisation, and another infant due to insufficient length of recording because of technical difficulties during recording. Thus, 49 infants were included in the analysis (Figure 4.1). The median (IQR) gestation was 39 (38·7 to 39·1) weeks and median (IQR) birth weight was 3500 (3245 to 3742) g. Twenty-nine (59%) infants were male. Indication for ECS were prior caesarean section in the majority of cases n=43 (88%), breech presentation n= 2 (4%), prior traumatic vaginal delivery n=2 (4%), and maternal reasons 2(4%). Two caesarean sections were performed under general anaesthesia and the remaining 47

under spinal anaesthesia (morphine, and fentanyl). Median (IQR) age at time of initial EEG recording was 3.0 (2·5 to 3·8) minutes. No infant was compromised at birth. Five infants were admitted to the neonatal unit. The discharge diagnosis for all five infants was transient tachypnea of the newborn, and all infants were discharged within the first three days of birth. Infant characteristics are summarised in Table 4.1

Figure 4.1 Flow diagram

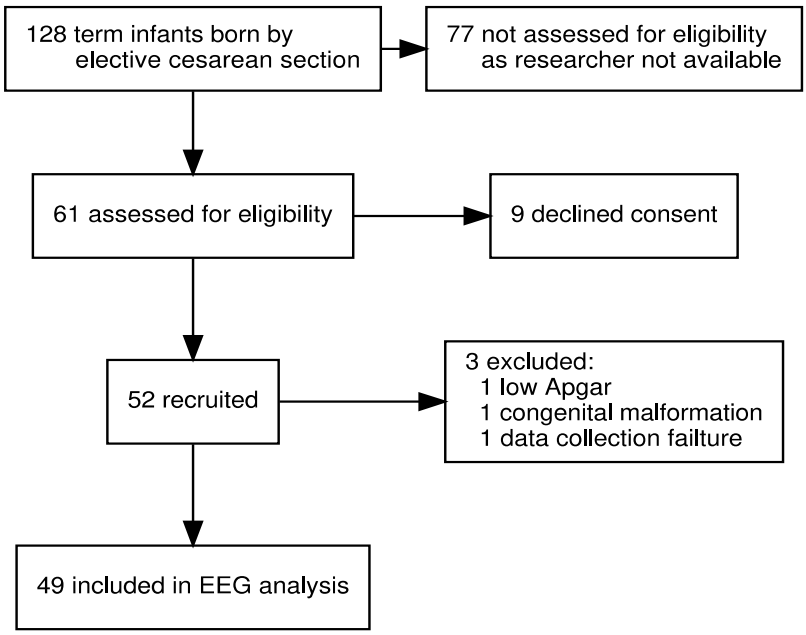


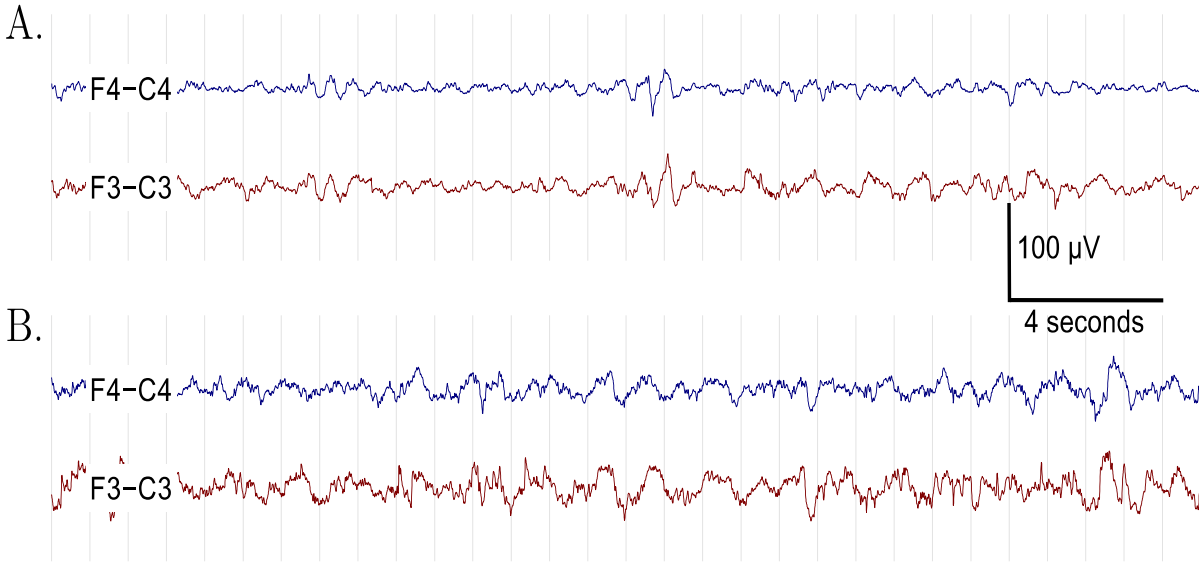
Table 4.1 Infant characteristics

	median (IQR)
Gestation (weeks)	39 (38.7, 39.1)
Birthweight (g)	3500 (3245,3742)
1 minute Apgar score	9 (9,9)
5 minute Apgar score	9 (9,10)

4.3.2 Visual analysis

Good quality continuous and symmetric mixed frequency EEG activity, appropriate for gestational age was seen in all infants with a range of 25-50μV, see example in Figure 4.2. Movement artefact contaminated many recordings but continuous EEG activity without artefact was measurable for a minimum of 3 minutes in all infants.

Figure 4.2 Example EEGs from 2 infants



4.3.3 Quantitative analysis

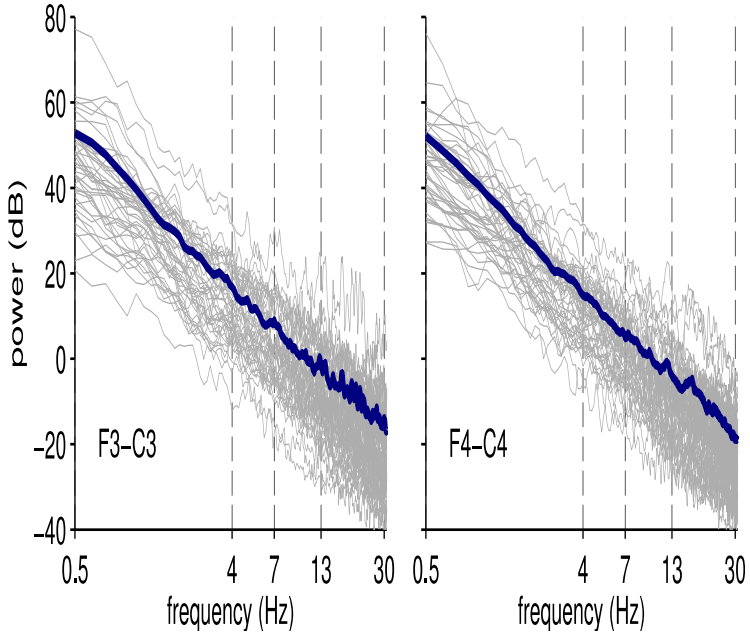
Quantitative features are summarized in Table 4.2. Total power decreased at the higher-frequency bands: median (IQR) relative delta power of 87·8% (83·7 to 90%) indicated that the majority of power is within the delta band, with 95% of power (spectral edge frequency) below a median of 7·56 Hz (IQR: 6·17 to 9·76 Hz). Total power was highest at lower frequencies. The highest values were in the 0·5-4 Hz band, with median (IQR) spectral power measuring 70·5 (42·8 to 171·4) μV^2. The lowest values for total power and relative power were in the 13-30 Hz band, measuring 2·5 (1·2 to 4·6) μV^2 and 2·5% (1·8 to 3·6%) respectively. Figure 4.3 illustrates a power-law spectrum, with decreasing power for increasing frequency, within the 0·5-30 Hz range for all infants' EEG. The median (IQR) fractal dimension of 1·1 (1·1 to 1·1) equates to a power law slope α of 2·8 (2·7 to 2·8). Median power-law slope, in turn, equates to a log-log spectral slope of -28 dB/decade, as highlighted in Figure 4.3.

For the median values over all EEGs, lower and upper margins of the rEEG spanned from 14·5 to 63·3 μV with a median rEEG of 24·4 μV.

Table 4.2 Quantitative features of the EEG

	median	IQR	95th percentile range
power 0·5-4 Hz (μV²)	70·5	42·8 to 171·4	22·3 to 846·4
power 4-7 Hz (μV²)	5·0	2·7 to 10·3	1·6 to 34·8
power 7-13 Hz (μV²)	3·3	1·7 to 6·2	0·9 to 24·9
power 13-30 Hz (μV²)	2·5	1·2 to 4·6	0·5 to 15·9
relative power 0·5-4 Hz (%)	87·8	83·7 to 90·0	72·4 to 96·0
relative power 4-7 Hz (%)	5·9	4·9 to 7·4	2·2 to 14·7
relative power 7-13 Hz (%)	3·6	2·8 to 5·0	1·0 to 8·0
relative power 13-30 Hz (%)	2·5	1·8 to 3·6	0·7 to 6·8
spectral edge frequency (Hz)	7·56	6·17 to 9·76	2·93 to 14·10
fractal dimension	1·11	1·10 to 1·13	1·08 to 1·17
rEEG: median (μV)	24·4	19·0 to 31·9	14·9 to 56·3
rEEG: lower margin (μV)	14·5	11·1 to 18·3	8·5 to 29·7
rEEG: upper margin (μV)	63·3	42·1 to 93·0	28·4 to 199·8
rEEG: asymmetry	0·52	0·39 to 0·67	0·26 to 0·82

Figure 4.3 Power spectral density (PSD) estimates for both channels of the EEG



4.4 Discussion

This study describes, for the first time, detailed features of continuous neonatal EEG during newborn transition. Continuous mixed frequency EEG was obtained within the first few minutes of birth, and quantitative EEG reference values for healthy newborn infants during the immediate newborn period have been produced.

Over the past 30 years neonatal EEG monitoring has become an essential tool for the assessment of neurological function in infants with perinatal asphyxia (231-234), seizures (200, 235, 236, 247), and more recently in the care of premature infants (248). Approximately 20 per 1000 deliveries will require significant stabilisation measures, with biochemical and clinical evidence of perinatal asphyxia (249). Of these only 1.5 per 1000 deliveries will go on to develop signs of evolving encephalopathy consistent with HIE (250). Given the potential benefit of early treatment with therapeutic hypothermia, the need to identify infants with HIE in the immediate newborn period is becoming increasingly important (251-253). However, to date our understanding of early newborn brain activity is based on studies in unwell infants, or in well infants after 3-6 hours of age (131, 221, 241, 245, 253). Many infants with HIE are born at regional hospitals which do not offer TH and require transfer to a tertiary facility, resulting in a delay in the initiation of TH. To address this, many infants are cooled passively during transport from the regional hospitals (254). It is therefore important that the correct infants are transferred and passively cooled. A simple method of assessing brain health at regional hospitals would also help to accurately identify those infants that require transfer to a tertiary centre.

Pichler et al. performed aEEG in infants > 34 weeks gestation following elective caesarean section (105). Recordings were feasible after three minutes in some infants. However, continuous reliable data was difficult to obtain in their initial study (105). The upper and lower limits of the aEEG were correlated with simultaneous values obtained from near infrared spectroscopy recordings (98). Low EEG values during immediate transition after birth concurrently showed low cerebral oxygenation values, but with associated increased cerebral oxygen extraction (194). These studies, along with the current study, show that EEG monitoring is feasible immediately after delivery. However, second by second EEG information was not reported in the previous studies, and importantly, the EEG was not analysed using objective quantitative measures. As mentioned previously, heavy signal processing used in the aEEG algorithm eliminates much of the detail (e.g. frequency band content) available in the EEG and many clinically important features are lost.

Continuous neonatal EEG can be assessed both qualitatively and quantitatively. Qualitative EEG analysis is mainly used for clinical purposes. It is based on visual interpretation of the EEG signal and describes such background features as amplitude, frequency, and continuity, symmetry and synchrony of the EEG. Reference values within the first 12 hours of age are available for healthy term newborns (241). Quantitative EEG analysis is a method predominantly used in research and includes time and frequency domain analysis. Quantitative analysis allows for standardized reporting of EEG values, which is imperative when establishing new reference ranges. Crucial to this standardization process is a precisely defined set of quantitative features, including implementation and parameter details. These details are available in reference (206). Quantitative analysis can also be used to objectively grade baseline

EEG activity in sick newborn infants and can provide decision support with EEG analysis when clinical neurophysiologists are not available (255).

Continuous mixed frequency EEG can be obtained in infants during the immediate newborn period. Activity with an amplitude of 25-50μV was seen in all healthy term infants immediately after birth. Early EEG suppression has been reported in infants following hypoxic-ischaemic injury and is associated with long-term outcomes (143, 197). Quantitative analysis has value in differentiating between HIE grades (256). Quantitative values for amplitude, power, and range EEG during newborn transition are now reported. As this is the first study to provide such values it is difficult to make comparisons. Total and relative spectral power change over time in infants as they mature and we found that the majority of power was in the delta EEG band during newborn transition (257). A prior study by our research group reported quantitative features for healthy term infants during active and quiet sleep in the first day of life (241). Mean relative delta power was 73% (5%) and 79·5 (4%) during active and quiet sleep respectively, displaying again that the majority of power was in the delta band.

This study has a number of limitations. We did not include data on the exact timing of cord clamping in each baby. Infants were monitored for relatively short periods of time. Longer EEG monitoring and serial studies within the early postnatal period might be useful. However, such studies are challenging in the immediate newborn period and we were reluctant to interfere with newborn bonding and the establishment of newborn feeding. The number of infants recruited was small. However, quantitative analysis produced values, which had narrow ranges in our homogenous

study group. Further studies are required to assess whether brain activity differs by mode of delivery, delivery room interventions and stabilisation methods utilized. EEG monitoring in the delivery room may have a key role to play in identifying those infants with mild perinatal asphyxia who may benefit from immediate intervention but again, significantly larger studies are required. Whilst EEG may also have the potential to direct therapy in the delivery room, in particular cessation of resuscitative efforts, there is an absolute lack of data in this regard and we would not advocate such an approach.

To our knowledge, this study is the first to describe normative quantitative EEG data in healthy full term infants during transition. These findings are relevant and clinically important. Therapeutic hypothermia must be administered to newborn babies with HIE within the first few hours of birth and delivery room EEG may help identify those babies that are most suitable for treatment, especially infants with clinically suspected mild encephalopathy. However, further trials are now warranted to assess the utility of EEG recordings during newborn transition.

In conclusion, EEG acquisition in the delivery room is feasible and brain activity in the first minutes of life can be recorded. Normative quantitative values for EEG during newborn transition have been produced for the first time. Future trials will need to assess EEG in the first minutes of life following in infants at risk for encephalopathy to assess its clinical utility.

Chapter 5

Neuromonitoring in the immediate newborn period in a randomized controlled trial of cord clamping in preterm infants less than 32 weeks: Clamping the Umbilical cord in Premature Deliveries (CUPiD)

5.1 Introduction

Preterm brain injury is a major worldwide public health problem. Approximately one in 70 babies (1.4%) are born before 32 week gestation; however as a group they account for over half (51%) of infant deaths (258). Of very preterm infants who survive, 5- 10% develop cerebral palsy, and those without severe disability have a twofold-increased risk for developmental, cognitive, and behavioural difficulties (259, 260).

Following delivery, the umbilical cord may be clamped immediately, or as an alternative procedure placental transfusion may occur, either by delaying cord clamping (DCC) for a period of time, or by milking the umbilical cord (UCM) (261). Allowing for placental transfusion of blood following preterm delivery, either by DCC or UCM, has been shown to decrease the incidence of intraventricular haemorrhage (IVH) by 50%, but has not affected neurodevelopmental or mortality outcomes (262). Although not fully understood, animal models suggest that a reduced incidence of IVH may be explained by a smoother cardiovascular transition when ventilation precedes cord clamping (263, 264).

Current recommendations on timing of cord clamping are not explicit (13). American and European guidelines have recommended a delay before clamping the umbilical cord to facilitate placental fetal transfusion in preterm infants who are not compromised at birth (265)(266). For compromised infants, ICC is still recommended, although it is postulated that compromised preterm infants may benefit the most from placental-fetal transfusion. The RCOG have highlighted the need for research centres to actively explore the feasibility of bedside resuscitation to allow for delayed cord clamping in compromised infants, and to consider UCM, although neither approach should be considered routine until more evidence is available (267).

Umbilical cord clamping is an important intervention in preterm infant health and gaps in our knowledge exist. It is surprising that a reduction in IVH following DCC or UCM has not translated into superior developmental outcomes compared to ICC (262). This study aims to investigate how different cord clamping strategies affect preterm infant short-term neurological wellbeing, and improve our understanding of how different cord clamping strategies affects cerebral activity and oxygenation. By design, EEG and NIRS monitoring in the immediate newborn period have been incorporated as primary outcome measures. The feasibility of monitoring cerebral activity (EEG) and oxygenation in preterm infants in the immediate newborn period following an interventional DR study will be assessed. Also, the benefits and limitations of using infant neuromonitoring as a primary outcome in a preterm randomized controlled trial will be determined.

5.2 Methods

5.2.1 Study Design and Population

This prospective randomized controlled trial was conducted in Cork University Maternity Hospital (CUMH), Ireland over a nine-month period from December 2015 – September 2016. Infants born at less than 32 weeks gestational age (from 23+0 weeks' up to and including 31+6 weeks' gestational age) based on the earliest ultrasound or last menstrual period were eligible for inclusion. Exclusion criteria included inability to obtain informed consent from parent, major congenital anomaly, bleeding from placenta praevia, clinical suspicion of placental abruption or accreta, monochorionic multiples with known or suspected twin to twin transfusion syndrome, with significant growth discordance (>10%), Rh sensitization, hydrops, and cord prolapse.

There were three arms - ICC, UCM and DCC with bedside respiratory support. A designated member of the neonatology research team started the Apgar timer at the time of delivery, and recorded the time of cord clamping. ICC was defined as clamping the infants' umbilicus within 20 seconds of delivery, and routine neonatal care commenced immediately. For UCM the obstetrician held the infant at or below the level of the placenta, and his/her assistant stripped the cord 3 times in the direction of the infant. Each stripping aimed to cover a maximum 20 cm of cord, at a speed of 20cm/2seconds, and 2 seconds were allowed in between each milking to allow the cord to refill. For DCC, infants were placed on a mobile resuscitation trolley (Lifestart, Inspiration Healthcare, UK) with the cord intact, and at or below the level of the placenta. Routine neonatal care was provided and the cord clamped at 60 seconds following delivery. All members of the resuscitation team were Neonatal

Resuscitation Program (NRP) trained and followed current NRP guidelines in the management of preterm infants in the delivery room. All infants were wrapped in sterile towels at the time of delivery until they were transferred to the Panda Resuscitator (GE Healthcare, Laurel, MD, USA).

5.2.2 Randomisation

Randomisation was performed using a computer based randomisation program and allocation concealment was achieved by using opaque, sequentially numbered, sealed envelopes. Randomisation was stratified by age (23+0 to 27+6 and 28+0 to 31+6 weeks) to ensure equal numbers of neonates born at <28 weeks' gestation in each arm with a 1:1:1 allocation ratio between the three groups using random block sizes of 3 or 6. Multiples received the same group allocation. Immediately before delivery, the investigator opened the envelope and made the obstetrician aware of the group allocation of the infant.

5.2.3 Ethical approval and consenting procedure

Antenatal written informed consent was obtained prior to delivery. The Cork Teaching Hospitals' Research Ethics Committee approved this study. This trial was registered on the ISRCTN registry with trial number ISRCTN92719670.

5.2.4 Neuromonitoring

All infants had cerebral near infrared spectroscopy and electroencephalography (EEG) monitoring commenced as soon as possible following delivery, which was dependent on infant stability, and monitoring continued until 72 hours of age. A NIRS neonatal probe, OxyAlertTM NIRSensor (Covidien IIc, Mansfield, MA, USA) was

applied in a fronto temporal location. EEG was recorded with the NicoletOne (CareFusion Co., San Diego, USA) or Moberg (Moberg Research Inc., PA, USA) EEG systems. Depending on infant size 4- 11 electrodes were positioned according to the international 10–20 system of electrode configuration over the frontal, central, temporal, and occipital regions, a reference electrode at Fz, and a ground electrode behind the left ear. The method for electrode placement in preterm infants in our unit has previously been described (205). A consultant radiologist (unaware of group assignment) performed a cranial ultrasound within 48 hours of delivery and then according to our neonatal unit's practice.

5.2.5 Outcome Measures

Primary neonatal outcome was standard quantitative measures of preterm newborn EEG and NIRS median values collected over 1 hour time frames at both 6 and 12 hours of life. The authors analyzing NIRS and EEG were blinded to randomization allocations. Primary outcome for maternal outcome was maternal hemoglobin at 24-36 hours post-partum.

All EEGs were assessed visually for quality and any epoch with poor signal was not used further. In addition, each EEG was visually assessed for overall discontinuity, amplitude and also symmetry and synchrony (where possible i.e. for recordings that utilized multiple channels of EEG). One channel of EEG, common to all recordings (C4-C3) was then assessed using a set of quantitative EEG measures to represent the complex waveforms of the preterm EEG (206). Before generating the feature set, an automated method removed segments of EEG corrupted by artefact (206). The feature set included spectral power, relative spectral power, and spectral flatness measures. These spectral measures were calculated in 4 frequency bands: 0.5–3, 3–8, 8–15, 15–

30 Hz (206). Features of the range-EEG and burst duration were also included in the feature set. The range-EEG used a 1–20 Hz bandpass filter and median, lower- and upper-margins were calculated (206). Features of the temporal organization of bursts included burst percentage and the 95th percentile of the duration of inter-burst intervals (IBI). Bursts and IBI were identified on the EEG using an automated method (268). IBI are the periods of relative quiescence (low voltage activity) that occur in between consecutive bursts of activity. Their duration has been shown to reflect brain maturation, being associated with the development of cortical folding (269). IBI duration decreases with GA and the EEG burst ratio is a standard quantitative measure used to characterize maturation (166). All quantitative measures were calculated using the software package NEURAL (v0.3.3), a neonatal EEG feature set in Matlab (206). NEURAL was developed to standardize quantitative analysis of newborn EEG by including full implementation details with freely available open source code (206). Cerebral oxygenation values were averaged over a one-hour period at 6 and 12 hrs of age.

Secondary neonatal outcome measures included mean blood pressure over 48 hours, temperature on admission, haemoglobin at 12 hours, IVH and BPD. Severe IVH was defined as Grade III/IV according to Papile classification (270). BPD was defined as oxygen requirement at 36 weeks corrected gestational age.

Echocardiographic measurements were performed on all infants at 12 hours +/-3 hours of age. Measurements were taken to assess systemic blood flow, by superior vena cava (SVC) flow (ml/kg/min), right ventricular output (ml/kg/min), and left ventricular output (LVO)(ml/kg/min) (208).

5.2.6 Sample Size

As this was a pilot study and preterm infants have not been previously studied in this context, a formal sample size calculation was not performed. During the 9-month study period, all infants who were assessed, met the eligibility criteria and consented were enrolled in the study.

5.2.7 Data Collection and Statistical analyses

All information was collected by research fellows or a research nurse and stored in a password-protected database. Categorical data was described numerically using frequency and percentage (%) and continuous data using median (interquartile range, IQR). Differences in categorical variables between the three groups were investigated using Fisher's exact test. Differences in continuous variables between the three groups were investigated using the Kruskal-Wallis test and if statistically significant differences were found between the three groups, pairwise comparisons were performed using the Mann-Whitney U test, with Bonferroni correction. All tests were two-sided and a p-value<0.05 was considered to be statistically significant.

The primary analysis was intention-to-treat (ITT). A linear mixed-model was used to test for differences among the 3 groups (DCC, UCM, and ICC) in each quantitative measure of the EEG and NIRS**.** Fixed effects included gestational age, time after birth (either 6 or 12 hours), group membership, and the interaction between group and time. Gestational age was included as many quantitative measures of the EEG are dependent on maturation (271). A backwards selection procedure was used to test to the significance of each fixed effect in the linear model; for more details on this

process, see example (272). All statistical analysis was performed using IBM SPSS Statistics version 22.

5.3 Results

5.3.1 Study Participants

There were 77 patients assessed for eligibility over the 9-month study period. A total of 45 participants were enrolled. A total of 12 infants (12/45, 27%) were randomized to ICC, 19 to UCM (19/45, 42%), and 14 to DCC with bedside resuscitation (14/45, 31%). Two infants randomized to DCC received ICC, both being delivered prior to the resuscitation trolley being prepared in time. There was no statistical difference in median gestation or birthweight between groups (Table 5.1). All infants received antenatal steroids and all but one (in ICC group) received antenatal magnesium. One infant was excluded at delivery as the infant was noted to be dysmorphic and subsequently died in the DR (see Figure 5.1).

Figure 1 Flow Diagram

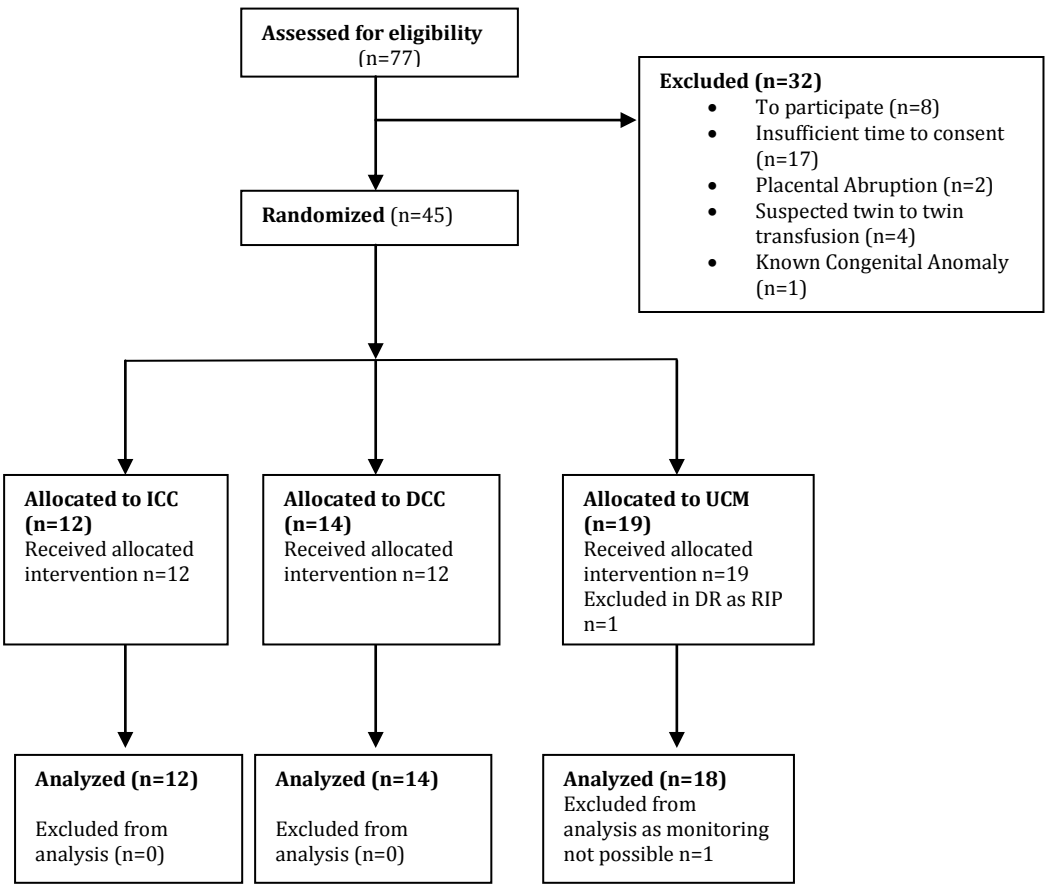


Table 5.1 Infant characteristics

	ICC (n=12)	DCC (n=14)	UCM (n=18)	
	median (IQR)[1]	median (IQR)[1]	median (IQR)[1]	p-value[2]
Gestation (weeks)	28.5 (25.7 to 30.5)	28.0 (26.4 to 29.6)	28.4 (25.7 to 29.6)	0.889
Birthweight (g)	1080 (755 to 1613)	925 (630 to 1490)	930 (700 to 1545)	0.798
Multiples: n(%)	2 (16.7)	4 (28.6)	13 (72.2)	0.005[3]
Antenatal steroids: n(%)	12 (100)	14 (100)	18 (100)	1[3]
Magnesium: n(%)	11 (91.7)	14 (100)	18 (100)	0.273[3]

[1]unless otherwise stated; [2]from Kruskal-Wallis test unless otherwise stated; [3]from Fisher's exact test

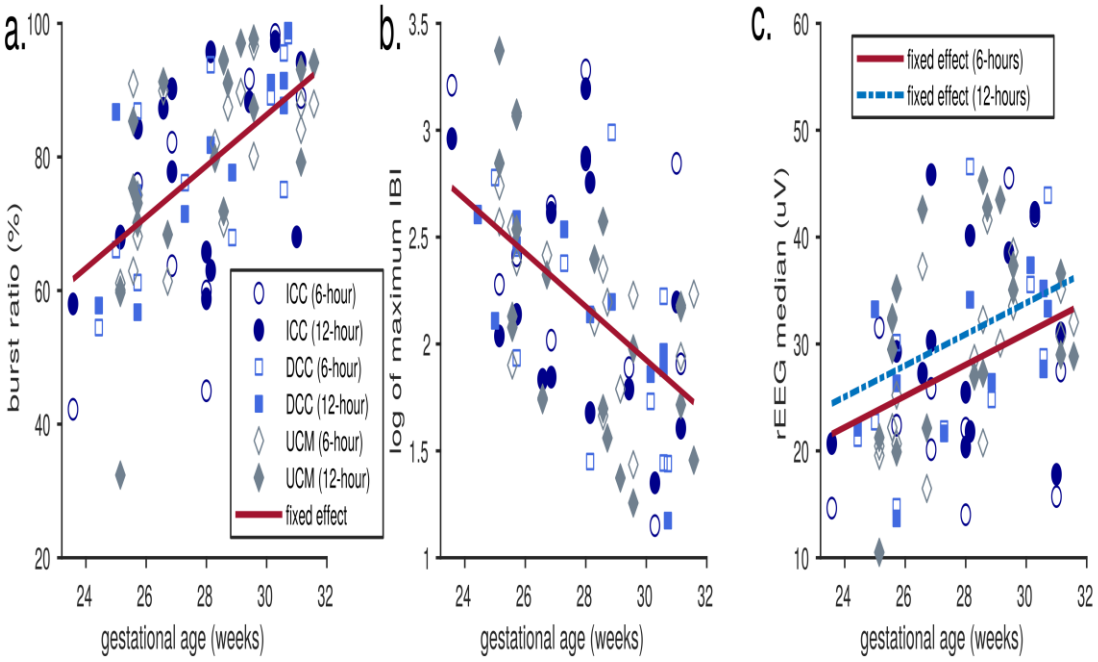
5.3.2 Primary Outcome Measures

A summary of primary outcome measures can be seen in Table 5.2. Tables 5.3 and 5.4 include a complete list of EEG features analyzed at 6 hour and 12-hour time points.

5.3.2.1 EEG Outcome

Application of EEG and acquisition of data was performed as early as possible. Seven infants had EEG monitoring commencing in the DR. Median (IQR) age at EEG application was 3.05 (1.85 to 5.38) hrs. For primary outcome measures, data on 42/44 (95%) was available at 6 hours and 44/44 (100%) at 12 hours. All but one EEG was deemed appropriate for age in terms of amplitude and continuity. One infant had a very immature EEG pattern for age and was not used in quantitative analysis. As Tables 5.3 and 5.4 show, no significant differences were found between the three groups at either time point in the unadjusted and adjusted analysis. Also, in the linear mixed models, the interaction of group by time (or group) was not significant for any of the 17 EEG features. GA was significant for some (7/17) features, as was time (8/17), but not group or group-by-time interaction (0/17). Figure 5.2a-c highlights the dependency of 3 EEG features on gestational age but not on intervention group.

Figure 5.2 EEG features (a. – c.) highlighting the dependency on gestational age. Mixed-effect models for the 3 features included gestational age as a fixed effect (lines in a. – c.). Time (either the 6 or 12 hour time point) was significant (*P* value <0.05) in the rEEG-median feature plotted in c. but not for the features in a. and b. The fixed effects of intervention group



5.3.2.2 NIRS Outcome

NIRS data was available for all 44 infants at both time points. There was no significant difference in rcSO2 values among the 3 groups at 6 or 12 hour time points (Table 5.2). Also, in the linear mixed model, the interaction of group by time (or group) was not significant.

5.3.2.3 Maternal haemoglobin

There were no significant differences between maternal haemoglobin values between groups (p=0.36). Median (IQR) values were highest in the ICM group (10.8, 10.3-11.6g/dL), and lowest in the UCC group (10.15, 9.5-11.9).

Table 5.2 Primary Outcome Measures

	UCM	DCC	ICC	*p*-value	*p*-value (adjusted)
burst ratio [6-hours] (%)	83 (69 to 89)	68 (59 to 86)	76 (67 to 91)	0.27	0.16
burst ratio [12-hours] (%)	83 (72 to 93)	81 (66 to 90)	82 (73 to 89)	0.95	0.96
rEEG: median [6-hours] (μV)	30 (21 to 33)	22 (18 to 30)	28 (22 to 33)	0.60	0.56
rEEG: median [12-hours] (μV)	31 (27 to 37)	30 (23 to 40)	28 (24 to 34)	0.61	0.57
$rcSO_2$ [6 hours] (%)	83 (76 to 88)	85 (74 to 87)	87 (72 to 89)	0.94	0.97
$rcSO_2$ [12 hours] (%)	80 (76 to 87)	81 (75 to 89)	79 (74 to 82)	0.91	0.88
Maternal Hb (g/dL)	10.2 (9.5 to 11.9)	10.3 (9.4 to 11.4)	10.8 (10.3 to 11.6)	0.36	

Table 5.3 Quantitative EEG analysis at 6 hours

qEEG feature	UCM mean (SD)	DCC mean (SD)	ICC mean (SD)	*P*-value	*P*-value (adjusted)
rEEG: median (μV)	28.8 (7.4)	25.9 (10.5)	28.9 (9.7)	0.60	0.56
rEEG: lower margin (μV)	11.1 (3.8)	9.5 (4.0)	10.8 (4.6)	0.55	0.48
rEEG: upper margin (μV)	134 (42)	140 (50)	118 (36)	0.45	0.43
burst ratio (%)	79 (13)	70 (19)	79 (15)	0.27	0.16
maximum IBI (seconds)	9.7 (4.2)	13.2 (7.6)	9.7 (5.3)	0.42	0.35
SP [0.5–3 Hz] (μV^2)	440 (270)	453 (305)	372 (173)	0.94	0.94
SP [3–8 Hz] (μV^2)	29 (14)	30 (15)	25 (15)	0.63	0.64
SP [8–15 Hz] (μV^2)	6.5 (2.6)	6.9 (3.2)	6.0 (2.4)	0.85	0.81
SP [15-30 Hz] (μV^2)	2.2 (1.2)	2.0 (1.0)	2.2 (1.3)	0.89	0.90
relative SP [0.5–3 Hz] (%)	90.8 (4.6)	91.4 (2.5)	91.6 (2.9)	0.81	0.81
relative SP [3–8 Hz] (%)	6.6 (2.6)	6.3 (1.7)	6.0 (2.5)	0.75	0.75
relative SP [8–15 Hz] (%)	1.66 (0.90)	1.65 (0.82)	1.68 (0.67)	0.97	0.97
relative SP [15–30 Hz] (%)	0.69 (0.74)	0.50 (0.25)	0.63 (0.32)	0.70	0.70
SF [0.5–3 Hz]	0.292 (0.087)	0.295 (0.038)	0.290 (0.042)	0.98	0.99
SF [3–8 Hz]	0.749 (0.064)	0.749 (0.060)	0.765 (0.055)	0.75	0.74
SF [8–15 Hz]	0.830 (0.031)	0.814 (0.028)	0.834 (0.036)	0.30	0.29
SF [15–30 Hz]	0.657 (0.072)	0.631 (0.036)	0.669 (0.044)	0.28	0.28

qEEG: quantitative EEG; SP: spectral power; SF: spectral flatness; UCM: umbilical cord milking; DCC: delayed cord clamping; ICC: immediate cord clamping

Table 5.4 Quantitative EEG analysis at 12 hours

qEEG feature	UCM mean (SD)	DCC mean (SD)	ICC mean (SD)	*P*-value	*P*-value (adjusted)
rEEG: median (μV)	31.5 (9.4)	31.7 (10.7)	28.3 (7.2)	0.61	0.57
rEEG: lower margin (μV)	11.0 (3.0)	11.0 (4.0)	10.1 (3.6)	0.77	0.67
rEEG: upper margin (μV)	150 (58)	156 (54)	127 (40)	0.38	0.35
burst ratio (%)	80 (16)	78 (14)	80 (14)	0.95	0.96
maximum IBI (seconds)	10.0 (6.8)	10.6 (6.4)	9.1 (3.3)	0.92	0.93
SP [0.5–3 Hz] (μV^2)	610 (384)	615 (503)	446 (227)	0.79	0.79
SP [3–8 Hz] (μV^2)	36 (20)	35 (24)	27 (19)	0.64	0.65
SP [8–15 Hz] (μV^2)	7.1 (3.1)	8.4 (4.8)	6.1 (2.3)	0.48	0.44
SP [15-30 Hz] (μV^2)	2.3 (1.0)	3.3 (3.3)	2.1 (0.7)	0.56	0.55
relative SP [0.5–3 Hz] (%)	92.2 (2.4)	92.1 (2.4)	92.3 (3.5)	0.99	0.98
relative SP [3–8 Hz] (%)	5.7 (1.5)	5.5 (1.4)	5.5 (2.8)	0.69	0.69
relative SP [8–15 Hz] (%)	1.37 (0.67)	1.59 (0.76)	1.51 (0.74)	0.63	0.53
relative SP [15–30 Hz] (%)	0.55 (0.41)	0.61 (0.52)	0.57 (0.37)	0.87	0.86
SF [0.5–3 Hz]	0.284 (0.062)	0.307 (0.047)	0.275 (0.040)	0.28	0.28
SF [3–8 Hz]	0.745 (0.068)	0.762 (0.061)	0.767 (0.052)	0.59	0.54
SF [8–15 Hz]	0.836 (0.024)	0.810 (0.048)	0.830 (0.031)	0.11	0.10
SF [15–30 Hz]	0.631 (0.077)	0.627 (0.038)	0.640 (0.047)	0.86	0.86

qEEG: quantitative EEG; SP: spectral power; SF: spectral flatness; UCM: umbilical cord milking; DCC: delayed cord clamping; ICC: immediate cord clamping

5.3.3 Secondary Outcome Measures

Whilst two infants in the ICC group had a severe IVH compared to one infant in the UCM group and no infant in the DCC group, the difference between groups was not statistically significant (*P* value 0.35). There was no difference in admission temperature, mean blood pressure on admission and at 6, 12, 18 and 24 hours, or BPD (Table 5.5).

Markers for systemic blood flow based on echocardiographic measurements did not differ significantly between groups (Table 5.5). Median (IQR) values for SVC flow were lowest in the ICC group 50 (47 to 77) and highest in the DCC with bedside resuscitation groups 106 (82.4 to 166).

Table 5.5 Secondary Outcome Measures

	ICC		DCC		UCM		
	n	median (IQR)[1]	n	median (IQR)[1]	n	median (IQR)[1]	p-value[2]
Temperature (on admission)	12	36.3 (36.2 to 36.8)	14	36.4 (36 to 36.6)	18	36.6 (36.3 to 36.8)	0.24
Hb (g/dl) 12 hrs	12	16.6 (15.8 to 17.9)	14	17.1 (16.0 to 18.8)	18	15.7 (14.2 to 17.7)	0.46
MBP (mmHg) 6 hrs	9	30 (25.5 to 38)	14	31 (27.5 to 33)	15	34 (26 to 37)	0.41
MBP (mmHg) 12 hrs	12	34.5 (31 to 40)	13	32 (27 to 36)	16	33.5 (29 to 36.8)	0.50
MBP (mmHg) 18 hrs	10	36.5 (32 to 42)	14	33 (29.8 to 37)	16	33.5 (30.3 to 39)	0.33
MBP (mmHg) 24 hrs	12	38.5 (36.3 to 40.8)	14	36 (33.5 to 37.3)	18	38 (33 to 40.3)	0.22
LVO (mls/kg/min)	7	95 (89 to 129)	7	120 (85 to 156)	9	142 (67 to 236)	0.58
RVO (mls/kg/min)	7	149 (89 to 174)	7	137 (136 to 183)	9	232 (92.5 to 442)	0.37
SVC (mls/kg/min)	7	50 (47 to 77)	7	106 (82.4 to 166)	8	69 (30 to 117.8)	0.11
IVH severe: n (%)	12	2 (17)	14	0 (0)	18	1 (6)	0.35[3]
BPD: n (%)	12	5 (42)	14	8 (57)	18	9 (50)	0.70[3]

[1]unless otherwise stated; [2]from Kruskal-Wallis test unless otherwise stated; [3]from Fisher's exact test

Hb- haemoglobin; MBP- mean blood pressure; LVO- left ventricular output; RVO- right ventricular output; SVC- superior vena cava flow; IVH severe- intraventricular haemorrhage Grade III or IV; BPD- bronchopulmonary dysplasia

5.4 Discussion

This prospective RCT assessed short-term neurological health in preterm infants < 32 weeks gestation following 3 different cord clamping strategies. Monitoring commenced as early as possible, and EEG application was prioritized over NIRS. EEG monitoring was achieved in 95% of infants by 6 hours, and 100% by 12 hours, which were the pre-specified primary outcome measurement times. NIRS data was available for 100% of infants at 6 and12 hours. Therefore, performing EEG and NIRs in the immediate newborn period is feasible in an interventional preterm infant study.

There were no significant differences in cerebral oxygenation values or quantitative EEG features between groups at either 6 or 12 hours. Whilst two infants in the ICC group had a severe IVH compared to one infant in the UCM group and no infant in the DCC group, the difference between groups was not statistically significant.

Until recently immediate cord clamping had been considered gold standard for preterm deliveries, as it allowed for immediate movement of the newborn infant to the resuscitation area for stabilization (273). Renewed interest in the area has been led by studies proposing benefits for newborn infants by utilizing alternative cord clamping strategies, namely umbilical cord milking, and delayed cord clamping, which with the advent of mobile resuscitation trolleys allows for immediate support if required. Improved neonatal outcomes, without maternal side effects, are based on large retrospective review studies. A recent Cochrane review (which included 15 studies, n= 738) by Rabe et al highlighted a 50% decrease in IVH of all grades when DCC is employed compared with ICC (262, 274-281). However there was no reduction in the incidence of severe IVH grades, which are more likely to result in long-term

neurodevelopmental problems. Also, the current evidence base is less robust for long-term neurodevelopmental outcomes. The review was unable to comment on whether DCC affected the incidence of grade 3 or 4 IVH, and developmental scores at 7 months were equivocal (262). In a meta-analysis of 3 trials (n=99) no difference in neurodevelopment outcomes at 18- 24 months was observed between ICC and DCC groups (282). Meta-analyses on UCM have found similar reductions in IVH when compared to ICC, without long-term neurodevelopmental benefits (1, 283). Two large randomized controlled trials have recently been published. The APTS study compared ICC versus DCC and found no difference in a composite outcome which included death and a number of neonatal morbidities (284). Mortality alone was higher in the immediate group (9%) compared to the delayed group (6.4%) but this difference was no longer significant when correction for multiple comparisons took place. Duley and colleagues compared cord clamping at less than 20 seconds to delayed cord clamping with bedside resuscitation (285). They found a difference in death before discharge (ICC: 11%, DCC: 5%), but this was based on a small number of events with a wide confidence interval. Also, there are no clear differences between the groups in IVH or any other serious morbidity that would potentially explain a difference in mortality. The authors concluded that further trials assessing DCC with bedside resuscitation are urgently needed (285).

Recent evidence from animal studies suggests that benefits from DCC result from a more stable haemodynamic transition (263, 264). Clamping the umbilical cord increases systemic peripheral resistance as the neonatal circulation abruptly switches from a parallel to a series circuit. Ideally pulmonary ventilation should precede cord clamping to enable pulmonary venous return to immediately replace umbilical venous

return and the large adverse changes in cardiac function that normally accompanies umbilical cord clamping can be avoided (263, 286). Increased fluctuations in cardiac output and immature cerebral vascular autoregulation might help explain the increased risk of IVH following ICC in premature infants (287). In a recent study in preterm lambs a smoother cardiovascular transition was observed when ventilation preceded cord clamping (263). Ventilation with delayed cord clamping was associated with less variability in carotid artery pressure, and carotid artery blood flow in newborn lambs. However, these findings do not explain why UCM should result in similar reduction in IVH rates. Our understanding of the physiological outcomes resulting from different cord clamping strategies remains limited, and our study aimed to investigate short-term neurological outcomes in such instances.

Our study displayed different patterns, although not significant, in preterm infant brain oxygenation following alternative cord clamping strategies. There were no significant differences in cortical activity when measured by a comprehensive set of quantitative EEG measures. Fewer severe IVHs occurred in the placental transfusion groups, but we acknowledge that there were low numbers and this finding was not statistically significant. Cerebral activity and maturation did not differ between the groups, which may reflect low study numbers, or alternatively, different cord clamping strategies may not affect cerebral activity at the time points assessed in our study.

There were no differences for maternal complications, neonatal stabilisation interventions, neonatal temperature, blood glucose, or phototherapy days. This is important as current recommendations now advise neonatal units to take part in

studies, which assess alternative cord clamping strategies (267). This study highlights, as an aside, the feasibility of safely conducting a single centre RCT with UCM and DCC with bedside resuscitation as experimental arms.

EEG monitoring was commenced as early as possible post delivery. However, only 16% (7/44) had EEG applied in the DR. All infants were < 32 weeks and were commenced on positive end expiratory pressure (PEEP) following delivery. The small preterm cranial sizes, and the position of the neonatologist's hands around the infants' head in order to apply effective PEEP, meant that it was virtually impossible to apply EEG electrodes without interference. Therefore, EEG monitoring was only commenced in larger, stable infants in the DR to ensure that newborn stabilisation was not affected. It was subsequently applied when the newborns were stabilised in the neonatal unit.

There are a number of limitations to this study. Firstly, the study was not powered to an appropriate level to display superiority between cord clamping strategies based on our primary outcome measures. We recruited small study numbers as it was designed as a single center study and studies have not been previously conducted which utilized EEG and NIRS in similar circumstances on which to calculate sample sizes. Of note, because of limitations in spatial EEG recording, we did not examine specific maturational features of the EEG that are known to correlate with poor outcomes, such as mechanical delta brushes, and positive rolandic sharp waves. Our analysis of the EEG was based entirely on the quantitative features of one central cerebral channel of EEG. The number of infants in each group with a comprehensive set of EEG recording electrodes was too small to analysis as a subset set for this study.

Secondly, our infants were not evenly randomized among interventional groups. This was as a result of multiples being randomized to the same intervention and a higher number of multiples receiving UCM. Finally, some research groups now believe that there is ample evidence for the benefits of UCM and DCC such that ICC should no longer be included in such studies. The recent results of the APTS and CORD trial have provided further information, which may be informative to future trials in this area.

In conclusion, preterm infant neuromonitoring is feasible as part of a RCT with a short term surrogate of brain health as a primary outcome determined in the first 12 hours of life. Acquiring data on brain activity and cerebral oxygenation at predefined times was feasible. There were no differences in quantitative EEG measures and cerebral oxygenation values between cord management strategies at 6 and 12 hours. Although our study numbers were small, rates for severe IVH differed among different cord clamping strategies. These findings did not reach statistical significance, but do add to our understanding of the short-term neurological outcomes following different cord clamping strategies.

Chapter 6

Conclusion and future directions

6.1 Conclusions

Neonatal mortality has decreased significantly in recent decades (271). As more infants survive following preterm delivery and birth asyphxia, achieving the best possible neurological outcomes for survivors is paramount. Whilst EEG has an essential role within the NICU in newborn neurological monitoring following birth asyphxia, and more recently in monitoring preterm infants, it is not routinely initiated in the immediate newborn period, and at present has no role during newborn stabilisation.

The studies performed and presented as part of this thesis set out to determine if firstly it was feasible to perform newborn EEG in the DR, and secondly to assess what information it provides about newborn brain activity in the immediate postnatal period. The potential role for preterm infant neuromonitoring in the immediate newborn period was also explored as part of an interventional preterm infant RCT.

Monitoring brain activity in term infants in the DR is feasible and can be obtained in the first minutes of life by an experienced user. Continuous mixed frequency EEG can be seen in all infants, and quantitative features have now been described for the first time. The quantitative features reported represent infants during the immediate newborn period following the establishment of functional residual capacity, and

stabilisation of tidal volumes and end tidal CO_2, in term infants following elective caesarean section.

Preterm infant neuromonitoring is also feasible in the immediate newborn period. The acquisition of EEG is not as straightforward as in healthy term infants with current application techniques. However, it is possible to obtain information on brain activity and cerebral oxygenation during the first hours of life. In the study reported, the majority of infants had information available early, within hours of birth.

6.2 Future directions

6.2.1 EEG as a biomarker for brain health in the immediate newborn period

Brain activity can be monitored in the immediate newborn period, and normative values have now been produced. This information is hugely important, beneficial and may help guide resuscitation teams and to determine the need for immediate passive cooling. Thoresen et al coined the phrase 'time is brain' in relation to the timing of cooling for neuroprotection (151). We strongly believe that EEG in the DR could help identify those infants who would benefit most from early neuroprotective strategies.

However, we still have a way to go before EEG monitoring is routine in the DR. Signal interpretation is difficult but huge advances have already been made in quantitative analysis of the neonatal EEG and we now have algorithms that can accurately grade the EEG in term and preterm newborns (180, 255, 288-292). Multiple channels of EEG are not required to assess the grade of EEG baseline activity in the DR, one channel of good quality EEG is perfectly acceptable to assess amplitude, continuity and frequency of the EEG. EEG sensors are constantly

evolving and newer disposable single application sensors are now available also making EEG electrode acquisition more feasible.

EEG has long been considered just too difficult to deploy in environments like the DR and NICU. There have been major recent advances to the adoption of EEG in the NICU primarily due to technological advances (204). Modern machine learning techniques are also advancing rapidly and will soon be able to provide non EEG experts with the help needed to assist in the interpretation of EEG patterns on a 24/7/365 basis. These difficulties should no longer be a barrier to the adoption of EEG in the DR and we believe further studies on EEG in the immediate newborn period are essential.

In conclusion, the time is now right to advance the objective monitoring of neurological function of newborn infants in the DR and more research is clearly warranted. Future studies assessing infants following normal vaginal deliveries are a logical next step, and ultimately studies assessing EEG in the immediate newborn period following suspected HIE are warranted.

6.2.2 Neuromonitoring as an outcome measure in preterm infant studies

Developmental outcomes are the most commonly accepted outcome measures for interventional preterm infant studies. However, developmental outcomes are difficult to interpret as they are inherently multifactorial, and not solely dependent on a single intervention in the newborn period.

Neuromonitoring in the immediate newborn period has the potential to provide critical real time information on preterm infant outcomes in infant studies. To date many investigators have concentrated on NIRS due to the simplicity of its application

and interpretation. EEG, however, which has proven efficacy in the management of term and preterm infants has been largely ignored, as its application and interpretation is perceived as complicated in preterm infant studies. This thesis has confirmed that EEG is feasible in preterm infant studies, and the information obtained is easily interpreted in a research setting.

Advances in our understanding of preterm brain activity have led to a number studies describing EEG characteristics which correspond to developmental outcomes. Continuous displays of inter-burst interval duration, which differs with gestational age, has been cited as useful prognostic measure in preterm infants in the near future (171, 180). The most common EEG biomarkers associated with poor outcomes are seizures, positive rolandic sharp waves, EEG suppression/increased interburst intervals, mechanical delta brush activity, and other deformed EEG waveforms, asymmetries, and asynchronies (154). A recent study assessing quantitative analysis of physiological signals, combined with gestational and graded EEG, displayed potential for predicting mortality or delayed neurodevelopment at 2 years of age (193).

Therefore, infant neuromonitoring, and specifically brain activity has an important future role as short term outcome measures in preterm infant clinical trials. It is hoped that the information gathered in this thesis will contribute to international practice in this area.

7.0 Appendix 1: Ethics approval

UCC
Tel: + 353-21-490 1901
Fax: + 353-21-490 1919
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 4 (rrr) 14/04/15 & ECM 3 (p) 01/09/15

14th August 2015

Dr Mairead O'Riordan
Department of Obstetrics & Gynaecology
5th Floor
Cork University Hospital
Wilton
Cork

Re: BabySAFEE: Study of ante and intra partum fetal electrocardiogram and electroencephalography.

Dear Dr O'Riordan

The Chiarman approved the following:

- Signed Application Form dated 8th August 2015
- Addition of Dr Elena Pavlidis and Dr Daragh Finn, Clinical Fellows as co-investigators in the above study
- Information Leaflet and Consent Form for Stage 1b Version 1.0 dated 4th August 2015
- Study Protocol Version 2.0 dated 4th August 2015
- Information Leaflet and Consent Form for Stage 1 Version 2 dated 4th August 2015.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospital



The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

Tel: + 353-21-490 1901
Fax: + 353-21-490 1919

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 4 (q) 03/03/15 & ECM 3 (q) 01/09/15

14th August 2015

Professor Eugene Dempsey
Consultant Neonatologist
Neonatal Unit
Cork University Maternity Hospital
Wilton
Cork

Re: Respiratory function monitoring in babies greater than 36 weeks born by an elective caesarean section.

Dear Professor Dempsey

The Chairman approved the following:

- Amendment Application Form dated 11th August 2015
- Addition of Dr Elena Pavlidis, Dr Daragh Finn and Ita Herlihy, Clinical Fellows as co-investigators in the above study
- Parent Information Leaflet and Informed Consent Form Version 2.0 dated August 2015.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

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Tel: + 353-21-490 1901
Fax: + 353-21-490 1919
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 4 (q) 03/03/15

27th February 2015

Professor Eugene Dempsey
Consultant Neonatologist
Neonatal Unit
Cork University Maternity Hospital
Wilton
Cork

Re: Respiratory function monitoring in babies greater than 36 weeks born by an elective caesarean section.

Dear Professor Dempsey

Expedited approval is granted to carry out the above study at:

- Cork University Maternity Hospital.

The following documents have been approved:

- Signed Application Form
- Study Protocol
- Parent Information Letter and Consent Form
- CV for Chief Investigator.

We note that the co-investigators involved in this study will be:

- Dr Julie De Meulemeester, Registrar in Neonatology and Dr Lisa Dann, SHO in Neonatology.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

UCC
Tel: + 353-21-490 1901
Fax: + 353-21-490 1919
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 3 (aaaa) 8/12/15

9th November 2015

Professor Eugene Dempsey
Consultant Neonatologist
Cork University Maternity Hospital
Wilton
Cork

Re: CUPID: Clamping the umbilical cord in premature deliveries: a randomised controlled pilot trial.

Dear Professor Dempsey

The Chairman approved the following:

- Revised Study Title to Title above
- Revised Study Protocol Version 2.1 dated 23th October 2015.
- Amendment Application Form signed 23rd October 2015
- Revised Consent Form Version 2.1 dated 23rd October 2015
- Parent Information Leaflet Version 2.1 dated 23rd October 2015.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

File
20·11·15

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

UCC
Tel: + 353-21-490 1901
Fax: + 353-21-490 1919
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 3 (fff) 13/10/15

9th September 2015

Professor Eugene Dempsey
Consultant Neonatologist
Cork University Maternity Hospital
Wilton
Cork

Re: Immediate cord clamping, delayed cord clamping and umbilical cord milking: a randomised controlled trial in premature infants.

Dear Professor Dempsey

The Chairman approved the following:

- Revised Consent Form Version 2.0 dated 31st August 2015: Change study title on this document to the registered study title above prior to use and forward a copy of the revised document to CREC for our files.

Full approval is now granted to implement this amendment.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

8.0 Appendix 2: Parent information and Consent







CONSENT BY SUBJECT FOR PARTICIPATION IN A RESEARCH PROTOCOL

Study Number:_____ Patient Name:_____

Title of Protocol:
BabySAFEE: Study of Ante and Intra partum Fetal Electrocardiogram and Electroencephalography

You are being asked to participate in a research study. The doctors at University College Cork and Cork University Maternity Hospital (CUMH) study the nature of disease and attempt to develop improved methods of diagnosis and treatment. In order to decide whether or not you want to be a part of this research study, you should understand enough about its risks and benefits to make an informed judgement. This process is known as informed consent. This consent form gives detailed information about the research study which will be discussed with you. Once you understand the study, you will be asked to sign this form if you wish to participate.

More Information about our study:

What is an EEG?
EEG stands for electroencephalography (EEG). It is a recording of the electrical activity of the brain and is captured using electrodes that are attached to the scalp. Electrodes are like small stickers and are easily removed with water or baby oil after use.

What you are being asked to do?
Enrol in our study. We are asking for your permission, to place a small set of electrodes on your baby's scalp to allow us to record the electrical activity of their brain in the moments immediately after birth. We will also place two sticky patches on either shoulder of your baby to allow us to record your baby's heart rate or ECG (electrocardiogram). EEG and ECG monitoring is routinely carried out in the Neonatal Unit of Cork University Maternity Hospital and causes no discomfort for the baby. We are also asking your permission to collect a sample of about 12mls of blood from the placenta immediately after birth. This sample will be used to measure biomarkers (chemicals in the blood) such as copeptin which may help us to analyse the EEG recording.

How will we monitor your baby?
After caesarean section babies are normally placed on a resuscitaire, which is like a high table, immediately after birth for a period of up to ten minutes. After vaginal delivery babies are placed 'skin to skin' with their mother. During this time a few small stickers (electrodes) will be placed on your baby's head. Sometimes we cover these electrodes with a small hat or cap. We will record the EEG signal for a period of approximately 5- 10 minutes. If it is not possible to place the electrodes immediately after vaginal deliveries the recording will be postponed until your baby is being weighed and dressed. Taking part in this study will not interfere with 'skin to skin' time or initiating breastfeeding.
EEG monitoring is a safe and accurate technique for monitoring brain activity in babies. We would also like to keep a copy of this EEG recording and some clinical information taken from your and your baby's medical notes.

What are biomarkers and how are the samples taken?
Biomarkers are chemicals that can be found in the blood during times of stress, such as copeptin. Higher levels of copeptin can be detected after vaginal deliveries compared with caesarean deliveries. Copeptin levels will allow us to interpret your baby's EEG reading more accurately.
After your placenta has been delivered a small sample of blood will be taken from it through the vessels in the umbilical cord. This sample will be frozen and sent for analysis. This study does not involve any extra blood sampling for you or your baby.

Potential risks and benefits:
The risks involved in this procedure are minimal, EEG monitoring is safe and painless and is routinely carried out in CUMH.

[redacted]

Confidentiality:
The records of this study will be kept confidential. Interesting findings from this research may be published in medical journals publications and presentations. All information on you and your baby will be kept anonymously and stored securely and only people involved in the study will have access to this information. Only personnel working at your hospital will have access to personal details about you or your baby and these will be stored securely in a locked cabinet in a restricted area accessible only to study personnel. We will not include any information that will make it possible to identify you as a subject. When required by law, the records of this research may be reviewed by government agencies and sponsors of the research.

Aim of the study
We aim collect EEG and ECG recordings during this study that will be used to identify methods to improve monitoring during labour and delivery.

Voluntary Nature of the Study:
Participation in this study is voluntary and you may withdraw consent at any time without affecting the medical care of you or your baby.

Contacts and Questions:
Contact the Principal Investigator Dr Mairead O'Riordan Phone: 087 2329572
You will be given a copy of this form to keep for your records.

AGREEMENT TO CONSENT
The research project and the treatment procedures associated with it have been fully explained to me. All experimental procedures have been identified and no guarantee has been given about the possible results. I have had the opportunity to ask questions concerning any and all aspects of the project and any procedures involved. I am aware that participation is voluntary and that I may withdraw my consent at any time. I am aware that my decision not to participate or to withdraw will not restrict my access to health care services normally available to me. Confidentiality of records concerning my involvement in this project will be maintained in an appropriate manner. When required by law, the records of this research may be reviewed by government agencies and sponsors of the research.
I understand that the sponsors and investigators have such insurance as is required by law in the event of injury resulting from this research.
I, the undersigned, hereby consent to participate as a subject in the above described project conducted at the Cork Teaching Hospitals.
I, the undersigned, agree to donate a sample of my baby's umbilical cord blood for this research project. I understand that this sample will be retained for up to two years and discarded after analysis. I have received a copy of investigator(s) listed above. If I have further queries concerning my rights in connection with the research, I can contact the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Lancaster Hall, 6 Little Hanover Street, Cork.

After reading the entire consent form, if you have no further questions about giving consent, please sign where indicated.

Investigator: _____ _____
Signature of Subject, Parent or Guardian

_____
Signature of Subject, Parent or Guardian

Witness: _____ Date:

Respiratory function monitoring in babies after an elective caesarean section: can it predict the risk for transient tachypnea of the newborn?

Dear Parents,

The team at Cork University Maternity Hospital are committed to providing the best care possible for you and your baby. Babies born by Caesarean Section have been shown to have an increased incidence of respiratory problems. These include transient tachypnoea of the newborn (wet lung) where the baby's breathing can be rapid. This can sometimes requires admission into the special care baby unit where they are monitored and sometimes require oxygen and other breathing support.

The purpose of this study:

The purpose of our study is to assess your baby's respiratory breathing pattern in the first ten minutes of life and then once again after 1-2 hours. We aim to identify any indicators which would be used to predict those that might need admission to the unit.

How will we monitor your baby?

Infants will be placed on the resuscitaire immediately after birth for a period of up to ten minutes which is the normal process. During this time a facemask connected to a monitor will be placed over your baby's mouth and nose and their breathing patterns recorded. Respiratory function monitoring is a safe and accurate technique for monitoring lung function in babies. The measurement causes no discomfort for the baby.

One to two hours later we will reassess your baby's respiratory function. This time frame has been chosen to allow flexibility so we do not interrupt feeding or bonding between you and your baby. Measurements will be taken in the same manner as at the time of delivery.

What happens if your baby requires resuscitation at birth?

A paediatric doctor will be present at your caesarean section which is usually not the case with elective sections. They will be present to assess and treat your baby. The monitor does not interfere with normal care or need for resuscitation.

Confidentiality:

While we aim to have this work presented and published internationally, your baby's information will remain secure. No confidential details will be published or disclosed to anyone outside the study.

Voluntary participation:

You are asked for voluntary consent for you and your baby to participate in this study. If you decide not to participate it will not have any effect on your baby's medical care. If you do give consent, you are still free to withdraw from the study at any time. You do not have to give a reason.





Research Team:

Professor Gene Dempsey, Consultant Neonatologist, Cork University Maternity Hospital

Dr Julie De Meulemeester, Registrar in Neonatology, Cork University Maternity Hospital

Dr Lisa Dann, SHO in Neonatology, Cork University Maternity Hospital

Dr Elena Pavlidis, Clinical Research Fellow, Department of Paediatrics and Child Health

Dr Daragh Finn, Clinical Research Fellow, INFANT Research Centre

Ita Herlihy, Clinical Research Nurse, INFANT Research Centre

Consent Form

I have read the information leaflet and had all my questions answered for me..... ☐

I consent for my baby to be included in the study..... ☐

I understand that I can withdraw consent at any time..... ☐

I consent for my baby's data to be used for the purposes of the study..... ☐

Name of the baby: _____

Name of the parent: _____

Signature of the parent: _____

Date: _____

Name of the researcher: _____

Signature of the researcher: _____

Date: _____

Clamping the Umbilical cord in Premature Deliveries (CUPID): A Randomised Controlled Pilot Trial

Parent Information Leaflet

You are being invited to give your permission for you and your baby to take part in a clinical research study. Before you decide it is important for you to understand why this research is being done and what it will involve. This process is known as informed consent. This leaflet gives detailed information about the research study, which will be discussed with you. Once you understand it fully, you will be asked to sign a consent form if you are happy to take part. A copy of this information leaflet will be given to you to keep. If anything is unclear, or if you would like more information, please do not hesitate to ask us. Take all the time you need to decide if you are to take part.

Why have you been invited to take part?
Your baby is at risk of being born prematurely and so this is why the doctors have provided you with this information. Being born prematurely puts your baby at a higher risk of having immediate and future medical problems. The doctors at Cork University Maternity Hospital are trying to find the best ways to care for premature babies and their mothers'. One of the ways to do this is through research studies like this one.

What is the study about?
At present your baby receives all of his/her blood and oxygen from you via your placenta. The connection between your placenta and your baby is known as the umbilical cord. After your baby is born you are still connected until the doctor cuts the umbilical cord. He/she does this by placing two clamps over the cord and then cutting the cord in between the two clamps. We believe the timing and way in which the doctor clamps the cord may be important for babies born prematurely and this study is investigating what the best approach is for you and your baby.

What are the different approaches to clamping the cord?
There are three options:

1. Immediate cord clamping: The cord will be clamped immediately (less than 20 seconds) after delivery.
2. Delayed cord clamping: The cord will be clamped after one minute. This approach allows for extra blood to flow from you, and your placenta into your baby before being separated. If your baby needs help to adapt after delivery this will not be affected, as this help will be provided at the bedside on a mobile trolley while you and your baby are still attached by the umbilical cord.
3. Umbilical Cord Milking: The doctor can 'milk' the cord and then clamp it. This means that the doctor will push blood down the umbilical cord towards your baby a few times after delivery, and then clamp the cord.

Why is it important to find out which approach is best?
Right now it is not clear which approach is best for you and your baby. Recently, studies from other countries have shown that by increasing the amount of blood your baby receives from you after delivery, either by delaying the clamping of the cord or by milking it, may result in better short term outcomes for premature babies. These include higher blood pressures, which are good for premature babies, less bleeds seen on head ultrasounds and less blood transfusions. These findings are all positive but we still do not know if they result in better long-term neurological outcomes for premature babies. Therefore, at present it is not clear what the best approach is, and more studies are required to find out. The majority still practice immediate cord clamping.

How will we decide what approach is best?
If you decide to take part we will take a blood sample from you the day after your delivery. This will help us decide which approach benefits mothers best. Your baby will have a number of tests all of which are routine investigations in premature infants. They include **EEG, Cranial ultrasounds, brain oxygen monitoring, and Echo**. These are all monitoring methods used in the intensive care unit. They will help us decide which approach benefits babies best, by looking at your baby's brain and heart function during the first days after delivery.

What is EEG?
EEG stands for electroencephalography. It is a recording of the electrical activity of the brain and is captured using electrodes that are attached to the scalp. Electrodes are like small stickers and are easily removed with water or baby oil after use. They take about 10 minutes to apply and after this they will be left in place for the first few days of life. Our EEG system also uses video to help us study movement patterns during sleep. This video recording is strictly confidential and will not be used for any other purposes.

What are cranial ultrasounds?
You have seen your baby on ultrasound during your pregnancy. We will use a similar but much smaller device to look at your baby's brain by ultrasound. All premature babies have a head ultrasound in the first few days of life. As part of the study your baby will have an extra one a few hours after being born.

What is NIRS?
Near Infrared Spectrometry (NIRS) is a method that is widely used for assessing the oxygen supply to the brain. NIRS is a test that picks up the oxygen level in the baby's brain. Similar to the EEG attachments, the NIRS probe (a small sticker) will also be applied to your baby's forehead and will be kept in place for the first few days of life. Once both tests (EEG and NIRS) are complete, these attachments will be safely removed from your baby's head.

What is echocardiography?
We will use the ultrasound probe to look at your baby's heart and the blood flow entering and leaving the heart.

It is important to note that these methods of monitoring are standard methods of assessment of preterm infants.

If I enter the study how will you decide what approach to clamping the cord will be taken?
This is decided through a process called randomisation. This means that the approach will be assigned randomly after you have consented to take part in the study. Your baby will have an equal chance of being assigned to each of the three approaches outlined above.

What will happen if I do not enter the study?
Your baby will still have their cord clamped by one of the three approaches mentioned above. There is no hospital policy on umbilical cord clamping so any of these approaches may occur.

Are there any risks to my baby by entering the study?
No. There is some evidence that babies that have delayed cord clamping or umbilical cord milking can become more jaundiced than babies whose cords are clamped immediately. However, there is no evidence that they require more treatment, or that it causes any harm to babies.

Voluntary Nature of the Study:
Participation in this study is voluntary and you may withdraw consent at any time without affecting the medical care of you or your baby. You can also ask to speak with a member of the research team at any time during the study and we would be happy to answer any questions that you may have.

Confidentiality:
The records of this study will be kept confidential. Interesting findings from this research may be published in medical journal publications and presentations. All information on you and your baby will be kept anonymously and stored securely and only people involved in the study will have access to this information. Only personnel working on the study will have access to personal details about you or your baby and these will be stored securely in a locked cabinet in a restricted area accessible only to study personnel. We will not include any information that will make it possible to identify you as a subject.

Contact Details for Chief Investigator:

Prof Eugene Dempsey
Consultant Neonatologist
INFANT Research Centre
Cork University Maternity Hospital
Wilton
Ireland
Tel: 0214920500

Version 2.1
23/10/2015

9.0 Appendix 3: Peer Reviewed Publications

ARTICLE IN PRESS

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

Clamping the Umbilical Cord in Premature Deliveries (CUPiD): Neuromonitoring in the Immediate Newborn Period in a Randomized, Controlled Trial of Preterm Infants Born at <32 Weeks of Gestation

Daragh Finn, MB[1,2], Deirdre Hayes Ryan, MB[2,3], Andreea Pavel, MB[1,2], John M. O'Toole, PhD[1,2], Vicki Livingstone, PhD[1,2], Geraldine B. Boylan, PhD[1,2], Louise C. Kenny, PhD[2,3], and Eugene M. Dempsey, MD[1,2]

Objective To compare cerebral activity and oxygenation in preterm infants (<32 weeks of gestation) randomized to different cord clamping strategies.

Study design Preterm infants born at <32 weeks of gestation were randomized to immediate cord clamping, umbilical cord milking (cord stripped 3 times), or delayed cord clamping for 60 seconds with bedside resuscitation. All infants underwent electroencephalogram (EEG) and cerebral near infrared spectroscopy for the first 72 hours after birth. Neonatal primary outcome measures were quantitative measures of the EEG (17 features) and near infrared spectroscopy over 1-hour time frames at 6 and 12 hours of life.

Results Forty-five infants were recruited during the study period. Twelve infants (27%) were randomized to immediate cord clamping, 19 (42%) to umbilical cord milking, and 14 (31%) to delayed cord clamping with bedside resuscitation. There were no significant differences between groups for measures of EEG activity or cerebral near infrared spectroscopy. Three of the 45 infants (6.7%) were diagnosed with severe IVH (2 in the immediate cord clamping group, 1 in the umbilical cord milking group; $P = .35$).

Conclusions There were no differences in cerebral EEG activity and cerebral oxygenation values between cord management strategies at 6 and 12 hours. *(J Pediatr 2019; ■:1-6)*.

Trial registration ISRCTN92719670.

Umbilical cord management allowing for placental transfusion of blood is an important intervention for preterm infant health. In some studies of preterm infants, delayed cord clamping or umbilical cord milking have been shown to decrease the overall incidence of intraventricular hemorrhage (IVH)[1] and reduce hospital mortality[2] compared with immediate cord clamping. Delayed cord clamping in preterm infants also has been shown to improve motor development at 18-22 months corrected age.[3] However, a decrease in the rate of severe IVH and improved developmental outcomes are not universally reported after placental transfusion.[1,4]

More evidence is needed on the feasibility of bedside resuscitation to allow for delayed cord clamping in compromised infants, and on the effects of umbilical cord milking before either of these approaches is considered routine.[5] Although not fully understood, animal models suggest that a reduced incidence of IVH may be explained by a smoother cardiovascular transition when ventilation precedes cord clamping.[6,7] Newborn cerebral activity and cerebral oxygenation, which may explain the differences in IVH rates, have not been previously investigated in this setting.

This study investigated how different cord clamping strategies affect preterm infants' short-term neurologic well-being and to improve our understanding of how different cord clamping strategies may affect cerebral activity and oxygenation in the first day after birth.

Methods

This prospective, randomized, controlled trial was conducted in Cork University Maternity Hospital, Ireland, between December 2015 and September 2016. Infants born at <32 weeks of gestation were eligible for inclusion. Exclusion criteria included major congenital anomaly, bleeding from placenta previa, placental abruption or accreta, twin-to-twin transfusion syndrome, hydrops, and cord prolapse. Because preterm infants have not been previously studied in this

EEG	Electroencephalogram
IVH	Intraventricular hemorrhage
NIRS	Near infrared spectroscopy

From the [1]Department of Pediatrics and Child Health and the [2]Department of Obstetrics, Cork University Maternity Hospital, Cork Ireland; and [3]Irish Centre for Fetal and Neonatal Translational Research, University College Cork, Cork, Ireland

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context, a formal sample size calculation was not performed. During the 9-month study period, all infants who were assessed, met the eligibility criteria, and consented were enrolled in the study.

The study had 3 arms, immediate cord clamping, umbilical cord milking, and delayed cord clamping, with bedside respiratory support if required. Immediate cord clamping was defined as clamping the umbilicus within 20 seconds of delivery. For umbilical cord milking, the obstetrician held the infant at or below the level of the placenta and an assistant stripped the cord, 20 cm over 2 seconds, 3 times in the direction of the infant. For delayed cord clamping, infants were placed on a mobile resuscitation trolley (Lifestart, Inspiration Healthcare, Leicester, UK) with the cord intact, at or below the level of the placenta. Routine neonatal care was provided, including positive end-expiratory pressure and the provision of positive pressure ventilation if required, and the cord was clamped at 60 seconds after delivery.

All infants were wrapped in sterile towels at the time of delivery until they were transferred to the Panda Resuscitator (GE Healthcare, Laurel, Maryland). Randomization of groups was performed using a computer program and allocation concealment was achieved by using opaque, sequentially numbered, sealed envelopes. Randomization was stratified by age ($23^{0/7}$ to $27^{6/7}$ and $28^{0/7}$ to $31^{6/7}$ weeks of gestation) to ensure equal numbers of neonates born at <28 weeks of gestation in each arm. Infants born from multiple pregnancies received the same group allocation.

The Cork Teaching Hospitals' Research Ethics Committee approved this study. Antenatal written informed consent was obtained by a member of the research team before delivery. This trial was registered on the ISRCTN registry (ISRCTN92719670).

Neuromonitoring

Cerebral near infrared spectroscopy (NIRS) and electroencephalogram (EEG) monitoring commenced as soon as possible after delivery, depending on infant stability. Monitoring continued until 72 hours of age. A NIRS neonatal probe, OxyAlertTM NIRSensor (Covidien IIc, Mansfield, Massachusetts) was applied in a frontotemporal location. The EEG was recorded with the NicoletOne (CareFusion Co, San Diego, California) or Moberg (Moberg Research Inc, Ambler, Pennsylvania) EEG systems. Depending on infant size, 4-11 electrodes were used. The method for electrode placement in preterm infants in our unit previously has been described.[8] A consultant radiologist (unaware of group assignment) performed a cranial ultrasound examination within 48 hours of delivery.

Outcome Measures

The primary neonatal outcome was standard quantitative measures of preterm newborn EEG and cerebral NIRS median values collected over 1-hour time frames at 6 and 12 hours of age. The primary outcome for maternal outcome was maternal hemoglobin at 24-36 hours post partum.

Each EEG was assessed visually for overall continuity, amplitude, and symmetry and synchrony by a researcher blinded to infant randomization. EEG epochs with poor signal quality were excluded from further analysis. Multiple quantitative EEG features were computed to represent the complex waveforms of the preterm EEG.[9] An automated method removed segments of EEG corrupted by artifact,[9] before computing features on C3-C4, a common channel to all EEG recordings. The feature set comprised of spectral features, amplitude features using the range EEG, and features of the temporal organization of bursts. Spectral features are calculated within 4 frequency bands, as defined elsewhere.[9,10] The range EEG, a measure of peak-to-peak voltage, was calculated using a 1-20 Hz bandpass filter. Bursts were identified using an automated method.[10] All features were calculated using the software package NEURAL (version 0.3.3),[9] a neonatal EEG feature set in Matlab.

Cerebral oxygenation values were selected over 1-hour epochs at 6 and 12 hours of age. To remove potential artifacts caused by poor sensor contact, a 30 second collar was applied to regional cerebral oxygenation values of 15% and removed from further analysis. The median value of regional cerebral oxygenation over the hour was then used to summarize each epoch.

Echocardiographic measurements were performed on all infants at 12 ± 3 hours of age by one of the investigators who was not blinded to infant randomization. Measurements were taken according to a standard operating procedure to assess systemic blood flow, by superior vena cava flow (milliliters per kilogram per minute), right ventricular output (milliliters per kilogram per minute), and left ventricular output (milliliters per kilogram per minute). These measurements were performed offline at a later time.

Statistical Analyses

For each quantitative measure of the EEG and NIRS, simple linear regression (unadjusted analysis) was used to test for differences among the 3 groups. Because EEG and NIRS are dependent on gestational age,[11,12] a multiple linear regression (adjusted analysis) was also performed to control for this factor. In addition, linear mixed models were used to assess if the time points (6 and 12 hours) influence group differences for each quantitative EEG and NIRS feature. Gestational age, time after birth, group membership, and the interaction between group and time were set as fixed effects with the infant as a random effect. Features that were not normally distributed were log-transformed before analyses. Differences in baseline characteristics and other outcomes between the 3 groups were investigated using the Kruskal-Wallis test when the variable was continuous and the Fisher exact test when the variable was categorical.

Statistical analyses were performed using IBM SPSS Statistics version 22 (SPSS Inc, Chicago, Illinois), except for the linear mixed models, which were conducted in *R* (version 3.4.2, The R Foundation of Statistical Computing, Vienna Austria; http://www.r-project.org) using the *lme4* package (version 1.1-10). Analyses were performed on an

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intention-to-treat basis. All tests were 2-sided and $P < .05$ was considered statistically significant.

Results

There were 77 infants assessed for eligibility over the 9-month study period and 45 were enrolled. Twelve infants (27%) were randomized to immediate cord clamping, 14 (31%) to delayed cord clamping with bedside resuscitation, and 19 (42%) to umbilical cord milking (**Figure 1**; available at www.jpeds.com). Uneven randomization was a result of multiple births randomized to the same intervention and a greater number of multiple births receiving umbilical cord milking. Two infants randomized to delayed cord clamping with bedside resuscitation were delivered before the research team was in place with the resuscitation trolley, and although delayed cord clamping was performed by the responsible healthcare professionals, there was no member of the research team to time the duration of delayed cord clamping; bedside resuscitation was not performed. Both infants were included in delayed cord clamping with bedside resuscitation arm for analysis on an intention-to-treat basis. There were more multiples in both the delayed cord clamping (4/14 [28.6%]) and the umbilical cord milking (13/18 [72.2%]) groups compared with the immediate cord clamping (2/12 [16.7%]) group. Infant characteristics and early secondary outcomes are provided in **Table I**.

Outcomes

There were no significant differences in the primary infant outcomes (**Table II**). There was no difference in maternal hemoglobin between groups ($P = .36$). **Table III** summarizes neonatal outcomes.

EEG Outcome. Application of EEG and acquisition of data were performed as early as possible. Seven infants had EEG monitoring commencing in the delivery room. The median age at EEG application was 3.05 hours (IQR, 1.85-5.38 hours). One infant had a very immature EEG pattern and was excluded from analysis. Data on 40 of the 44 infants (91%) were available at 6 hours and 43 of the 44 (98%) at 12 hours. **Tables IV** and **V** (available at www.jpeds.com) include a complete list of EEG features analyzed at the 6-hour and 12-hour time points. A median of 0% (IQR, 0%-0%; range, 0%-22%) of the EEG was removed by the artifact detection algorithm. No significant differences were found between the 3 groups at either time point in the unadjusted and adjusted analysis. For the linear mixed models, gestational age was significant for some (7/17) features, as was time (8/17), but not group or group-by-time interaction (0/17). **Figure 2**, A-C (available at www.jpeds.com) highlights the dependency of 3 EEG features on gestational age but not on intervention group.

NIRS Outcome. NIRS data on 40 of the 44 infants (91%) were available at 6 hours and 41 of the 44 (93%) at 12 hours. A median of 0% (IQR, 0%-0%; range, 0%-41%) of the NIRS data was removed by the artifact detection algorithm. There was no significant difference in regional cerebral oxygenation values among the 3 groups at the 6- or 12-hour time points (**Table II**). In the linear mixed model, both group and group-by-time interactions were not significant.

Secondary Outcome Measures

Although 2 infants in the immediate cord clamping group had a severe IVH compared with 1 infant in the umbilical cord milking group and no infant in the delayed cord clamping group, the difference between groups was not statistically significant ($P = .35$). There was no difference in admission temperature, mean blood pressure on admission and at 6, 12, 18, and 24 hours, or rates of bronchopulmonary dysplasia (**Table I**).

Markers for systemic blood flow based on echocardiographic measurements did not differ significantly between groups (**Table I**). The median values for superior vena cava flow were lowest in the immediate cord clamping group 50 (IQR, 47-77) and highest in the delayed cord clamping with bedside resuscitation groups 106.0 (IQR, 82.4-166.0). There were no significant differences in neonatal outcomes throughout neonatal intensive care unit stay (**Table III**).

Discussion

This prospective, randomized, controlled trial assessed short-term neurologic health in preterm infants born at <32 weeks of gestation following 3 different cord clamping strategies. There were no significant differences in cerebral oxygenation values or quantitative EEG features between groups at either 6 or 12 hours.

Until recently, immediate cord clamping had been considered the gold standard for preterm deliveries, because it allowed for immediate movement of the newborn infant to the resuscitation area for stabilization.[13] Renewed interest in the area has led to a number of randomized controlled trials and a number of meta-analyses proposing benefits for newborn infants by using alternative cord clamping strategies.[1,14-21] Also, the introduction of mobile resuscitation trolleys now allows for immediate respiratory support if required, without adverse neonatal events.[22,23] A recent meta-analysis by Fogarty et al included 18 randomized, controlled trials comparing delayed vs early clamping in 2834 infants.[2] Delayed cord clamping was found to decrease hospital mortality (risk ratio, 0.68; 95% CI, 0.52-0.90; risk difference, −0.03; 95% CI, −0.05 to −0.01; $P = .005$). However, the current evidence base is less robust than initially expected and a 2014 meta-analysis of 3 trials (n = 99) displayed no difference in neurodevelopmental outcomes at 18-24 months of age between the immediate cord clamping and the delayed cord clamping groups,[4] despite Mercer et al reporting

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Table I. Infant characteristics and early secondary outcomes

Characteristics/outcomes	Immediate cord clamping (n = 12) n	Median (IQR)†	Delayed cord clamping (n = 14) n	Median (IQR)†	Umbilical cord milking (n = 18) n	Median (IQR)†	*P* value*
Gestation (wk)	12	28.5 (25.7-30.5)	14	28 (26.4-29.6)	18	28.4 (25.7-29.6)	
Birthweight (g)	12	1080 (755-1613)	14	925 (630-1490)	18	930 (700-1545)	
Temperature (on admission)	12	36.3 (36.2-36.8)	14	36.4 (36-36.6)	18	36.6 (36.3-36.8)	.24
Hb (g/dL) 12 h	12	16.6 (15.8-17.9)	14	17.1 (16.0-18.8)	18	15.7 (14.2-17.7)	.46
MBP (mm Hg) 6 h	9	30.0 (25.5-38)	14	31.0 (27.5-33.0)	15	34 (26-37)	.41
MBP (mm Hg) 12 h	12	34.5 (31.0-40.0)	13	32 (27-36)	16	33.5 (29.0-36.8)	.50
MBP (mm Hg) 18 h	10	36.5 (32.0-42.0)	14	33.0 (29.8-37.0)	16	33.5 (30.3-39.0)	.33
MBP (mm Hg) 24 h	12	38.5 (36.3-40.8)	14	36.0 (33.5-37.3)	18	38.0 (33.0-40.3)	.22
LVO (mL/kg/min)	7	95 (89-129)	7	120 (85-156)	9	142 (67-236)	.58
RVO (mL/kg/min)	7	149 (89-174)	7	137 (136-183)	9	232.0 (92.5-442.0)	.37
SVC (mL/kg/min)	7	50 (47-77)	7	106.0 (82.4-166.0)	8	69.0 (30.0-117.8)	.11
IVH severe, n (%)	12	2 (17)	14	0 (0)	18	1 (6)	.35‡
BPD, n (%)	12	5 (42)	14	8 (57)	18	9 (50)	.70‡

Hb, Hemoglobin; *LVO*, left ventricular output; *MBP*, mean blood pressure; *RVO*, right ventricular output; *SVC*, superior vena cava.
*From the Kruskal-Wallis test unless otherwise stated.
†Unless otherwise stated.
‡From the Fisher exact test.

superior motor development in preterm infants randomized to delayed cord clamping compared with immediate cord clamping at 18-22 months of corrected age.[3]

Two large randomized, controlled trials also were inconclusive. The APTS study compared immediate cord clamping vs delayed cord clamping and found no difference ($P = .96$) in a composite outcome that included death and a number of neonatal morbidities.[24] Mortality alone was higher in the immediate group (9%) compared with the delayed group (6.4%), but this difference was not statistically significant with correction for multiple comparisons ($P = .39$). Duley et al compared cord clamping at <20 seconds with delayed cord clamping with bedside resuscitation.[22] They found a difference in death before discharge (immediate cord clamping, 11%; delayed cord clamping, 5%), but this finding was based on a small number of events with a wide CI. Also, there were no clear differences between the groups in IVH or any other serious morbidity that would potentially explain a difference in mortality. The authors concluded that further trials assessing delayed cord clamping with bedside resuscitation are urgently needed.[2,22]

Our understanding of the physiological outcomes resulting from different cord clamping strategies remains limited, and our study aimed to investigate short-term neurologic outcomes in such instances. Our study displayed nonsignificant differences in preterm infant brain oxygenation after alternative cord clamping strategies. There were no significant differences in cortical activity when measured by a comprehensive set of quantitative EEG measures. Cerebral activity and maturation did not differ between the groups, which may reflect low study numbers or, alternatively, different cord clamping strategies may not affect cerebral activity at the time points assessed in our study. In addition, we may not have identified differences that existed immediately after delivery as our primary outcomes were at 6 and 12 hours of age. Katheria et al displayed significantly lower cerebral oxygenation levels at 8-10 minutes of life in preterm infants who developed severe IVH, but did not find differences in

Table II. Comparison of EEG and NIRS among the 3 groups

EEG/NIRS	Umbilical cord milking ($n_1 = 18$; $n_2 = 18$)	Delayed cord clamping ($n_1 = 11$; $n_2 = 14$)	Immediate cord clamping ($n_1 = 11$; $n_2 = 11$)	*P* value*	*P* value Adjusted†
Burst ratio [6 h] (%)	83 (69-89)	68 (59-86)	76 (67-91)	.27	.16
Burst ratio [12 h] (%)	83 (72-93)	81 (66-90)	82 (73-89)	.95	.96
rEEG: median [6 h] (μV)	30 (21-33)	22 (18-30)	28 (22-33)	.60	.56
rEEG: median [12 h] (μV)	31 (27-37)	30 (23-40)	28 (24-34)	.61	.57
	($n_1 = 18$; $n_2 = 17$)	($n_1 = 12$; $n_2 = 13$)	($n_1 = 10$; $n_2 = 11$)		
$rcSO_2$ [6 h] (%)	83 (76-88)	85 (74-87)	87 (72-89)	.94	.97
$rcSO_2$ [12 h] (%)	80 (76-87)	81 (75-89)	79 (74-82)	.91	.88

n_1, Number of infants included at the 6-hour time point; n_2, number of infants included at the 12-hour time point; $rcSO_2$, regional cerebral oxygenation; *rEEG*, range EEG.
Values are median (IQR); *P* values are from the Kruskal-Wallis test.
Full list of EEG features are available in Tables IV and V online.
*From simple linear regression with group as the independent variable.
†From multiple linear regression with group and gestational age as the independent variables.

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Table III. Neonatal outcomes

Outcomes	Immediate cord clamping (n = 12) n (%)*	Delayed cord clamping (n = 14) n (%)*	Umbilical cord milking (n = 18) n (%)*	*P* value†
Heart rate >100 bpm at 60 s of age	8 (66.7)	7 (50.0)	11 (61.1)	.74
Spontaneous respirations at 60 s of age	8 (66.7)	12 (85.7)	14 (77.8)	.54
Apgar at 1 minute of age: median(IQR)	6 (4.3-8.0)	6 (5-7)	5 (4.8-6.0)	.33‡
Apgar <7 at 5 minutes of age	2 (16.7)	1 (7.1)	2 (11.1)	.85
Inotropes	2 (16.7)	2 (14.3)	3 (16.7)	>.99
Neonatal blood transfusion	8 (66.7)	9 (64.3)	13 (72.2)	.92
Number of transfusions§,¶: median(IQR)	2.5 (1-3)	3 (1.3-3.0)	2 (1-4)	.89‡
Age (d) at first transfusion: median(IQR)	20.5 (7.0-28.3)	15 (3.5-39.0)	18 (5.5-27.0)	.94‡
Phototherapy	10 (83.3)	14 (100.0)	15 (83.3)	.25
Number of days on phototherapy**: median(IQR)	3.5 (2.0-7.3)	4 (2-6)	2 (2-4)	.34‡
Surfactant therapy	7 (58.3)	9 (64.3)	13 (72.2)	.73
NICU surfactant	5 (41.7)	4 (28.6)	7 (38.9)	.79
Age (h) when received NICU surfactant††: median(IQR)	1 (1-11)	1 (1.0-3.6)	2.3 (1-12)	.42‡
Mechanical ventilation	8 (66.7)	9 (64.3)	13 (72.2)	.92
Number of days on mechanical ventilation‡‡: median(IQR)	9 (2.5-29.5)	4 (2.0-13.5)	7 (5.0-36.5)	.26‡
Late sepsis	0 (0.0)	2 (14.3)	3 (16.7)	.42
Necrotizing enterocolitis	1 (8.3)	0 (0.0)	1 (5.6)	.73
Retinopathy of prematurity	0 (0.0)	1 (7.1)	0 (0.0)	.59

NICU, Neonatal intensive care unit.
Values are number (%) or median (IQR).
*Unless otherwise stated
†From Fisher exact test unless otherwise stated.
‡From Kruskal-Wallis test.
§For those who received a blood transfusion.
¶Missing data for 1 infant in the delayed cord clamping group.
**For those who received phototherapy.
††For those who received NICU surfactant.
‡‡For those who received mechanical ventilation.

brain activity or cerebral oxygenation at later times.[25] Delayed cord clamping also increases the transfer of hematopoietic stem cells, endothelial cell precursors, mesenchymal progenitors, and pluripotent lineage stem cells, which we were unable to document but may play an important role.[26]

A number of groups have evaluated NIRS in the delivery room,[27] and over the first days of life.[12,28-30] It is important to note device differences between these studies.[31] We have published delivery room data and data over the first days after birth.[12] A large study looking at NIRS data over the first day by Alderliesten et al used an adult probe with the INVOS device.[28] Our data provide similar results when the discrepancy between the probes is factored in.

There were no differences for maternal complications, neonatal stabilization interventions, or standard neonatal outcomes. This finding is important because current recommendations advise neonatal units to take part in studies assessing alternative cord clamping strategies.[5] This study highlights the feasibility of safely conducting a single-center, randomized, controlled trial with umbilical cord milking and delayed cord clamping with bedside resuscitation as experimental arms.

There are a number of limitations to this study. First, the study was not powered to an appropriate level to display superiority between cord clamping strategies based on our primary outcome measures, and numbers were too small for gestational subgroup analysis (<28 and >28 weeks of gestation). We recruited small study numbers because it was designed as a single-center study, and studies have not been previously conducted that used EEG and NIRS in similar circumstances on which to calculate sample sizes. Of note, because of the limitations in spatial EEG recording, we did not examine specific maturational features of the EEG that are known to correlate with poor outcomes, such as mechanical delta brushes and positive rolandic sharp waves.[32] Our analysis of the EEG was based entirely on the quantitative features of 1 central cerebral channel of EEG. The number of infants in each group with a comprehensive set of EEG recording electrodes was too small to analyze as a subset for this study.

Finally, some research groups now believe that there is ample evidence for the benefits of umbilical cord milking and delayed cord clamping such that immediate cord clamping should no longer be included in such studies. The recent results of the APTS and CORD trials have provided further information, which may be informative to future trials in this area.

Our study showed that there were no differences in quantitative EEG measures and cerebral oxygenation values between cord management strategies at 6 and 12 hours of age. Although our study numbers were small, our findings do add to our understanding of the short-term neurologic outcomes following different cord clamping strategies. ■

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Reprint requests: Daragh Finn, MB, University College Cork, Irish Center for Fetal and Neonatal Translational Research, Cork University Maternity Hospital, Wilton, Cork, Ireland. E-mail: daragh.finn@hse.ie

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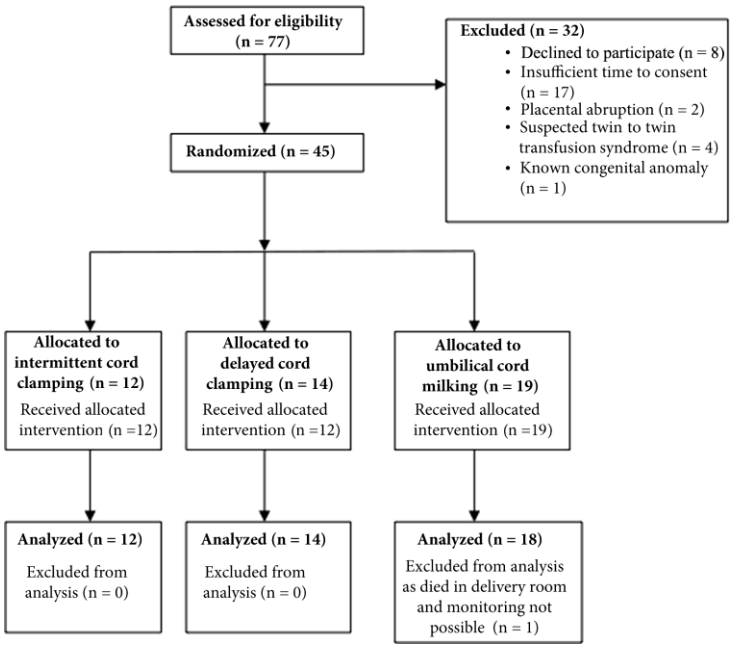


Figure 1. Flow diagram.

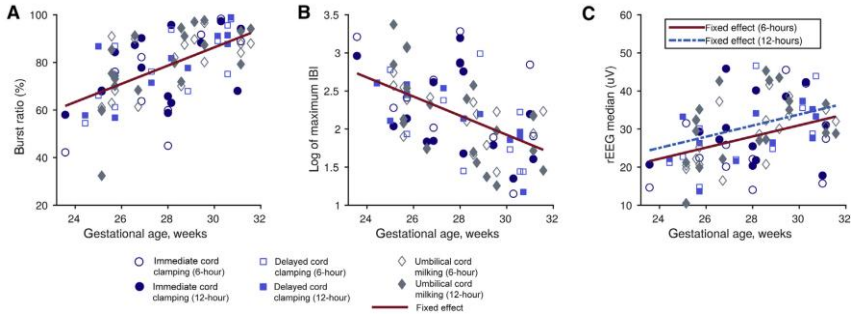


Figure 2. EEG features (**A-C**) highlighting the dependency on gestational age. Mixed-effect models for the 3 features included gestational age as a fixed effect (lines in **A-C**). Time (either the 6- or 12-hour time point) was significant ($P < .05$) in the range EEG (rEEG)-median feature plotted in **C**, but not for the features in **A** and **B**. The fixed effects of intervention group and group–time interaction were not significant ($P > .05$) and therefore are not included here.

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Table IV. Quantitative EEG analysis at 6 hours after birth

qEEG features	Umbilical cord milking (n = 18) Median (IQR)	Delayed cord clamping (n = 11) Median (IQR)	Immediate cord clamping (n = 11) Median (IQR)	*P* value*	*P* value†
rEEG: median (μV)	30 (21-33)	22 (18-30)	28 (22-33)	.60	.56
rEEG: lower margin (μV)	11 (8-12)	9 (7-11)	9 (8-13)	.55	.48
rEEG: upper margin (μV)	140 (100-171)	133 (107-168)	122 (92-138)	.45	.43
Burst ratio (%)	83 (69-89)	68 (59-86)	76 (67-91)	.27	.16
Maximum IBI (s)	9.1 (6.8-11.1)	11.2 (7.1-17.3)	9.2 (5.0-12.5)	.42	.35
SP [0.5-3.0 Hz] (μV^2)	332 (313-591)	418 (206-598)	368 (231-477)	.94	.94
SP [3-8 Hz] (μV^2)	29 (18-41)	33 (17-39)	25 (12-31)	.63	.64
SP [8-15 Hz] (μV^2)	6.1 (4.8-8.6)	5.5 (4.3-9.5)	5.4 (4.0-7.6)	.85	.81
SP [15-30 Hz] (μV^2)	2.0 (1.6-2.4)	1.7 (1.2-2.6)	1.7 (1.5-2.3)	.89	.90
Relative SP [0.5-3.0 Hz] (%)	92 (91-93)	92 (91-93)	92 (91-93)	.81	.81
Relative SP [3-8 Hz] (%)	6.2 (5.1-7.0)	6.2 (5.1-7.2)	5.5 (4.9-6.4)	.75	.75
Relative SP [8-15 Hz] (%)	1.4 (1.1-1.6)	1.6 (1.0-1.8)	1.4 (1.1-2.3)	.97	.97
Relative SP [15-30 Hz] (%)	0.41 (0.38-0.68)	0.44 (0.36-0.54)	0.55 (0.40-0.84)	.70	.70
SF [0.5-3.0 Hz]	0.27 (0.24-0.30)	0.29 (0.27-0.32)	0.29 (0.26-0.33)	.98	.99
SF [3-8 Hz]	0.75 (0.72-0.78)	0.74 (0.71-0.80)	0.75 (0.74-0.81)	.75	.74
SF [8-15 Hz]	0.84 (0.80-0.85)	0.82 (0.80-0.83)	0.84 (0.80-0.87)	.30	.29
SF [15-30 Hz]	0.64 (0.63-0.69)	0.65 (0.61-0.65)	0.68 (0.64-0.69)	.28	.28

IBI, interburst interval; *qEEG*, quantitative EEG; *rEEG*, range EEG; *SF*, spectral flatness; *SP*, spectral power.
*From simple linear regression with group as the independent variable.
†From multiple linear regression with group and gestational age as the independent variables.

Table V. Quantitative EEG analysis at 12 hours after birth

qEEG feature	Umbilical cord milking (n = 18) Median (IQR)	Delayed cord clamping (n = 14) Median (IQR)	Immediate cord clamping (n = 11) Median (IQR)	*P* value*	*P* value†
rEEG: median (μV)	31 (27-37)	30 (23-40)	28 (24-34)	.61	.57
rEEG: lower margin (μV)	11 (8-13)	12 (8-13)	10 (7-12)	.77	.67
rEEG: upper margin (μV)	160 (113-194)	136 (124-188)	120 (109-138)	.38	.35
Burst ratio (%)	83 (72-93)	81 (66-90)	82 (73-89)	.95	.96
Maximum IBI (s)	8.2 (5.5-12.2)	8.1 (6.1-15.2)	8.5 (6.9-12.2)	.92	.93
SP [0.5-3 Hz] (μV^2)	579 (300-849)	461 (263-737)	394 (273-588)	.79	.79
SP [3-8 Hz] (μV^2)	33 (20-57)	27 (17-46)	19 (15-31)	.64	.65
SP [8-15 Hz] (μV^2)	6.8 (5.3-8.8)	7.5 (5.2-9.9)	6.2 (4.3-7.1)	.48	.44
SP [15-30 Hz] (μV^2)	2.3 (1.8-2.7)	2.2 (1.6-3.8)	1.9 (1.8-2.6)	.56	.55
Relative SP [0.5-3.0 Hz] (%)	93 (91-94)	93 (90-94)	93 (91-95)	.99	.98
Relative SP [3-8 Hz] (%)	5.4 (4.7-6.2)	5.5 (4.6-6.5)	4.6 (3.9-6.6)	.69	.69
Relative SP [8-15 Hz] (%)	1.1 (0.8-1.9)	1.3 (1.0-2.1)	1.0 (1.0-2.3)	.63	.53
Relative SP [15-30 Hz] (%)	0.40 (0.25-0.75)	0.43 (0.34-0.60)	0.42 (0.30-0.73)	.87	.86
SF [0.5-3.0 Hz]	0.28 (0.24-0.31)	0.29 (0.27-0.34)	0.29 (0.25-0.31)	.28	.28
SF [3-8 Hz]	0.75 (0.70-0.79)	0.76 (0.72-0.82)	0.76 (0.73-0.80)	.59	.54
SF [8-15 Hz]	0.84 (0.82-0.85)	0.83 (0.80-0.84)	0.83 (0.80-0.86)	.11	.10
SF [15-30 Hz]	0.62 (0.59-0.63)	0.63 (0.62-0.66)	0.65 (0.61-0.67)	.86	.86

IBI, interburst interval; *qEEG*, quantitative EEG; *rEEG*, range EEG; *SF*, spectral flatness; *SP*, spectral power.
*From simple linear regression with group as the independent variable.
†From multiple linear regression with group and gestational age as the independent variables.

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EEG for the assessment of neurological function in newborn infants immediately after birth

Daragh Finn,[1] John M O'Toole,[1,2] Eugene M Dempsey,[1,2] Geraldine B Boylan[1,2]

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[1]Department of Paediatrics and Child Health, University College Cork, Cork, Ireland
[2]Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Cork, Ireland

Correspondence to
Professor Geraldine B Boylan, Department of Paediatrics and Child Health, University College Cork, Cork T12 K8AF, Ireland; g.boylan@ucc.ie

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ABSTRACT

Objective To assess the neurological function of newborn infants in the first minutes after birth using EEG.

Design and patients We obtained electroencephalography (EEG) recordings in term infants following elective caesarean section. After delivery, disposable EEG electrodes were attached to the infants' scalp over the frontal and central regions bilaterally and EEG was recorded for 10 min. Both visual and quantitative measures were used to analyse the EEGs.

Setting The operative delivery theatre of Cork University Maternity Hospital, Ireland.

Results Forty-nine infants had EEG recordings over the frontal and central regions. The median (IQR) age at time of initial EEG recording was 3.0 (2.5–3.8) min. While movement artefact contaminated parts of many recordings, good-quality EEG, with mixed-frequency activity with a range of 25–50 µV, was observed in all infants. The majority of EEG spectral power was within the delta band: the median (IQR) relative delta power was 87.8% (83.7%–90%). Almost all (95%) spectral power was below a median (IQR) of 7.56 Hz (6.17–9.76 Hz).

Conclusions EEG recording is very feasible in the immediate newborn period. This study provides valuable objective information about neurological function during this transitional period.

What is already known on this topic?

- Neonatal electroencephalography (EEG) monitoring is essential for monitoring brain function in infants with hypoxic ischaemic encephalopathy (HIE) during therapeutic hypothermia.
- The need to identify infants with HIE in the immediate newborn period is becoming increasingly important given the benefits of early treatment with therapeutic hypothermia.

What this study adds?

- Good-quality dual-channel EEG monitoring during newborn transition is feasible.
- Mixed-frequency EEG is present and quantitative features are described in the frontal and central regions.
- An immediate EEG after birth provides much-needed information about brain function.

INTRODUCTION

Neonatal electroencephalography (EEG) monitoring has well-documented applications in the management of infants with hypoxic ischaemic encephalopathy (HIE)[1–5] and is essential for the diagnosis of neonatal seizures.[6–8] HIE is a leading cause of neonatal death and long-term neurological disability, with an estimated incidence of 1.5 per 1000 live births.[9] Therapeutic hypothermia (TH) is now the standard treatment for infants with moderate or severe HIE, and results in a significant reduction in mortality, without an increase in major disability among survivors.[10] The optimal timing to commence TH is within 6 hours of birth, and thus eligibility for TH should be decided as soon as possible.[11 12]

Information about newborn electrocortical activity to date is almost exclusively based on EEG recordings performed after 6 hours of age, or occasionally from around 3 hours in infants that are unwell.[13 14] Currently infants are stabilised in the delivery room following potentially severe hypoxic ischaemic events without objective information about brain function. Clinical assessments of newborn well-being are limited and liable to inter-rater and intra-rater variability.[15 16] Therefore, EEG monitoring in the immediate newborn period may be a useful adjunct in certain circumstances. The first step in evaluating its use is to assess whether it is feasible to perform, and if so to describe EEG features in a cohort of healthy newborn infants. We set out to assess qualitative and quantitative features of EEG during newborn transition and to provide data for healthy term infants during this important time period.

METHODS

We recruited infants born in Cork University Maternity Hospital (CUMH), Ireland, over 2 months between September and October 2015. CUMH is a tertiary university maternity hospital with approximately 8500 deliveries annually. Infants >37 weeks' gestational age, born by elective caesarean section (ECS), were eligible for inclusion in the study. Infants with major congenital abnormalities were excluded. Infants requiring intervention to support stabilisation beyond being warmed, dried and stimulated, or with Apgar scores <7 at 1 min, were also excluded from the study.

Following delivery, infants were brought immediately to a Panda Resuscitator (GE Healthcare, Laurel, Maryland, USA). All EEG studies were performed by one of the authors following a standardised protocol. The infants' scalp was first

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cleaned using an alcohol wipe. As per usual clinical practice previously described in our neonatal intensive care unit (NICU), the hair was then parted at EEG sensor sites, and the skin gently abraded three to four times using a sterile cotton bud and skin preparation gel (Nuprep).[17] Six sterile, disposable, flat-surfaced EEG electrodes were attached to the infants' scalp over the frontal and central regions (F4, C4, F3, C3, ground and reference) bilaterally using the 10–20 system of electrode placement and the EEG was recorded for up to 10 min. Two channels of a bipolar recording were displayed (F4–C4, F3–C3) on the monitor. All recordings were performed and stored using the Unique EEG system (Inspiration Healthcare, Leicester, UK). Each EEG study was video-recorded and recordings commenced after delivery of the infant. This allowed for future accurate documentation of infant age (in seconds) when monitoring commenced, and to correlate recordings with infant movements and newborn care. As all infants were born by caesarean section, monitoring did not interfere with skin-to-skin time or initiation of breast feeding. Maternal and infant demographics were recorded, including the type of anaesthesia used and the Apgar scores. Newborn admissions to the NICU and discharge diagnosis on chart review were also documented.

Data collection and analyses

EEG data were sampled at 256 Hz and stored on a computer disc for offline analysis. All EEG recordings were visually analysed. First, the recordings were assessed for quality, and periods of artefact-free EEG were identified for analysis. The EEG was then assessed for overall voltage, continuity, frequency, and maturity.

Three minutes of artefact-free EEG segments were then selected from each infant's recording for quantitative analysis. Quantitative measures were calculated using the software package NEURAL, a neonatal EEG feature set in MATLAB (V.0.3.4), which runs within the MATLAB environment (The MathWorks, Natick, Massachusetts, USA). NEURAL was developed to standardise quantitative analysis of newborn EEG by including full implementation details,[18] and is freely available as open-source software (https://github.com/otoolej/qEEG_feature_set).

We used quantitative measures that capture amplitude and frequency characteristics:

- Total and relative spectral power for four frequency bands: delta (0.5–4 Hz), theta (4–7 Hz), alpha (7–13 Hz) and beta (13–30 Hz).
- Median, lower and upper margins, and asymmetry of the range EEG (rEEG) within the 1–20 Hz band.
- Spectral edge frequency and fractal dimension over the 0.5–30 Hz band.

A comprehensive description of each measure, including implementation details is available in.[18] Spectral power and rEEG features capture the amplitude characteristics of the EEG; spectral edge frequency and fractal dimension features capture the spectral characteristics. The edge frequency estimates the extent of spectral spread, with higher values indicating a more disperse spectrum and lower values indicating a more condensed spectrum around the lower frequencies. Fractal dimension captures the shape of the spectrum. Within a frequency band, typically 0.5–30 Hz, neonatal EEG is known to follow a spectral power law, with a linear log-log spectral relation defined as $P(f) \propto 1/f^{\alpha}$,[19] where α represents the slope of spectrum. The fractal dimension estimate D provides an estimate of this slope, as $\alpha = 5 - 2D$.[20] rEEG was included as it quantifies peak-to-peak voltage.[21] rEEG was proposed as an alternative to amplitude-integrated EEG (aEEG) because there is no clear definition of aEEG and most EEG machines implement different versions of the aEEG algorithm.[18 22]

All features, except for the rEEG, are computed on a 32 s epoch of EEG with a 50% overlap. The median value over all epochs is used to summarise the feature. The median value is also used to summarise across the two channels. Parameter values for all features are in online supplementary table S1.

Mean values, SD, and minimum and maximum values were used to describe symmetrical data. Median, IQR, and minimum and maximum values were reported on non-Gaussian data.

Ethics

Antenatal written informed consent was obtained after maternal admission on the day of delivery.

RESULTS

Study participants

Fifty-two infants born by ECS at term were recruited. Forty-nine infants were included in the analysis. Three infants were excluded: one infant due to unexpected congenital malformation noted following delivery, one infant due to the need for positive pressure ventilation during newborn stabilisation, and another infant due to insufficient length of recording because of technical difficulties during recording. Thus, 49 infants were included in the analysis (figure 1). The median (IQR) gestation was 39 (38.7–39.1) weeks, and the median (IQR) birth weight was 3500 (3245–3742) g. Twenty-nine (59%) infants were male. Indication for ECS was prior caesarean section in the majority of cases (n=43, 88%), breech presentation (n=2, 4%), prior traumatic vaginal delivery (n=2, 4%) and maternal reasons (n=2, 4%). Two caesarean sections were performed under general anaesthesia and the remaining 47 under spinal anaesthesia (morphine and fentanyl). The median (IQR) age at time of initial EEG recording was 3.0 (2.5–3.8) min. No infant was compromised at birth. Five infants were admitted to the neonatal unit. The discharge diagnosis for all five infants was transient tachypnoea of the newborn, and all infants were discharged within the first 3 days of birth. Infant characteristics are summarised in table 1.

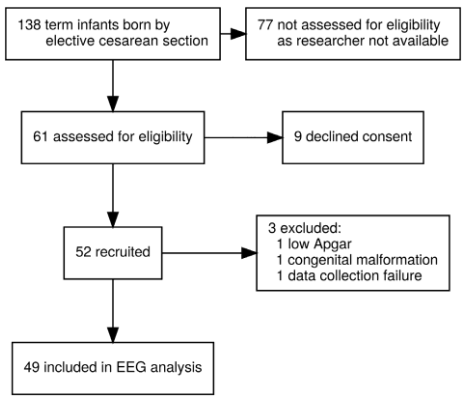


Figure 1 Flow diagram. EEG, electroencephalography.

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Table 1 Infant characteristics

	Median (IQR)
Gestation (weeks)	39.0 (38.7–39.1)
Birth weight (g)	3500 (3245–3742)
1 min Apgar score	9 (9–9)
5 min Apgar score	9 (9–10)

Visual analysis

Good-quality contiguous and symmetric mixed-frequency EEG activity appropriate for gestational age was seen in all infants with a range of 25–50 µV (see example in figure 2). Movement artefact contaminated many recordings, but EEG activity without artefact was measurable for a minimum of 3 min in all infants.

Quantitative analysis

Quantitative features are summarised in table 2. The total power decreased at the higher frequency bands: the median (IQR) relative delta power of 87.8% (83.7%–90%) indicates that the majority of power is within the delta band; the lowest relative power was in the beta band, with a median (IQR) of 2.5% (1.8%–3.6%). Almost all (95%) of the spectral power was below a median of 7.56 Hz (IQR: 6.17–9.76 Hz), as calculated by the spectral edge frequency. Figure 3 illustrates a power law spectrum, with decreasing power for increasing frequency, within the 0.5–30 Hz range for all infants' EEG. The median (IQR) fractal dimension of 1.1 (1.1–1.1) equates to a power law slope α of 2.8 (2.7–2.8). The median power law slope, in turn, equates to a log-log spectral slope of −28 dB/decade, as highlighted in figure 3. For the median values over all EEGs, lower and upper margins of the rEEG spanned from 14.5 to 63.3 µV with a median rEEG of 24.4 µV. Quantitative EEG features (reported as percentiles relating to overall distributions) for the two infants delivered under general anaesthesia are available in online supplementary table S2. The full data set of features is also freely available.[23]

DISCUSSION

This study describes, for the first time, detailed features of neonatal EEG during the immediate newborn transitional period. Good-quality mixed-frequency EEG was obtained within the first few minutes of birth, and we have produced quantitative EEG values for healthy newborn infants during the immediate newborn period. Approximately 20 per 1000 deliveries will require significant stabilisation measures, with biochemical and clinical evidence of perinatal asphyxia.[24] Of these, 1.5 per 1000 deliveries will go on to develop signs of evolving encephalopathy consistent with HIE.[25] Given the potential benefit of early treatment with TH, the need to identify infants with HIE in the immediate newborn period is becoming increasingly important.[26–28] However, to date our understanding of early newborn brain activity is based on studies in unwell infants, or in well infants after 3–6 hours of age.[1 13 20 28 29] Many infants with HIE are born at regional hospitals which do not offer TH and require transfer to a tertiary facility, resulting in a delay in the initiation of TH. To address this, many infants are cooled passively during transport from the regional hospitals.[30] It is therefore important that the correct infants are transferred and passively cooled. A simple method of assessing brain health at regional hospitals would also help to accurately identify those infants that require transfer to a tertiary centre.

Pichler *et al* performed aEEG in infants >34 weeks' gestation following ECS.[31] Recordings were feasible after 3 min in some infants. However, reliable data were difficult to obtain in their initial study. Low EEG values during immediate transition after birth concurrently showed low cerebral oxygenation values, but with associated increased cerebral oxygen extraction.[32] These studies, along with the current study, show that EEG monitoring is feasible immediately after delivery. However, aEEG is useful for examining gross trends rather than specific neurophysiological states at a point in time and requires expertise to interpret well. As mentioned previously, signal processing used in the aEEG algorithm eliminates much of the detail (eg, frequency band content) available in the EEG and many clinically important features are lost.

Neonatal EEG can be assessed both qualitatively and quantitatively. Qualitative EEG analysis is mainly used for clinical purposes. It is based on visual interpretation of the EEG signal and describes such background features as amplitude, frequency, continuity, variability, symmetry and synchrony of the EEG. Reference values within the first 12 hours of age are available for healthy term newborns.[13]

Quantitative EEG analysis is a method predominantly used in research studies and includes time and frequency domain analysis. Quantitative analysis allows for standardised reporting of EEG features, which is imperative when establishing potentially new reference ranges. Crucial to this standardisation process is a precisely defined set of quantitative features, including implementation and parameter details. These details are available in [18] and in online supplementary table S1 and S2. Quantitative analysis can also be used to objectively grade baseline EEG activity in sick newborn infants,[33] and can provide decision support with EEG analysis when clinical neurophysiologists are not available.

We found that the acquisition of the EEG in the immediate newborn period was feasible using a commercially available EEG system. We have also shown that mixed-frequency EEG can be obtained in healthy infants during the immediate newborn period. Activity with an amplitude of 25–50 μV was seen in all healthy term infants immediately after birth. These values are lower than those from say FP1-C3 as the interelectrode distance is double. Early EEG suppression has been reported in infants following hypoxic ischaemic injury and is associated with poor long-term outcomes.[34 35] Quantitative analysis has value in differentiating between HIE grades.[36] We have documented quantitative values

Table 2 Quantitative features of the EEG

	Median	IQR	95th percentile range
Power 0.5–4 Hz (μV^2)	70.5	42.8–171.4	22.3–846.4
Power 4–7 Hz (μV^2)	5.0	2.7–10.3	1.6–34.8
Power 7–13 Hz (μV^2)	3.3	1.7–6.2	0.9–24.9
Power 13–30 Hz (μV^2)	2.5	1.2–4.6	0.5–15.9
Relative power 0.5–4 Hz (%)	87.8	83.7–90.0	72.4–96.0
Relative power 4–7 Hz (%)	5.9	4.9–7.4	2.2–14.7
Relative power 7–13 Hz (%)	3.6	2.8–5.0	1.0–8.0
Relative power 13–30 Hz (%)	2.5	1.8–3.6	0.7–6.8
Spectral edge frequency (Hz)	7.56	6.17–9.76	2.93–14.10
Fractal dimension	1.11	1.10–1.13	1.08–1.18
rEEG: median (µV)	24.4	19.0–31.9	14.9–56.3
rEEG: lower margin (µV)	14.5	11.1–18.3	8.5–29.7
rEEG: upper margin (µV)	63.3	42.1–93.0	28.4–199.8
rEEG: asymmetry	0.52	0.39–0.67	0.26–0.82

EEG, electroencephalography; rEEG, range EEG.

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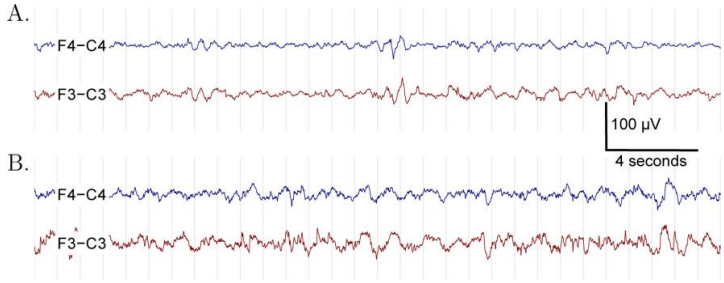


Figure 2 Examples of electroencephalography from two infants in A and B.

for amplitude, frequency and rEEG during newborn transition. As this is the first study to provide such values, it is difficult to make comparisons. Total and relative spectral power change over time in infants as they mature,[37] and we found that the majority of power in the frontal and central regions was in the delta EEG band during newborn transition. A prior study by our research group reported quantitative features for healthy term infants during active and quiet sleep in the first day of life.[13] The mean (SD) relative delta power was 73% (5%) and 80% (4%) during active and quiet sleep, respectively, suggesting again that the majority of power was in the delta band.

This study has a number of limitations. We did not include data on the exact timing of cord clamping in each baby. All of our previous publications have been based on recordings from similar electrode positions, and therefore our results directly compare with reference values that we have recorded in older term newborns.[13 34 36] However, brain activity was not assessed in more posterior regions, such as parietal, which is often typical in limited channel EEG recordings. Infants were monitored for relatively short periods of time. Longer EEG monitoring and serial studies within the early postnatal period might be useful. However, such studies are challenging in the immediate newborn period and we were reluctant to interfere with newborn bonding and the establishment of newborn feeding. The number of infants recruited was small. However, quantitative analysis produced values which had ranges within expected norms in our homogeneous study group. Further studies are required to assess whether brain activity differs by mode of delivery, delivery room interventions or stabilisation methods used. EEG monitoring in the delivery room may have a key role to play in the early identification of those infants with mild perinatal asphyxia who may benefit from immediate intervention, but again significantly larger studies are required. While EEG may also have the potential to direct therapy in the delivery room, in particular cessation of resuscitative efforts, there is an absolute lack of data in this regard and we would not advocate such an approach.

To our knowledge, this study is the first to describe normative quantitative EEG data in healthy full-term infants immediately after birth. These findings are relevant and clinically important. TH should be administered to newborn babies with HIE within the first few hours of birth, and delivery room EEG may help identify those babies that are most suitable for treatment, especially infants with clinically suspected mild encephalopathy. However, further trials are now warranted to assess the utility of EEG recordings during newborn transition in infants with suspected encephalopathy.

In neonates with encephalopathy, the severity of the encephalopathy can be estimated using a limited number of EEG channels as the goal is not to identify seizures but to estimate if EEG activity is present and to grade this activity, that is, mild, moderate or severe grades. In addition, only a short recording (1–2 min) is needed to establish the presence of activity and the grade. As advances in machine learning using EEG continue, it is only a matter of time before software to automatically grade newborn EEG is available.[33 38] This, combined with easy-to-use

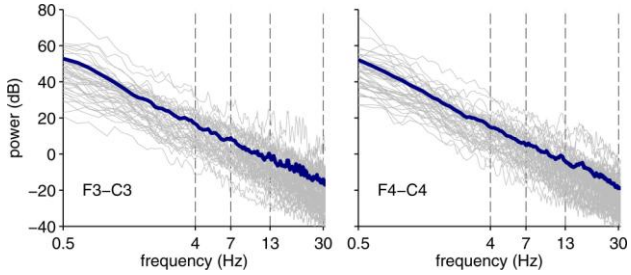


Figure 3 Power spectral density (PSD) estimates for both channels of the electroencephalography (EEG) within the 0.5–30 Hz frequency range. The thin grey lines represent the PSD for each infant's EEG, and the thick blue line is the mean across all infants (n=49). The PSD is estimated using the Welch's method with an 8 s Hamming window and 75% overlap for approximately 3 min of EEG. Both plots highlight a linear log-log spectrum known as a power law spectrum.

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neonatal EEG acquisition sensors, will make EEG monitoring in the first minutes after delivery even more possible.

In conclusion, we have shown that the EEG recording in the delivery room is feasible and brain activity can be recorded in the first few minutes after delivery. We have produced quantitative values for EEG in the frontal and central regions during very early newborn transition for the first time. Future trials will need to assess the role of EEG monitoring in the first minutes of life in infants at risk of encephalopathy to assess its clinical utility.

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Contributors GBB, EMD and DF conceived and designed the study. DF performed all data collection. JMO'T performed the quantitative analysis of data. GBB performed the visual analysis of data. DF and JMO'T drafted the initial manuscript. All authors interpreted the data, edited the manuscript for intellectual content and approved the final version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests None declared.

Patient consent Parental/guardian consent obtained.

Ethics approval Ethical approval was obtained within each participating country according to their national guidelines.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement EEG in its raw format for all infants in this trial is saved on a secure server in University College Cork. In this article we publish all of the findings resulting from the qualitative and quantitative analyses of data.

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Respiratory adaptation in term infants following elective caesarean section

Daragh Finn,[1,2] Julie De Meulemeester,[1] Lisa Dann,[1] Ita Herlihy,[1,2] Vicki Livingstone,[2] Geraldine B Boylan,[1,2] C Anthony Ryan,[1,2] Eugene M Dempsey[1,2]

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[1]Department of Paediatrics and Child Health, Cork University Maternity Hospital, Cork, Ireland
[2]Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Cork, Ireland

Correspondence to
Dr Eugene M Dempsey, INFANT Research Centre, Cork University Maternity Hospital, University College Cork, Cork, Ireland; g.dempsey@ucc.ie

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ABSTRACT

Objective To determine respiratory rate (RR), tidal volume (TV) and end-tidal carbon dioxide ($EtCO_2$) values in full-term infants immediately after caesarean section, and to assess whether infants that develop transient tachypnoea of the newborn (TTN) follow the same physiological patterns.

Design and patients A Respironics NM3 Monitor (Philips, Netherlands) continuously measured RR, TV and $EtCO_2$ for 7 min in infants >37 weeks' gestation following elective caesarean section (ECS). Monitoring was repeated at 2 hours of age for 2 min. Gestation, birth weight, Apgar scores and admissions to neonatal unit were documented.

Setting The operative delivery theatre of Cork University Maternity Hospital, Ireland.

Results There were 95 term infants born by ECS included. Median (IQR) gestation was 39 weeks (38.2–39.1) and median (IQR) birth weight 3420 g (3155–3740). Median age at initiation of monitoring was 26.5 s (range: 20–39). Data were analysed for the first 7 min of life. Mean breaths per minute (bpm) increased over the first 7 min of life (44.31–61.62). TV and $EtCO_2$ values were correlated and increased from 1 min until maximum mean values were recorded at 3 min after delivery (5.18 mL/kg–6.44 mL/kg, and 4.32 kPa–5.64 kPa, respectively). Infants admitted to the neonatal unit with TTN had significantly lower RRs from 2 min of age compared with infants not admitted for TTN.

Conclusions TV and $EtCO_2$ values are correlated and increase significantly over the first few minutes following ECS. RR increases gradually from birth, and rates were lower in infants that develop TTN.

What is already known on this topic?

- During the first minutes of life, newborn infants must establish functional residual capacity to allow gas exchange.
- Following normal vaginal delivery, tidal volume and end-tidal CO_2 increase over the first minutes of life and are correlated.
- Rates of caesarean section are increasing and are associated with increased frequency of transient tachypnoea of the newborn (TTN).

What this study adds?

- Following caesarean section, tidal volume and end-tidal CO2 are correlated, with both increasing over the first 3 min of life before stabilising.
- Infants admitted with TTN were found to have lower respiratory rates after the first 2 min compared with infants not admitted.

INTRODUCTION

Our understanding of newborn respiratory adaptation is the result of many innovative clinical trials and collaborative efforts over the past 60 years.[1–8] Lung aeration and the establishment of functional residual capacity (FRC) are critical in newborn transition from fetal life.[1]

In recent years, technological advances in neonatal monitoring have facilitated real-time monitoring of physiological parameters during newborn transition.[9 10] Dawson and colleagues produced centile charts detailing the normalisation of oxygen saturations over time during newborn adaptation, and these findings have directly affected oxygen therapy during newborn stabilisations.[11] More recently, Schmolzer and colleagues used respiratory function monitors (RFM) to document exhaled CO_2, and tidal volumes (TV) for term infants immediately after vaginal deliveries.[12]

However, gaps in our understanding of newborn adaptation remain. Respiratory function monitoring values in infants born by elective caesarean section (ECS) and thus not exposed to the mechanical and hormonal adjustments that occur during labour and vaginal delivery have not been reported. Rates of caesarean section have increased in recent decades, despite their association with increased neonatal respiratory complications when compared with vaginal delivery.[13] Transient tachypnoea of the newborn (TTN) accounts for the majority of neonatal unit (NNU) admissions in infants following ECS.[14 15] The aim of this study is to define newborn physiological ventilation parameters (respiratory rate (RR), TV, end-tidal carbon dioxide ($EtCO_2$)) over the first minutes of life in healthy-term infants following ECS, and also to assess whether infants that develop TTN follow the same physiological patterns.

METHODS

We recruited infants born in Cork University Maternity Hospital (CUMH), Ireland over 4 months between May–June and September–October 2015. CUMH is a tertiary university maternity hospital with approximately 8500 deliveries annually. Infants >37 weeks' gestational age, born by ECS, were eligible for inclusion in the study. Infants with

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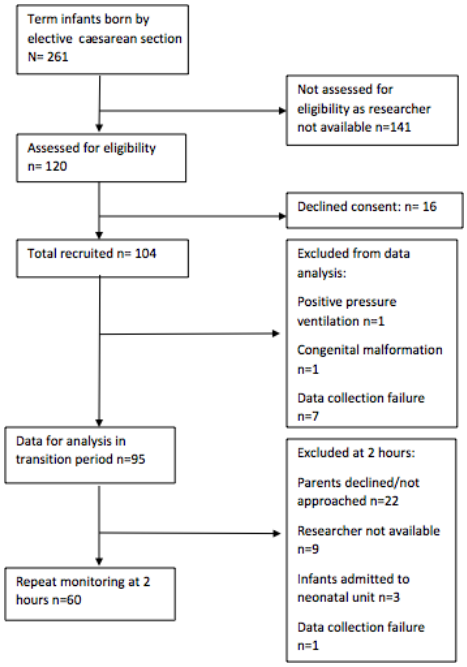


Figure 1 Flow diagram.

major congenital abnormalities affecting newborn respiratory adaptation were excluded. Infants requiring intervention to support stabilisation beyond being warmed, dried and stimulated or Apgar scores <7 at 1 min were also excluded from the study.

Following delivery, infants were brought immediately to a Panda Resuscitator (GE Healthcare, Laurel, Maryland, USA) which has a continuous-flow, pressure-limited, T-piece device with a built-in manometer and a positive end expiratory pressure (PEEP) valve. We used a Respironics NM3 Monitor (Philips, Amsterdam, Netherlands), which is a non-invasive RFM with combined mainstream capnography and flow monitoring (Capnostat 5 sensor, Philips). The dead space volume as reported by the manufacturer is ~1 mL. The CO_2/flow sensor was attached to a face mask (Laerdal infant mask; Stavanger, Norway) and placed over the infants' mouth and nose on arrival to the resuscitator. Each infant was monitored for up to 10 min. EtCO2 was measured by infrared absorption spectroscopy, while RR, TVs and airway pressures were measured by a gas flow sensor (Capnostat 5 sensor). All infants included in the study were breathing spontaneously without additional flow or oxygen. As all infants were born by caesarean section, monitoring did not interfere with skin-to-skin time or initiation of breast feeding. Follow-up RFM was performed, where appropriate, for 2 min at 2 hours of age using the same RFM.

All measurements were performed by one of the authors (DF, JdM, LD, IH) following a standardised protocol. Each infant was video recorded during study measurements. Recordings were commenced once an infant's whole body was delivered and captured infants once they were placed on the resuscitaire. This allowed for future accurate documentation of the age (in seconds) when monitoring commenced. There is no hospital protocol on the timing of umbilical cord clamping following ECS, and timing of clamping was not influenced by this research study. We did not record the time of cord clamping. Maternal and infant demographics were recorded. Newborn admissions to the NNU and discharge diagnosis on chart review were also documented. Specifically, a diagnosis of TTN was based on initial presentation, chest X-ray findings, inflammatory markers and clinical course.

DATA COLLECTION AND STATISTICAL ANALYSES

For the duration of each recording, a breath-by-breath analysis was exported from the Respironics NM3 Monitor (Philips) to SAS, V.9.4 (SAS Institute, Cary, North Carolina, USA). RRs, TV, inflation time and $EtCO_2$ means were calculated for each minute of the recording, starting from time of birth. In our initial study design, we had expected to record all infants for the first 10 min of life. However, the practical needs requiring infants to be weighed, dressed and brought to their parents within the time constraints of a busy obstetric theatre led to many recordings being terminated early and we did not report beyond the first 7 min. Breaths were excluded if mask leak was >30%. At each minute time point, the data for the features were summarised descriptively using the number of observations (n), mean and SD.

To investigate how each feature (RR, TV and EtCO2) changed over time, a mixed modelling approach was used. The optimal functional form of the trajectory over time was identified by considering the family of polynomial functions (a straight line, a quadratic curve and a cubic curve),[16] and identifying the best fitting model. A bottom-up strategy was used,[17] beginning with an empty random intercepts model (no fixed effects and individual as a random effect) and then adding each fixed time effect (linear, quadratic, cubic), followed by its corresponding random time effect (linear, quadratic, cubic), in turn. Likelihood ratio tests were used to compare the difference between the deviance statistics across consecutive models to test the impact of each new term. Model fit was evaluated using the deviance statistic (−2 log likelihood) and the Akaike Information Criterion. For each feature, the predicted values from the best-fitting mixed model and their corresponding SE were used to construct a 95% reference range, assuming a normal distribution. For all analysis, time was centred at 1 min (start of study). To investigate if changes over time differed by admission group (admitted/not admitted), the fixed effects of admission group and the interactions of admission group by time (linear, quadratic and cubic, as appropriate) were added to the mixed model. Pearson's correlation coefficient was calculated between RR, TV and $EtCO_2$ for each time point and between the first minutes of $EtCO_2$ and the 2-hour values. All statistical analyses were performed using PROC MIXED in SAS, V.9.4 (SAS Institute). All tests were two-sided and a p value <0.05 was considered to be statistically significant.

RESULTS

Study participants

One hundred and four infants born by ECS at term were recruited. Ninety-five infants were included in the analysis (figure 1). One infant was excluded due to unexpected congenital malformation

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Table 1 Descriptive statistics of features at each time point

Minutes after birth	RR (breaths per minute)			TV (mL/kg)			$EtCO_2$ (kPa)		
	n	mean	(SD)	n	mean	(SD)	n	mean	(SD)
1	88	44.307	(14.538)	87	5.180	(2.467)	84	4.315	(1.151)
2	86	48.209	(11.831)	87	5.713	(2.215)	85	5.303	(1.138)
3	90	53.006	(15.000)	91	6.442	(2.077)	89	5.635	(1.224)
4	89	57.109	(15.091)	90	6.257	(2.377)	88	5.631	(1.265)
5	94	57.686	(16.710)	93	6.051	(2.436)	93	5.481	(1.363)
6	87	61.554	(16.284)	86	5.869	(2.503)	83	5.516	(1.321)
7	68	61.618	(18.294)	67	5.070	(2.507)	65	5.741	(1.376)

ETCO2,end-tidal carbon dioxide; RR,respiratory rate; TV,tidal volume.

noted following delivery, and one infant due to the need for positive pressure ventilation (PPV) during newborn stabilisation. The Respironics RFM stored measurements sequentially for each infant breath. However, for seven infants, measurements were not automatically saved from the beginning of the recording and the timing of subsequent values recorded could not be fully ascertained. Therefore, these infants were excluded from the data analysis. The median (IQR) gestation was 39 weeks (38.2–39.1) and median (IQR) birth weight was 3420 g (3155–3740). Forty-seven (49%) infants were male. Indication for ECS were prior caesarean section n=81 (85%), breech presentation n=8 (8%), prior traumatic vaginal delivery n=5 (5%), IVF pregnancy n=1 (1%). Median time from birth until initiation of monitoring was 26.5 s (range: 20–39). Nine infants were admitted to the NNU. The discharge diagnosis for all nine infants was TTN.

Measures of TV, RR and $EtCO_2$

It was intended for measurements to be performed on all infants (n=95) for the first 10 min of life. However, for practical reasons, many recordings were terminated early and we do not report beyond the first 7 min of life. The mask was removed and replaced on a number of occasions for each baby due to loss of seal, movement of newborn and/or presence of secretions. These values (12% of all breaths) were omitted from the analysis and the mixed model effect analysis was used to account for these over time.

Descriptive statistics for RR, TV and $EtCO_2$ at each time point are presented in table 1. Mean RR increased for each time point between 1 min (44.31) and 7 min (61.62) of life. Mean TV increased over the first 3 min (5.18 mL/kg–6.44 mL/kg) and then decreased over time (5.07 mL/kg at 7 min). Mean $EtCO_2$ measurements also increased over the first 3 min (4.32 kPa–5.64 kPa) and then stabilised (5.74 kPa at 7 min). The mixed modelling approach found that the trajectories for mean RR, TV and $EtCO_2$ changed significantly over the first minutes of life. The best fitting models included fixed cubic time effects and random cubic time effects for TV and $EtCO_2$ and a fixed quadratic time effect and a random quadratic time effect for RR. The results of random effects regression models for RR, TV and $EtCO_2$ can be seen in online supplementary tables 1–3 . Trends over time can be appreciated in figures 2–4.

Repeat $EtCO_2$ monitoring was performed at 2 hours of age (n=60). The aim was to repeat monitoring between 120 and 130 min of life. However, 22 parents either declined verbal consent or were not approached during this time as monitoring would have interrupted feeding attempts which we had agreed a priori not to interfere with. No statistically significant correlations were found between the $EtCO_2$ values in the initial recording and 2-hour values at any time point (p>0.05 for all Pearson's correlation coefficients, online supplementary table 4).

Correlations between RR, TV and $EtCO_2$

Pearson's correlation coefficients between pairs of features were calculated for each time point (minutes 1–7 separately, online supplementary table 5). TV and $EtCO_2$ are positively correlated, while no correlation between TV/RR nor $EtCO_2$/RR exists.

Admissions to neonatal intensive care unit

Nine infants were admitted and 86 were not admitted. The trajectory of $EtCO_2$ did not differ by admission group (p=0.970 for admission; p=0.934 for admission*time; p=0.793 for admission*$time^2$; p=0.743 for admission*$time^3$). The trajectory

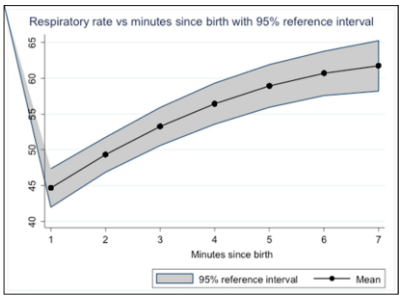


Figure 2 Respiratory rate (breaths per minute) between 1 and 7 min after birth.

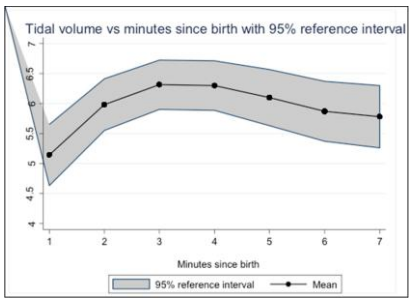


Figure 3 Tidal volume (mL/kg) between 1 and 7 min after birth.

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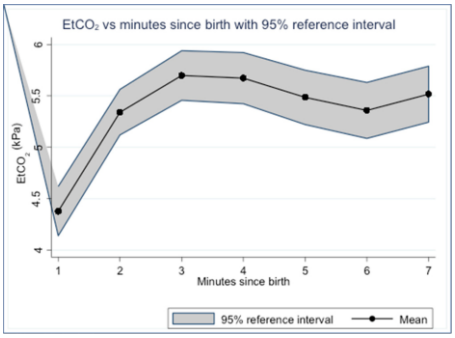


Figure 4 End-tidal carbon dioxide ($EtCO_2$) (kPa) between 1 and 7 min after birth.

of TV did not differ by admission group (p=0.315 for admission; p=0.433 for admission*time; p=0.451 for admission*time^2; p=0.456 for admission*time^3). The trajectory of RR did differ by admission group (p=0.215 for admission; p=0.020 for admission*time; p=0.095 for admission*time^2)(figure 5). Overall, after 2 min of life, infants admitted had lower RRs when compared with infants not admitted.

DISCUSSION

This study describes changes in RR, TV and $EtCO_2$ over the first minutes following elective caesarean section in a large number of healthy-term infants. Following delivery, the trajectories of TV and $EtCO_2$ correlated, with both increasing over the first 3 min. RRs increased continuously from birth until recordings ceased. Infants admitted with TTN were found to have lower RRs after the first 2 min compared with infants not admitted.

Over the past 50 years, a number of novel studies have informed our understanding of how newborn infants clear fluid from their lungs and establish FRC to facilitate gas exchange.[2 5 7 18 19] However, for compromised newborn infants requiring to establish FRC, normative ranges for rates, volumes, pressures or gas exchange are not available. Effective face mask PPV can be challenging, and may be unsuccessful secondary to mask leak or airway obstruction. Conversely, it may cause lung damage secondary to overzealous TV administration.[20 21] Portable RFM can accurately provide real-time information on volumes, pressure and exhaled CO_2 in newborn infants and can aid in the recognition of obstruction, leak and high TVs.[22] For RFM to be of true value during newborn stabilisation, we must first establish normative values for these parameters.

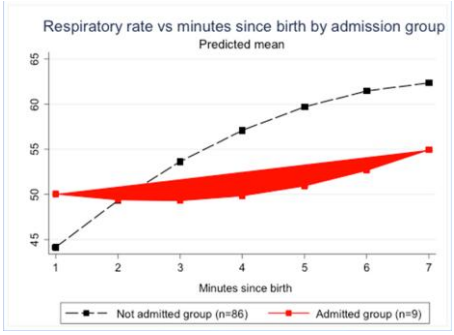


Figure 5 Respiratory rate over time by admission group.

Schmolzer *et al* performed RFM in 20 term infants during the first 2 min of life following vaginal delivery.[12] They found that FRC is partially established soon after delivery and exhaled CO_2 can be detected within 1–8 breaths after birth. Similar to our findings, CO_2 levels were closely associated with TVs and increased as FRC was established over the first few minutes. Similar absolute values for TV and $EtCO_2$ are also reported in their study, but peak levels were reached earlier in their cohort of infants following vaginal delivery. $EtCO_2$ peaked at 3 min in our cohort at mean values of 5.69 kPa, while Schmolzer *et al* reported exhaled CO_2 values of 5.73 kPa at 2 min. TV of 6.3 mL/kg were reached at 2 min in Schmolzer's cohort. Similar volumes (when corrected for mean weights) were reached at 3 min in our infant cohort. These findings are not surprising, as previous studies have described variations in transition between infants born by caesarean section and vaginal delivery.[4 8]

Newborn transition begins prior to delivery for infants born following spontaneous vaginal labour.[23 24] FRC was established later in infants following caesarean section compared with vaginally delivered infants in studies using plethysmography.[4] Our findings in infants born by caesarean section support this work. Increased interstitial pulmonary fluid in these infants may delay the establishment of FRC and time to reach optimum gas exchange levels. However, our cohort had peak levels of $EtCO_2$ at 3 min while Palme-Kilanders' cohort of infants born by caesarean section had increasing levels of CO_2 over the first 5 min, which is delayed compared with our findings. Comparisons between historical studies may not be appropriate as they all had small study numbers, high levels of intervention in the DR and relied on chart-based analogue equipment compared with current digital RFM.

RRs increased continuously over time during our study and plateau levels were not captured during the first 7 min. Interestingly, we found that infants admitted to the NNU with TTN had lower RRs compared with infants not admitted. This may imply that infants with a higher respiratory drive following delivery are less likely to develop TTN. It is somewhat surprising that the trajectory of RR differed but $EtCO_2$ did not, given that CO_2 elimination should be reflected by the minute volume. However, only a small number of infants were admitted to the NNU (n=9) from this cohort and these results would need confirmation in a larger study. Also, respiratory patterns were not studied, and may be more important than the actual rate in clearing interstitial fluid. The interpretation of newborn $EtCO_2$ may also be affected by different respiratory patterns such as expiratory braking, which is common in newborn infants, and occurs when expiratory flow is followed by a period of low or absent flow and results in short or multiple expiratory flow peaks.[1]

This study has a number of limitations. The Respironics RFM recorded values on a breath-by-breath basis, which allowed for accurate documentation of values and to monitor the progression of physiological parameters over time. However, an intrinsic error within the monitoring system resulted in the monitor failing to record all measurements, with up to 3% of breaths being missed in an individual baby. A mixed model analysis was performed to allow for missing data entries. The mixed model has the advantage over other statistical tests (such as a repeated one-way analysis of variance) as it uses all available data, and infants are not excluded

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from the analysis if they are missing data at some of the time points. However, seven infants were excluded as initial breaths were not recorded and the timing of the values that were recorded could not be ascertained. Also, many recordings were terminated early for practical reasons and we were unable to report findings beyond the first 7 min of life. These limitations highlight the challenges in performing such studies in the immediate newborn period. It must also be noted that monitoring is associated with additional dead space, which may theoretically increase the work of breathing and confound results.

In conclusion, this study documents for the first time values for RR, TV and $EtCO_2$ during newborn transition following ECS in a large cohort of healthy -term infants. These findings provide valuable information pertaining to physiological respiratory parameters during newborn transition to extrauterine life following ECS. The results of this study may provide values, which may be useful for physicians utilising respiratory function monitoring to guide term newborn stabilisations. However, future trials are required to quantify whether there are short-term or long-term outcome benefits from such respiratory function monitoring during newborn stabilisations.

Contributors DF designed the study, carried out the data collection, drafted the intial manuscript and revised the final manuscript. JDM, LD, and IH helped design the study, and carried out data collection, revised and critically assessed the final manscript. VL carried out the data analysis and drafted the manuscript. GBB critically reviewed and revised the manuscript. CAR and EMD supervised and assisted with the design of the study, data collection instrument, and critically reviewed and revised the manuscript. All authors interpreted the data, edited the manuscript for intellectual content and approved the final version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REVIEW
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Enhanced Monitoring of the Preterm Infant during Stabilization in the Delivery Room

*Daragh Finn[1,2], Geraldine B. Boylan[1,2], C. Anthony Ryan[1,2] and Eugene M. Dempsey[1,2]**

[1] Department of Paediatrics and Child Health, University College Cork, Cork, Ireland, [2] Irish Centre for Fetal and Neonatal Translational Research, University College Cork, Cork, Ireland

Monitoring of preterm infants in the delivery room (DR) remains limited. Current guidelines suggest that pulse oximetry should be available for all preterm infant deliveries, and that if intubated a colorimetric carbon dioxide detector should provide verification of correct endotracheal tube placement. These two methods of assessment represent the extent of objective monitoring of the newborn commonly performed in the DR. Monitoring non-invasive ventilation effectiveness (either by capnography or respiratory function monitoring) and cerebral oxygenation (near-infrared spectroscopy) is becoming more common within research settings. In this article, we will review the different modalities available for cardiorespiratory and neuromonitoring in the DR and assess the current evidence base on their feasibility, strengths, and limitations during preterm stabilization.

Keywords: preterm, newly born infant, monitoring, neuromonitoring, delivery-room, stabilization, resuscitation

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Elizabeth Foglia,
University of Pennsylvania School of Medicine, USA

****Correspondence:***
Eugene M. Dempsey
g.dempsey@ucc.ie

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KEY POINTS

Current ILCOR Guidelines recommend for all preterm infant deliveries:

- Pulse oximetry for SpO_2 monitoring and titration of O_2 therapy
- Pulse oximetry and consideration of ECG as an adjunct for heart rate monitoring
- CO_2 detectors to verify correct endotracheal tube positioning

INTRODUCTION

In recent decades, we have witnessed a significant increase in the number of monitoring options for preterm infants in the neonatal intensive care unit (NICU) setting. Examples include cardiac (echocardiography and non-invasive cardiac output monitoring), respiratory (capnography and respiratory function monitoring), and neurological monitoring [electroencephalography (EEG) and near-infrared spectroscopy (NIRS)]. By contrast, over the same timeframe, monitoring of preterm infants in the delivery room (DR) has changed very little, other than the introduction of pulse oximetry approximately 10 years ago.

As adjuncts to clinical monitoring during initial preterm stabilization in the DR, the recent 2015 ILCOR recommendations advise the use of two objective assessment tools: (1) pulse oximetry (with or without ECG) to regulate oxygen delivery and (2) exhaled carbon dioxide (CO_2) detectors for confirmation of correct endotracheal (ET) tube placement (1). These two devices generate real-time accurate physiological data and, if recorded, chronicle changing observations over time.

The information provided assists in clinical decision-making and has the potential to improve both short- and long-term outcomes for preterm infants.

The relative lack of monitoring options in the DR is both a reflection of the difficulties in acquiring the information and interpreting these data for decision-making in real-time. As Bradley and Field reflected, "not all that is measurable is of value, and not all that is of value can be measured" (2). Introducing new monitoring devices into clinical care remains challenging. Feasibility studies are initially required to assess whether new devices can be applied safely, useful information acquired, interpreted, and acted upon in the simulation environment. Human factors need to be considered and evaluated prior to introduction of new technology into the clinical environment. This may involve additional team training, possibly in the form of newborn resuscitation simulations, and it should be highlighted that new devices should not distract team members from complying with current resuscitation recommendations. Preterm adaptation represents a unique physiological time in life. Ideally, both short- and long-term benefits should be evaluated by randomized controlled trials prior to the introduction of a new device into routine clinical care.

This review will present an overview of current methods of preterm newborn monitoring in the DR, from simple clinical evaluation to the potential role of newer monitoring devices, including monitoring cerebral activity and cerebral oxygenation during the first minutes of life (**Table 1**).

HISTORICAL CONTEXT: CLINICAL ASSESSMENT OF THE PRETERM INFANT AND THE APGAR SCORE

Dr. Virginia Apgar, in 1953, was the first to describe newborn monitoring in the DR in a methodical manner. *The Apgar score* is the sum of values based on the newborn respiratory (respirations, skin color), cardiovascular [heart rate (HR), skin color], and neurological (muscle tone, reflex irritability) systems (3). With the exception of HR, all of the variables are based on visual inspection of the infant and as such are somewhat subjective. Large cohort studies identified that 5-min Apgar scores of <7 were associated with increased risk of neonatal death and cerebral palsy in both term and preterm infants (4–6), indicating that early clinical assessments may be reliable and meaningful for newborn infants. On addressing the interrater variability of the score, Apgar reported that, "When two or more people decide independently, we find a range of one value above or below a decided score to be the widest variation" (7, 8). Currently, Apgar scores remain central to our interpretation of a newborn's condition at birth. They are routinely assigned to all infants in the immediate postnatal period and are usually collected as part of research trials both to assess baseline characteristics of study participants and in some cases as outcome measures. Newborn resuscitation guidelines advise initiating support during infants' transition based on the assessment of respirations, tone, and HR, which are all components of the Apgar score (9–11).

However, more recent studies have shown poor inter- and intrarater reliability with regard to Apgar score assignment, especially when the infant is preterm or ventilated (12, 13). The ability of the 5-min Apgar score to predict outcome seem less likely than previously thought. Singh et al. have shown that in very preterm infant delivery, there is no Apgar score cutoff below which "a burdensome outcome was assured or above which an unscathed outcome was likely." Five-minute Apgar score and HR values also displayed poor sensitivity and specificity for either survival or survival without disability (14). Manley and colleagues asked clinicians to predict the outcome of preterm infants (<26 weeks gestation) based on their clinical appearance in the DR, at prespecified time points of 20 s, 2 min, and 5 min. This study was based on video recordings of the preterm infants, and monitors displaying HR and oxygen saturation (SpO_2) values were visible. Trainees and staff neonatologists predicted infant survival poorly at each time point. The authors concluded that neonatologists' "reliance on initial appearance and early response

TABLE 1 | Summary of monitoring devices.

Variable	Monitor	Data acquisition feasible	Normative values established[a]	Comments	Strength of recommendation
SpO_2	Pulse oximeter	+	+	Accurate but unable to detect hyperoxemia	Class I
HR	Pulse oximeter	+	+	Accurate but time delay in data acquisition	Class I
	ECG	+	+	Rapid accurate data acquisition	Class I
Peripheral perfusion	Echocardiography/NICOM	+	–	Not assessed in preterm infants	Class III
	Perfusion index	+	+	Normative values highly variable in newborns	Class III
ETT position	CO_2 detector	+	n/a	Reduces time to confirmation of correct placement	Class I
Facemask ventilation effectiveness	CO_2 detector	+	n/a	Reduces mask leak and obstruction Further RCTs required	Class IIa
	Capnography	+	–	Reduces mask leak and obstruction Further RCTs required	Class IIa
	Respiratory function monitor	+	–	Reduces mask leak and obstruction Further RCTs required	Class IIa
Cerebral oxygenation	NIRS	+	+	Advise as part of further RCTs	Class IIb
Cerebral activity	EEG	+	–	Advise further feasibility trials and establishment of normative reference values	Class III

[a]*For preterm infants, <32 weeks gestation in the immediate newborn period.*

to resuscitation in predicting survival for extremely premature infants is misplaced" (15).

Updated Apgar scoring systems have been proposed and allow for more appropriate descriptions of the condition of the preterm infant at birth. The *Combined-Apgar score* reports the infants' score in each of the five components of the Apgar score (specified Apgar score), and the interventions required to achieve this score (expanded Apgar score) (16, 17). This combined-Apgar score has been shown to be superior in predicting outcome in preterm infants when compared to the conventional-Apgar score (18). However, this updated scoring system has yet to be universally adopted and the relevance of conventional Apgar scores in preterm infants remains limited.

OXYGEN SATURATION MONITORING

Clinically, infants transition from blue (cyanotic) to pink (normal oxygen saturations) in color during uncomplicated newborn transition. O'Donnell and colleagues assessed clinical perceptions of newborn infant color in the DR (19). They found wide variation in observations and concluded that, "clinical assessment of a newborn infant's color may be unreliable." Assessment of arterial oxygen saturation by *pulse oximetry* is based on the Beer–Lambert law that relates the attenuation of light to the properties of the materials through which the light is traveling; and photoplethysmography, a non-invasive optical technique used to detect blood volume changes in the microvascular bed of the tissue (20). Aoyagi and Kishi, who realized that oxygenated hemoglobin absorbs more light at infrared wavelengths and deoxygenated hemoglobin absorbs more light at red wavelengths, developed arterial oxygen saturation monitoring by pulse oximetry in 1972. The changes during systole and diastole in the ratio of red and infrared light energy absorption are used to produce the pulse oxygen saturation (21).

The device was first commercialized in 1981, and the use of pulse oximetry for continuous oxygen monitoring in newborns was first described in 1986 (22). The clinical benefits of pulse oximetry were quickly recognized, and it has become the mainstay of non-invasive, continuous SpO_2 monitoring in newborns (23). Oxygen saturation monitoring of preterm infants is now standard in the DR, and these values serve as a guide to stabilization (22, 23), and the titration of oxygen therapy in preterm newborn stabilization is now routine to achieve targeted saturations by 10 min of age (24, 25). Dawson and colleagues have published oxygen saturation percentile charts for the first 10 min of life (24). In their study of over 450 infants, they observed the SpO_2 values of preterm infants increased at a slower pace than term infants. At 5 min, the median (interquartile range) SpO_2 was 86% (80–92) in preterm and 92% (83–96) in term infants. They have published three sets of percentile charts based on gestation (>37, 32–37, and <32 weeks), which may guide neonatal teams in titrating oxygen therapy in the DR. However, these ranges were developed in a cohort of infants born when immediate cord clamping was frequently practiced following delivery. Smit and colleagues assessed over 100 term infants with delayed cord clamping and concluded that the Dawson curves are still relevant; however, they documented higher initial SpO_2 values, lower HRs, and a slower increase over the first 3 min of life (26).

Pulse oximetry has gained widespread acceptance in neonatal care over the past three decades because of its reliability, ease of use, and lack of heat-related complications. The main physiological limitation of pulse oximetry is the inability to detect hyperoxemia in the higher SpO_2 range (>90%) because of the shape of the oxygen–hemoglobin dissociation curve. Thus, relatively small increases in SpO_2 can be associated with a large increase in PaO_2 (27–29). This is particularly important for preterm infants receiving supplemental oxygen because of their vulnerability to oxygen toxicity and oxidative stress (30). Despite this limitation, pulse oximetry is the gold standard for monitoring oxygen saturation during preterm infant stabilization, and it should be used following all preterm deliveries.

HEART RATE MONITORING

Monitoring HR helps to guide newborn transition and the need for intervention in the DR. Current recommendations advise that HR should be assessed clinically, and if positive pressure ventilation is commenced HR should be monitored by pulse oximetry, with the option of additional ECG monitoring (1).

Although *clinical assessment of HR* by auscultation at the apex is more accurate than assessment by palpation of the umbilicus (31), all clinical assessments may misrepresent the actual HR. Kamlin et al. compared palpation and auscultation of HR to ECG determined HR in term newborns in the DR. They found that clinical assessments were inaccurate, and infant HR was underestimated when compared with ECG HRs (32). Hawkes et al. studied health-care professionals as they palpated a simulated pulsating umbilicus, listened to a tapping HR, or auscultated a simulated HR. They found that while study participants performed well at identifying HR > 100 beats per minute (bpm), almost two-thirds of participants failed to recognize a HR <60 bpm for all methods of assessment (33). These findings emphasize the importance of early accurate objective HR monitoring during preterm infant transition for identification of infants who may require support or active resuscitation (HR <60 bpm).

Pulse oximetry provides real-time accurate information about the HR of the preterm infant (34). However, pulse oximetry values are not available immediately as the sensor takes time to apply correctly and once applied, there is a delay before the monitor provides a reading. Limb perfusion will affect the time taken to achieve a pulse oximeter HR (34). Studies that have assessed the feasibility of obtaining prompt and reliable pulse oximetry readings have reported times to signal acquisition of between 1 and 2 min after delivery (25, 35). There is conflicting evidence as to whether quicker signal acquisitions are obtained by applying the sensor to the oximeter first or applying it to the infant first. Observational studies reported that the quickest method involved turning on the pulse oximeter prior to delivery, applying the sensor to the infant's right hand and then connecting the cable of the sensor to the oximeter. This results in mean readings within 25 s of reaching the resuscitation table in a research setting (35, 36). A recent RCT in the DR contradicted these findings and found significantly faster signal acquisition times in infants who

had the sensor attached to the oximeter first (37). A limitation of pulse oximetry HR monitoring is that HRs <100 bpm are not consistently detected, and in a study by Kamlin et al. were only reported 89% of the time (34).

ECG monitoring can provide accurate HR values sooner than pulse oximetry following delivery (34, 38). The electrodes can be applied quickly, and there is little lapse in time waiting for monitor readings to appear. Katheria and colleagues reported that median times to acquire a signal from ECG and pulse oximetry were 4 and 32 s, respectively (38). A limitation of ECG monitoring is the risk of pulseless electrical activity being misinterpreted as HR on ECG (39). *Doppler ultrasound* blood flow HR assessments in the DR are accurate compared with clinical and pulse oximetry assessments (40). Measurements can be taken through a polyethylene bag. However, clinical experience is required for accurate assessments and continuous measurements are not practical.

ECG monitoring cannot replace the need for pulse oximetry, which is necessary for SpO_2 monitoring. However, given that ECG monitoring is more accurate than clinical estimations, ECG may prevent unnecessary interventions secondary to falsely low clinical HR estimations. Alternatively, it could increase interventions, which may or may not be appropriate, because of earlier accurate bradycardia detection. Although awaiting further evidence, there are a few important points to be made: initiation of ECG monitoring in the DR is easily achievable, is more accurate than clinical assessment and provides HR values more expediently than pulse oximetry. Therefore, at present, our practice is to have ECG monitoring available, as an adjunct to SpO_2 monitoring, for all preterm deliveries <32 weeks gestation and in situations where advanced resuscitation is anticipated. Clinical trials are required to assess whether ECG monitoring affects the frequency of stabilization interventions, and ultimately whether its use affects stabilization outcomes.

PERIPHERAL PERFUSION MONITORING

Peripheral perfusion is determined by cardiac output and the caliber of the vessels transporting blood to the peripheries. Current clinical methodologies for non-invasive monitoring of peripheral perfusion include assessments of capillary refill time, peripheral temperatures, and palpation of peripheral pulses. Each method relies on subjective assessments and continuous measurements are impractical. *Blood Pressure monitoring* by Doppler and oscillometric methods are feasible in the DR and measurements for term infants have been reported (41). However, non-invasive measurements are not reliably consistent in preterm neonates, and invasive BP monitoring is not practical within the DR setting.

A recent review by Baik et al. identified four studies of *echocardiographic monitoring* during newborn stabilization (42). Each study assessed term infants only (43–46). Increased left ventricular output and stroke volume increased over the first 15 min of life (44–46) and one study reported an increase in left-to-right shunting across the ductus (46). The studies did not assess echocardiographic measurements of HR. The authors of the review concluded that echocardiographic monitoring in the DR would enhance our knowledge about "cardiac function changes" (42). However, it does not add useful clinical information during newborn stabilization, has not been assessed in preterm infants in the DR, and routine monitoring is not advised.

Non-invasive continuous cardiac output monitoring (NICOM) is an alternative method for assessing cardiac output in neonates. This technology is based on the assumption that changes in the resistance to electrical currents captured by electrodes on the thorax are directly related to changes in aortic volume during different stages of the cardiac cycle (30). NICOM measurements are feasible in neonates and correlate well with timed echocardiographic measurements (47, 48). However, NICOM may underestimate the actual CO value (47). Katheria and colleagues performed NICOM on 20 term infants during delayed cord clamping in the DR. They found that for the majority of infants, CO and stroke volume continued to increase in value from the second minute of life until the cord was clamped at 5 min (49). However, NICOM has yet to be assessed in preterm infants in the DR.

Perfusion index (PI) monitoring is a non-invasive method of assessing real-time peripheral perfusion, derived from, and displayed by the pulse oximeter. Pulse oximetry values are derived from red (660 nm) and infrared wavelengths (910–940 nm) (50). By using a third wavelength (800 nm), the overall hemoglobin content can be calculated and the pulsatile component of arterial blood can be distinguished from the non-pulsatile component (51). PI has been utilized to monitor preterm infants in a number of clinical areas (52). These include screening for congenital cardiac disease (53, 54), predicting low systemic blood flow (55), and assessing perfusion following blood transfusion (56). However, while PI values are easily obtained in the DR, and normative values for preterm infants in the first day of life have been published (57, 58), they are highly variable in the immediate newborn period, for both term and preterm infants (59). There are neither trials comparing PI and clinical assessments of peripheral perfusion in preterm care nor trials assessing whether PI monitoring affects preterm outcomes. Therefore, evidence in favor or against PI monitoring in the DR is lacking.

RESPIRATORY SUPPORT MONITORING

Lung aeration is a critical point in newborn transition from fetal life. Newborn preterm infants are at an increased risk of needing respiratory support following delivery. Inadequate ventilation may result in hypoxia and resultant bradycardia. International guidelines advise a stepwise approach to achieving optimal ventilation following preterm delivery and prior to escalating cardiovascular support; therefore, positive pressure ventilation is the cornerstone of neonatal resuscitation (60, 61). It is provided either by mask ventilation, single or double nasal prongs, nasopharyngeal tube, or *via* an ET tube. Adequate airway ventilation is assessed clinically by chest rise, an increase in HR, and auscultation for air entry on both sides of the lung fields during DR stabilization. Visual assessments of chest rise are not reliable (62). After initiating mask ventilation and if the clinical response is suboptimal, guidelines advise repositioning of the mask to reduce leak, and airway opening manoeuvers to combat airway obstruction. If there is no clinical improvement after such interventions a definitive airway,

in the form of ET intubation is advised (1). The mnemonic MRSOPA identifies these methods, improve *M*ask seal, *R*e-position the airway, *S*uction and/or *O*pen the mouth, increase the inflation *P*ressure, and consider an *A*lternative airway.

Monitoring ventilatory efficacy in infants in the NICU is achieved by monitoring carbon dioxide (CO_2) levels, which can be achieved by measuring either transcutaneous or exhaled CO_2 levels. There is very little information on CO_2 assessment at birth. Studies in the DR have focused on exhaled CO_2 detection, either by qualitative or semiquantitative disposable *colorimetric CO_2 detectors* that change color upon contact with CO_2, or *quantitative capnography that provides a breath-by-breath end tidal CO_2 measurement* (63). Quantitative capnography is achieved either by mainstream capnography that utilizes an infrared absorption technique or by side stream capnography that continuously transports a sample of gas to a sampling cell within a monitor. Both capnography methods provide a continuous visual display of CO_2 values (capnometry) (63). Absolute CO_2 values may be unreliable in the immediate newborn period prior to the establishment of functional residual capacity. The lungs are partially fluid filled with resultant low pulmonary blood flow, and mask leak or rebreathing may also affect absolute values. Therefore, during DR mask ventilation, members of the resuscitation team are advised to follow the CO_2 trace and not absolute CO_2 values.

CO_2 detectors are routinely used to aid in the assessment of correct ET tube placement (9). The use of CO_2 detectors reduces the time to confirmation of ET tube placement and has been endorsed in resuscitation guidelines (9, 64). Their use may be limited by false negative readings, during cardiopulmonary arrest and severe airway obstruction (65, 66). Employing quantitative capnography following ET tube placement also results in quicker and more accurate confirmation of correct placement when compared with clinical assessments (67, 68). There are no clinical trials comparing CO_2 detector and capnography use to confirm correct ET tube placement.

The use of CO_2 detectors during facemask ventilation has been shown to help determine airway patency on an almost breath-to-breath basis and can aid resuscitation teams in recognizing airway obstruction and leak during DR positive pressure ventilation (69–72). CO_2 detectors can also verify the efficacy of positive pressure facemask ventilation during sustained inflations, as practiced in some centers (73). However, CO_2 monitoring is not routine during mask ventilation. van Os and colleagues displayed the benefits of CO_2 detectors in helping resuscitation teams to recognize airway obstruction in 24 very low birth weight infants during positive pressure support in the DR (69). Quantitative capnography during mask ventilation has been shown to improve CO_2 elimination with the onset of an infant's respiratory efforts; however, other authors have not found that it reduces the occurrence of hypocapnia or hypercapnia (74, 75). In a recent mannequin study, quantitative capnography was superior to CO_2 detectors in improving efficacy of facemask ventilation (76). The results of the first clinical trial comparing the two methods of CO_2 detection have yet to be published (CAPNO trial, unpublished, ISRCTN registration number: 10934870).

In the DR, the user controls ventilation pressures delivered to the infants' lungs. The lungs of the preterm infant are susceptible to injury if exposed to high airway pressures. Immature animal models have shown that lung injury can occur after a few manual inflations at high pressure (77). On the other hand, facemask ventilation can be inadequate secondary to leak, even if the user is highly experienced (78, 79). In NICUs, ventilation adequacy can be assessed by *respiratory function monitors* (*RFMs*), which are incorporated into modern ventilators (80). They provide information not only on airway pressures but also on delivered tidal volumes. The monitor displays breathing pattern, tidal volumes, flow and pressure waves, and percentages of gas leak. RFMs have also been used to guide positive pressure ventilation in newborn resuscitations (81, 82). Schmolzer and colleagues found that RFM use during mask ventilation of preterm infants' results in significantly less leak, more mask adjustments and a lower rate of excessive tidal volume given (82). RFMs have also been used in a RCT, which displayed improved ventilation with masks compared with nasal tubes during stabilization of preterm infants (83). However, the use and interpretation of a RFM can be technically challenging for many inexperienced users. Milner and colleagues recently surveyed 51 neonatal trainees who had used RFMs during preterm stabilization (84). They found that the usefulness of respiratory function monitoring was dependent on the trainee's level of experience, and that appropriate responses to the RFM data were more frequent in the hands of senior clinicians compared with their junior colleagues. The composition of resuscitation teams may also play a role in the effectiveness of RFM use. Having an extra member present to interpret the RFM data and to advise on mask ventilation adjustments may improve its effectiveness but are difficult to justify in many centers with limited staff resources.

We look forward to further evidence on RFM use in preterm infants during DR stabilization, as they have the potential to monitor efficacy of ventilation while helping to protect premature lungs from unintended pressure related injury. However, at present, user difficulty remains a major limitation of RFM. In the meantime, we recommend that when positive pressure ventilation is initiated in the DR, consideration should be given to monitor ventilation efficacy. The superiority of which device has yet to be elucidated. Confirmation of ET tube placement should be confirmed with a CO_2 detector as per current international guidelines.

NEUROMONITORING

As survival rates and short-term outcomes continue to improve for preterm infants, focus has shifted on neuroprotection strategies. The recent SafeBoosC trial suggests that brain oxygenation monitoring in the NICU results in a reduction in the percentage of cerebral hypoxia sustained by preterm infants (85). At present, assessment of neurological well-being in the DR is based on clinical assessment alone. Assessments of muscle tone and reflex irritability are incorporated into the Apgar score (3). The brain is the most vulnerable organ in newborn infants. As survival of the most immature infants increase, concerns have been raised about increased risks of adverse neurodevelopmental outcomes (86, 87). Resuscitative measures should aim for the best possible neurological outcomes and a non-invasive, continuous measurement

of cerebral oxygenation and activity would be ideal, but these currently are not routine and their role has yet to be evaluated.

Studies that sought to introduce neurological monitoring into the DR initially focused on *cerebral blood flow* using Doppler measurements of cerebral or carotid arteries (44, 88–92). Monitoring was found to be technically difficult and did not provide continuous data (93). Furthermore, there is conflicting evidence on the role of cerebral Doppler in identifying impaired cerebral autoregulation and resultant abnormal cranial ultrasound findings (94, 95).

More recently, researchers have concentrated on *NIRS*, which provides non-invasive monitoring of cerebral tissue oxygenation (StO_2) (96–109). NIRS utilizes the transparency of biological tissue to light in the near-infrared spectrum to measure tissue oxygenation (110). Cerebral tissue oxygen saturations in preterm infants have been shown to correlate well with superior vena cava flow and left ventricular output in the first days of life (111, 112). A number of studies have displayed the feasibility of obtaining cerebral oxygenation values using NIRS in the DR (93), and normative values for infants not requiring resuscitation have been published recently (103). However, the vast majority of these infants were full term infants. **Table 2** summarizes the studies that have assessed NIRs in preterm infants in the DR.

Cerebral NIRS in the DR remains limited to research studies, but emerging data suggest that it may have a significant role in preterm stabilization in the future (113). NIRS measurements are readily obtained and, in a recent study conducted by this group, the NIRS values were obtained within seconds of application of the device in the DR, in contrast to the variable time for pulse oximetry readings. Binder et al. performed NIRS on 49 preterm infants in the immediate newborn period (100). They reported different StO_2 transition time courses for infants requiring respiratory support and those with normal transitions. Infants requiring respiratory support had lower StO_2 values over the first 10 min of life before reaching similar steady-state levels as their counterparts. Fuchs et al. reported StO_2 values for 51 infants weighing <1500 g (108). Low median StO_2 values (37%) were reported at 1 min of life, which continuously rose to steady-state levels (61–84%) at 7 min of age. StO_2 values did not differ in relation to the degree of resuscitation required in the DR, but it was noted that two infants with subsequent IVHs had StO_2 values that were <10th percentile for their cohort. Kenosi et al. evaluated transitional cerebral NIRS values in preterm infants <32 weeks and found that preterm infants requiring >30% oxygen to maintain peripheral saturations had a significantly higher degree of cerebral hypoxia (114). All infants initially received a FiO_2 of 0.3 and oxygen was titrated according to standard resuscitation guidelines. There were no differences in cerebral hyperoxia between the two groups. These findings suggest that some preterm infants may require a more rapid increase in oxygen titration in the DR. At present, NIRS remains in the realm of DR research, but as more studies emerge, we believe that it will have a future role in monitoring preterm infants and guiding oxygen titration during DR resuscitations. Pichler and colleagues have recently performed a pilot RCT, in which infants <34 weeks were randomized in the DR either to cerebral NIRS and SpO_2 monitoring or SpO_2 monitoring alone to guide titration of oxygen therapy (115). They found that additional NIRS monitoring significantly reduced the time that infants' cerebral StO_2 was <10th percentile in the first 15 min of life. There was no difference in rates of IVH or abnormal neurological assessments at discharge. Further trials are required to ascertain how oxygen therapy should be guided when StO_2 and SpO_2 values are both available in the DR.

Cerebral NIRS monitoring may also have a future in providing outcome measures for DR studies. A recent RCT randomized infants (28–33 + 6 weeks gestation) to receive either one to three sustained lung inflations (SLIs) (30 cmH_2O for 15 s) followed by standard respiratory care, or standard respiratory care only (116). Cerebral tissue oxygenation values were similar for both groups over the first 15 min of life. However, cerebral blood volume (CBV) patterns differed between groups. CBV decreased in the control group over time, but remained static in the intervention group who received SLIs. The authors hypothesized that differences may have been caused by impaired venous return secondary to increased thoracic pressures during SLI, with resultant cerebral

TABLE 2 | Summary of preterm DR NIRS studies.

Reference	Neonates	Number (*N*)	Design	Resuscitation group included	Observation
Fuchs et al. (109)	Preterm VLBW (<1500 g)	24	Observational	Yes All infants had SLI followed by CPAP	Increases in cerebral StO_2 and HR preceded increases in SpO_2 following SLI
Fuchs et al. (108)	Preterm VLBW (<1500 g)	51	Observational	Yes	Increases in cerebral StO_2 values from 1 to 7 min of life before steady-state values reached Percentile charts produced
Binder et al. (100)	Late preterm 30 + 0 to 36 + 6 weeks	42	Observational	Yes	StO_2 values were consistently higher in normal transitional group compared with stabilization group
Pichler et al. (103)	Term and preterm	*N* = 381 Preterm *n* = 27	Observational	No	Preterm infants post cesarean delivery had higher StO_2 than term infants Percentile charts produced
Kenosi et al. (114)	Preterm <32 weeks	47	Observational	Yes	Infants requiring FiO_2 > 3.0 had increased cerebral hypoxia, but no increase in cerebral hyperoxia compared to infants requiring FiO_2 < 3.0
Pichler et al. (115)	Preterm <34 weeks	60	RCT	Yes	Reduction in cerebral hypoxia burden in group with NIRS and SpO_2 monitoring in the DR

venous stasis. These findings highlight the importance of assessing cerebral hemodynamics during interventional DR studies.

Electroencephalography provides a real-time measure of electrocortical brain activity and has become more common in NICUs over the past two decades. In contrast to cerebral blood flow and NIRS, EEG has well-documented applications for the clinical management of newborn infants (117). Its usefulness includes monitoring infants with perinatal asphyxia (118–121), the detection of seizures (122–124), and more recently in assessing the long-term prognosis of both full term and preterm infants (125).

Despite its importance in monitoring the newborn brain in the NICU, only one study has assessed the feasibility of EEG monitoring in the DR. At present, we resuscitate infants at gestational ages that are at the borderline of viability without any information about brain activity. Pichler et al. performed aEEG (a modified form of EEG recording that filters, rectifies, amplifies, and compresses one to two channels of EEG activity) in infants >34 weeks gestation following elective cesarean section and achieved recordings after 3 min in some infants. However, continuous reliable data were difficult to obtain within their study of 63 infants (102). The two main factors restricting the introduction of EEG into the DR have been (1) the technical difficulties in acquiring reliable data in this setting and (2) the ability of people to interpret the data (93). Technical difficulties can be overcome especially given the recent introduction of easy to apply neonatal EEG sensors. The recent increase in research aiming to develop novel algorithms for neonatal EEG interpretation will also have an impact on DR brain monitoring in the near future (126). Further trials are required to assess the feasibility and utility of EEG recordings during transition for preterm infants.

VIDEO RECORDING

Video recordings provide objective measures of DR performance in the stabilization of preterm infants and can be utilized for education, research, and audits. Fifteen years ago, Carbine and colleagues reported that video recordings in the DR are feasible quality assurance tools (127). Video recordings can help assess neonatal teamwork in the DR, facilitate debriefings, and improve performance (128, 129).

Video analysis of newborn resuscitation and stabilization has shown that the availability of real-time information is less than optimal when compared with recommended guidelines (127, 130). In one study, <50% of high-risk infants had a pulse oximeter reading 60 s after transfer to the resuscitation table (130). These findings are important, as they emphasize the need to maintain clinical skills given that the availability of real-time physiological data from monitors can be delayed. In addition, they suggest that the feasibility of enacting current resuscitation guidelines should be constantly reassessed. Real-time video communication has been shown to improve adherence to neonatal resuscitation guidelines and may provide support for resuscitations in peripheral maternity centers (131). Nadler and colleagues assessed 19 neonatal newborn resuscitations, before and after the introduction of video recordings to facilitate debriefings. They found that all measures of teamwork improved after the intervention (129). Prior to introducing video recordings into DRs, ethical, legal, and practical obstacles must be overcome at a local level. These obstacles leave video recordings in the realms of research at present, despite their known practical benefits (132).

CONCLUSION

Preterm infant monitoring during DR stabilization remains relatively basic when compared to the enhanced monitoring available in the NICU. At present, clinical assessments are the dominant paradigm; however, these have many limitations and so additional monitoring is required. All preterm infant stabilizations should have pulse oximetry monitoring to monitor HR and SpO_2. ECG monitoring should also be available as an adjunct to ongoing clinical assessment and pulse oximetry when advanced resuscitation is anticipated. We believe that such monitoring should be initiated immediately after delivery. We also advise, while awaiting further research, that if positive pressure ventilation is commenced, either capnography or a RFM should be considered to monitor ventilation efficacy. Cerebral oxygenation monitoring, by NIRS and/or EEG, may have an important role to play in newborn transition. We look forward to further research in this area and recognize the challenges in performing such studies.

AUTHOR CONTRIBUTIONS

ED conceived and designed the review. DF drafted the initial manuscript. All authors (DF, CR, GB, and ED) critically revised the manuscript for important intellectual content, agreed on the final manuscript, and approved its submission for publication.

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frontiers in Pediatrics

GENERAL COMMENTARY
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Response: Commentary: Enhanced Monitoring of the Preterm Infant during Stabilization in the Delivery Room

*Daragh Finn[1,2], Geraldine B. Boylan[1,2], C. Anthony Ryan[1,2] and Eugene M. Dempsey[1,2]**

[1] Department of Paediatrics and Child Health, University College Cork, Cork, Ireland, [2] Irish Centre for Fetal and Neonatal Translational Research, University College Cork, Cork, Ireland

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A commentary on

Commentary: Enhanced Monitoring of the Preterm Infant during Stabilization in the Delivery Room
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We read with interest Dr. Hutchon's commentary on our recent review entitled "Enhanced Monitoring of the Preterm infant during Stabilization in the Delivery Room" (1). We would like to thank him for his kind comments. He raised a number of important points related to one aspect of our review, namely heart rate acquisition in the delivery room. He was disappointed by our "characterization of the usefulness of Doppler ultrasound" in monitoring newborn heart rates (HR) and wondered why we "failed to comment on the impact of delayed cord clamping (DCC) on HR in the first minutes of postnatal life."

Our review specifically concerned the monitoring of preterm infant stabilization, and we are unaware of any studies, which have assessed the feasibility of Doppler ultrasound monitoring in this population of preterm infants (<32 weeks GA). Doppler ultrasound is certainly a useful method for monitoring newborn infant HR, but it is not commonly practiced, and its use has not been addressed by international guidelines on newborn stabilization (2, 3). Dr. Hutchon has shown that ultrasound HR is readily obtained immediately after birth in a newborn piglet weighing 1 kg (4). He has also shown that Doppler ultrasound can provide immediate heart sounds and that HR can be calculated through a polyethylene wrap from the moment of application in a mannequin model (1). Goenka et al. presented a study at the Pediatric Academic Societies and Asian Society for Pediatric Research meeting in 2014 on Doppler ultrasound in 92 stable infants >35 weeks gestation in the delivery room (5). They found that Doppler ultrasound measurements were feasible in term infants; HR values were comparable to both electrocardiogram (ECG) and pulse oximetry (PO) values; and that these values were available sooner than PO values. The published abstract from this study did not provide details on other important findings, including exact timeframes, in which Doppler ultrasound and ECG values were obtained. We await this detail in a future publication.

Our practice is to have ECG available for HR monitoring, as an adjunct to PO monitoring, for all preterm deliveries <32 weeks gestation (6). This approach is based on a number studies in preterm infants, highlighting the feasibility, accuracy, and availability of HR data within seconds of application (7–10). Simulation training and enhanced teamwork is required to enhance ECG application times, and in our setting, continuous heart rate data are available within seconds of arrival onto the resuscitaire. Based on the current paucity of evidence, it is difficult to comment on the feasibility of HR monitoring using Doppler ultrasound in preterm infants in the DR, and whether there is an added benefit when utilized in conjunction with ECG. Future studies of Doppler certainly seem warranted and should address clinically relevant short-term outcomes. Until these data are available, we cannot make any recommendations on its potential usefulness.

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***Correspondence:**
Eugene M. Dempsey
g.dempsey@ucc.ie

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Dr. Hutchon also discusses the impact of DCC on newborn HR, which is an interesting point, and one which deserves increased attention. Guidelines now recommend that for uncompromised term, and preterm infants, DCC should be practiced (2, 3). It is also advised that strategies for providing bedside stabilization during DCC should be explored (11). Dr. Hutchon formed the team, which developed the LifeStart mobile resuscitation trolley (Inditherm, UK, 2013), and stabilization at all gestational ages during DCC is feasible (12). However, we do not know the normal HR range for preterm infants during DCC. Our understanding of newborn HR is derived from the studies of Dawson and colleagues, which were performed in an era when immediate cord clamping was a standard practice (13, 14). As described by Hutchon, Smit et al. have reported HR values obtained by PO ($N = 109$) during DCC, and Katheria et al. have reported values obtained by non-invasive cardiac monitoring (NICOM) ($N = 20$) (15, 16). These studies included term infants only, and one was a feasibility study with small numbers. The studies reported conflicting results, and neither can be extrapolated for preterm infants. Further studies, with adequate study size, are necessary to establish normative HR ranges for preterm infants during DCC. Doppler ultrasound may have a very valuable role in such studies.

Mobile resuscitation trolleys are not equipped with HR monitoring devices, and prospective studies in term and preterm infants are warranted to ascertain which external monitoring device is more feasible in this new stabilization setting and which device is the most appropriate. Once this has been established, larger studies should be performed and normative values obtained. A portable lightweight ultrasound transducer that produces continuous hands-free measurement of HR as described by Hutchon is one such device that deserves further study (1). However, at this current time, we are unsure of the feasibility or appropriateness of placing a large amount of transducer gel onto the thorax of an extremely low birth weight infant and holding the Doppler probe *in situ*. This practice, demonstrated in the accompanying video of Hutchon's commentary, may be appropriate for term infants, but the device would require modifications to enable hands-free use in preterm infants.

In summary, we wholeheartedly agree that further research is warranted to establish the normative HR range in preterm infants during DCC, and we look forward to further studies that utilize PO, ECG, NICOM, or Doppler ultrasound in this area.

AUTHOR CONTRIBUTIONS

DF drafted the initial response. GB, CR, and ED critically revised the manuscript for important intellectual content. All authors agreed on the final manuscript and approved its submission for publication.

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Lost in Transition: A Systematic Review of Neonatal Electroencephalography in the Delivery Room—Are We Forgetting an Important Biomarker for Newborn Brain Health?

*Daragh Finn[1,2], Eugene M. Dempsey[1,2] and Geraldine B. Boylan[1,2]**

[1] Department of Paediatrics and Child Health, University College Cork, Cork, Ireland, [2] Irish Centre for Fetal and Neonatal Translational Research, University College Cork, Cork, Ireland

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****Correspondence:***
Geraldine B. Boylan
g.boylan@ucc.ie

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Background: Electroencephalography (EEG) monitoring is routine in neonatal intensive care units (NICUs) for detection of seizures, neurological monitoring of infants following perinatal asphyxia, and increasingly, following preterm delivery. EEG monitoring is not routinely commenced in the delivery room (DR).

Objectives: To determine the feasibility of recording neonatal EEG in the DR, and to assess its usefulness as a marker of neurological well-being during immediate newborn transition.

Methods: We performed a systematic stepwise search of PubMed using the following terms: infant, newborns, neonate, DR, afterbirth, transition, and EEG. Only human studies describing EEG monitoring in the first 15 min following delivery were included. Infants of all gestational ages were included.

Results: Two original studies were identified that described EEG monitoring of newborn infants within the DR. Both prospective observational studies used amplitude-integrated EEG (aEEG) monitoring and found it feasible in infants >34 weeks' gestation; however, technical challenges made it difficult to obtain continuous reliable data. Different EEG patterns were identified in uncompromised newborns and those requiring resuscitation.

Conclusion: EEG monitoring is possible in the DR and may provide an objective baseline measure of neurological function. Further feasibility studies are required to overcome technical challenges in the DR, but these challenges are not insurmountable with modern technology.

Keywords: newborn, electroencephalography, neuro-monitoring, delivery room, hypoxic–ischemic encephalopathy, prematurity

INTRODUCTION

Electroencephalography (EEG) has become a routine component of neurological monitoring in the neonatal intensive care unit (NICU) (1, 2). It has well-documented benefits in monitoring newborn infants with perinatal asphyxia (3–6) and seizures (7–13) and in predicting long-term outcome (14–21). Five to ten percent of newborn infants require some measure of stabilization in

the delivery room (DR) (22). The majority of infants who require complex stabilization are either extremely premature or have sustained birth asphyxia. In recent decades, the survival rates for both preterm and asphyxiated infants have improved, but neurodevelopmental morbidity has not decreased in corresponding order (23, 24). An increased focus on the early identification and prevention of brain injury in newborn infants is now a major focus of newborn care in the setting of the NICU. However, neurological monitoring is not routine during newborn stabilizations in the DR, nor is it recommended in recent international guidelines (25, 26). First, we will discuss the current methods for assessing brain health in the DR, and then we outline our rationale for considering EEG as a very useful biomarker of brain health in the DR. **Table 1** summaries the different assessment tools discussed.

CURRENT METHODS FOR ASSESSING BRAIN HEALTH IN THE DR

At present, neonatal stabilization teams rely on clinical parameters to assess a newborn infant's neurological status during immediate newborn transition. Assessments of muscle tone and reflex irritability are incorporated into the Apgar score, which is routinely assigned to infants after 1 and 5 min (27, 28). However, Apgar scores are subjective and inter-rater variability is high (29). Neonatal objective hemodynamic monitoring with reliable, continuous, non-invasive measurements of physiological parameters such as heart rate and pre-ductal oxygen saturations (with pulse oximetry) is now routine in the DR (29–32). However, neonatal stabilization teams do not have objective information available about neurological function during resuscitation. The availability of accurate and objective baseline neurological information may help guide resuscitation and plan appropriate early interventions for neonates that may not have tolerated the stresses of labor so well.

Studies that have previously sought to introduce neurological monitoring into the DR initially focused on cerebral blood flow using Doppler measurements of cerebral or carotid arteries (33–38). More recently, studies have concentrated on near infrared spectroscopy (NIRS), which provides non-invasive monitoring of cerebral tissue oxygenation in the DR (39–46). Guidelines for the use of NIRS monitoring and EEG in NICUs overlap, and it is advised that they should be used simultaneously (6).

RATIONALE FOR PROPOSING EEG AS A BIOMARKER OF NEWBORN BRAIN HEALTH IN THE DR

Electroencephalography is not a new technique, but its application in neonatology in the past has been hampered by a lack of appropriate technology for recording and analysis. This has changed dramatically in the last decade, and there are now high quality digital amplifiers available that can record excellent EEG signals even in very noisy environments. The time is now right to reexplore the use of EEG as a valuable biomarker of neurological function in the DR; an environment where previously, it was just not possible.

The signal measured by the EEG is of the order of microvolts and represents a direct measure of postsynaptic neuronal activity in the cortex. Research has shown that the EEG of fetal sheep can be recorded during labor (47–49). Thaler and colleagues performed intrapartum EEG on fourteen women with uncomplicated pregnancies (50), and a clinical trial of EEG monitoring during labor is currently underway (https://clinicaltrials.gov/ct2/show/NCT03013569). During normal labor, the fetus is exposed to brief but repeated episodes of hypoxia, which are balanced by the fetus's striking ability to adapt to these episodes (51). Fetal EEG monitoring in both human and animal studies during labor has shown that these episodes are associated with rapid EEG amplitude reduction and also with fast amplitude recovery as soon as the uterine contraction ends (48, 52). The EEG is exquisitely sensitive to any impairment in oxygen delivery to the brain. A reduction in oxygen leads to an immediate suppression of synaptic transmission with a reduction (often complete

TABLE 1 | Current and possible future tools for assessing neonatal brain health in the delivery room (DR).

	Method	Strengths	Limitations
Clinical assessment	Muscle tone and reflex irritability as part of the APGAR score	Immediate score	Subject to inter- and intra-rater variability
Cerebral blood flow	Ultrasound Doppler of cerebral or carotid artery	Immediate assessment of cerebral blood flow	Technically challenging and continuous data acquisition not feasible
Near infrared spectroscopy (NIRS)	Non-invasive monitoring of cerebral tissue oxygenation by application of NIRS pad to frontal area	Feasible to obtain continuous reliable data in the DR Normative values established	Wide range for normative values
Fetal electroencephalography (EEG)	Application of >1 EEG electrodes to fetal scalp during labor	Would allow for real time assessment of fetal brain health	Technically challenging Can only be applied during late stages of labor Not established as method for assessing fetal health Paucity of normative data
EEG	Application of >1 EEG electrodes to neonatal scalp after delivery	Would allow for real time assessment of neonatal brain health Established method for monitoring neonatal brain health in neonatal care	Technically challenging Paucity of normative data

suppression) in EEG amplitude (48, 53). This adaptive response, believed to be mediated by multiple inhibitory neuromodulators including adenosine, to hypoxia may be protective by decreasing energy consumed by the generation of synaptic potentials (54). If cerebral hypoxia is sustained, however, EEG amplitudes remain severely reduced and membrane failure will eventually occur accompanied by energy depletion and cell damage (52). Thus, sustained changes in the EEG signal a risk of impending brain injury.

In neonates with hypoxic–ischemic encephalopathy (HIE), an EEG showing sustained suppression for hours after birth has long been associated with a very poor outcome (5, 15, 55, 56). Neonatal EEG monitoring is recommended for all infants with moderate and severe HIE, and neonatal teams are now familiar with its application in NICUs. Fetal EEG monitoring has clear benefits for the early recognition of HI injury but requires considerable research before it is adopted as a routine tool for fetal surveillance. Immediate EEG acquisition in the DR on the other hand is much more feasible and may quickly identify those neonates that have not tolerated labor and delivery very well, which will be seen as disrupted patterning on the EEG.

An early EEG in the DR of an infant requiring resuscitation will indicate if EEG activity is present or not or if EEG activity returns following this stabilization process. As we know that EEG activity should recover immediately following restoration of oxygen delivery to the brain, if EEG activity does not return immediately post resuscitation or activity is severely disrupted, this indicates that the infant is at risk of hypoxic–ischemic brain injury. This could provide a clear indication for immediate passive cooling prior to transfer to the NICU. This early indication of cerebral function is very important as Thoresen et al. have shown that infants cooled within 3 h of birth have better neurodevelopmental outcomes when compared to infants whose cooling commenced between 3 and 6 h (57). Further improvements in outcome are highly likely to arise from earlier improved identification of affected infants that would allow earlier initiation of treatment after resuscitation.

Therefore, early EEG monitoring could provide neonatal stabilization teams with valuable, much needed, information about the neurological status of the newborn infant immediately after birth. Thus, we set out to assess whether any studies had already attempted to measure the human EEG in the DR by conducting a systematic review of available literature. We also aimed to establish the feasibility of EEG monitoring in the DR, and determine whether valuable information has been acquired from its application thus far.

METHODS

Search Strategy

We performed a systematic stepwise search of PubMed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (58). Articles up to and including February 2017 were included. Studies had to involve EEG monitoring in the DR. Search terms included the following: infant, newborns, neonate, DR, afterbirth, transition, and EEG. Only human studies were included, and this was incorporated into the initial search. Additional published reports identified in review articles or referenced in articles screened were also included. Publication bias was not assessed.

Study Selection

Articles identified by our search strategy were screened for inclusion by one author (DF). Titles and abstracts were initially screened. Articles had to pertain to EEG monitoring immediately after birth. Studies that focused on infants post birth asphyxiation or infants who had intracranial pathology were excluded as the subjects were, by nature, recruited post-delivery and not relevant to our search. Studies that specified a time frame for initial EEG monitoring outside of the first 15 min of life, or initial recruitment outside of the DR were also excluded. Where uncertainty remained regarding eligibility for inclusion the full text was reviewed. Studies that were not available in English were excluded.

RESULTS

Our initial search identified 215 articles (see Appendix 1 in Supplementary Material). After assessment of these articles, two original studies were identified that described EEG monitoring of the newborn infant within the DR (**Figure 1**). One study also contributed to a review article identified by our search, which was excluded from our study to avoid duplication (59). **Table 2** summarizes the two studies identified.

Pichler et al. performed a prospective observational study of infants born by elective cesarean section over 34 weeks gestational age (60). Infants at lower gestational ages were excluded due to concerns about their small head size, and the feasibility in applying EEG leads and NIRS to a small surface area. Four gold electrodes (two frontal and two parietal) were applied with contact gel, along with an NIRS pad to the left forehead, and overlying elastic bandages for support. Amplitude-integrated EEG (aEEG), a rectified, filtered, and compressed form of EEG, was acquired and stored. Overall, they found that aEEG monitoring of the newborn infant in the DR is feasible, but it is difficult to obtain continuous reliable data. Of a total number of 63 infants, 17 (27%) were excluded due to unreliable data. Of the remaining 46 infants, no data were recorded prior to 3 min of delivery, 25% had data available at 3 min, and just over 50% were available at 5 min. aEEG data were analyzed for mean minimum and mean maximum voltages every minute, and then correlated with cerebral oxygenation, heart rate and pre-ductal oxygen saturations. Findings were then compared between infants who were uncompromised at birth ($n = 31$) and infants who required neonatal resuscitation ($n = 16$).

Different cerebral activity patterns were identified between uncompromised newborns and those requiring resuscitation. They reported that infants in the uncompromised transition group started with initially high voltages on aEEG, followed by a significant decrease to baseline voltages at 4–5 min. In contrast, infants in the group requiring respiratory support did not show this pattern. However, there were no significant differences between minimum and maximum voltages when the two groups

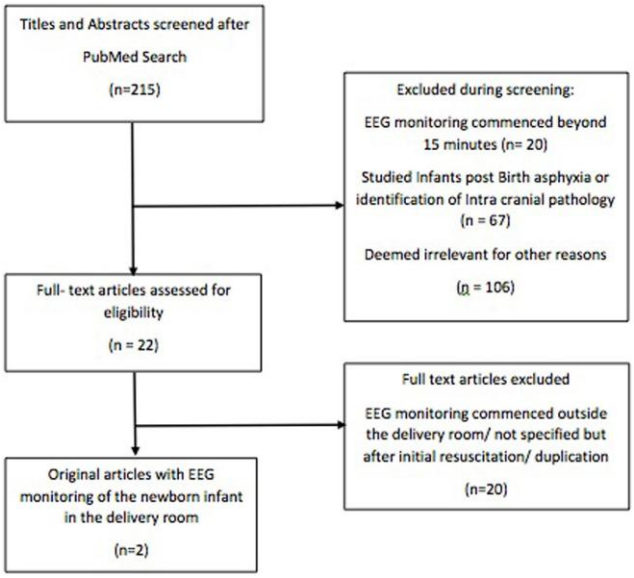


FIGURE 1 | Flow diagram of literature search.

TABLE 2 | Summary of electroencephalography (EEG) studies in the delivery room.

Reference	Neonates	Number recruited and monitored	Design	Number included in analysis	Observation
Pichler et al. (42, 60)	>34 weeks	46	Observational Amplitude-integrated EEG (aEEG) analysed for minimum and maximum voltages Near infrared spectroscopy (NIRS)	*N* = 46 31 uncompromised 15 required respiratory support	No significant differences between minimum and maximum voltages when the 2 groups are compared Uncompromised infants had higher V max in minute 3 and 4 compared with minute 10
Tamussino et al. (61)	Term	244	Observational aEEG analysed for minimum and maximum voltages Infants with initial low voltages which normalized were compared to infants with normal voltages throughout NIRS	*N* = 59 9 met inclusion criteria 50 control studies	Neonates with initially low cerebral activity during immediate transition after birth displayed lower cerebral saturations (<10th percentile) on NIRS, but increased cerebral oxygen extraction (cFTOE >90th percentile)

were compared, which the authors attribute to low numbers in the respiratory support group.

Tamussino et al. recorded simultaneous aEEG and NIRS in 244 term neonates during the first 15 min after delivery (61). Similar to the study of Pichler et al., aEEG data were analyzed for mean minimum and mean maximum voltages every minute, and then correlated with cerebral oxygenation, heart rate, and pre-ductal oxygen saturations. Neonates with initial low voltages, which normalized during transition, were compared to neonates with normal aEEG values throughout the monitoring period. Nine neonates had low initial aEEG voltages and were compared to 50 neonates with normal aEEG voltages throughout. Therefore, of 244 infants recruited, 59 aEEG recordings were included in the analysis. Neonates with initially low cerebral activity during immediate transition after birth displayed lower cerebral saturations (<10th percentile) on NIRS, but increased cerebral oxygen

extraction (cFTOE >90th percentile). The authors concluded that neuro-monitoring with aEEG and NIRS might provide useful information on the neonates' condition during immediate transition.

DISCUSSION

Neonatal mortality has decreased significantly in recent decades (24). As more infants survive following preterm delivery and birth asphyxia, achieving the best possible neurological outcomes for survivors is paramount. Whilst EEG has an essential role within the NICU in newborn neurological monitoring following birth asphyxia, and in monitoring preterm infants, it is not routinely initiated in the DR, and at present has no role during newborn stabilizations. We set out to determine if first it was feasible to perform newborn EEG in the DR, second to assess what information it provides about newborn brain activity in the immediate postnatal period and most importantly, to determine if this early objective information about brain activity would be useful. We found two studies that had performed aEEG during the first 15 min of birth. They found aEEG to be feasible in infants >34 weeks, but technically difficult to obtain continuous reliable data. Patterns of brain activity differed between infants that required newborn stabilization measures and infants that transitioned from the fetal to neonatal period without the need for medical intervention (60). Also, newborn infants with initially low cerebral activity during immediate transition after birth displayed lower cerebral saturations and increased cerebral oxygen extraction, compared with normal voltages throughout (61). The authors proposed a number of possible explanations for the differences between groups. They postulated that apnea, respiratory distress, and bradycardia in the immediate newborn may result in a lower cardiac output and resultant lower brain activity in compromised infants (60). For uncompromised infants who had initially high levels of activity, they suggested that catecholamine release may be responsible (62).

The brain is the most vulnerable organ in newborn infants. A non-invasive, continuous method to measure cerebral activity (EEG) is already available but it has not transitioned to the DR. Initial research focused on cerebral blood flow measurements but they were found to be technically difficult and did not provide continuous data (59). NIRS has shown great promise in providing continuous data on cerebral tissue oxygenation values. It utilizes the transparency of biological tissue to light in the near infrared spectrum to measure cerebral tissue oxygenation (63). A number of studies have examined cerebral oxygenation using NIRS in the DR (59), and recently, normative values for infants not requiring resuscitation have been published (42).

As the importance of the early instigation of neuroprotective strategies for term newborns with perinatal asphyxia has become evident, EEG monitoring (usually aEEG) has become more common in NICUs (1, 7). In contrast to cerebral blood flow and NIRS, EEG has well documented applications in the clinical management of newborn infants. It is the gold standard method for the accurate detection of all neonatal seizures in term and preterm infants (6, 9). It has well-proven efficacy in predicting outcomes following perinatal asphyxia, based on patterns of poor background activity and the timing of sleep wake cycling reestablishment (14, 15, 64, 65). Prediction of outcome following preterm delivery is more complicated, but investigations are ongoing (20). Several studies have shown that early background EEG suppression correlates with severity of periventricular hemorrhage (66–68). Also, continuous displays of inter-burst interval duration, which differs with gestational age, may become a useful prognostic measure in preterm infants in the near future (69, 70).

Despite its importance in monitoring the newborn brain in the NICU, EEG monitoring in the DR is currently not recommended. Stabilization of newborn infants in the DR, including infants with perinatal asphyxia, occurs without any objective measure of brain activity, and we found only two studies that have assessed the feasibility of obtaining a newborn EEG recording in the DR. Both studies used the aEEG trend and both found it possible to obtain aEEG tracings within 3 min in some cases, but obtaining continuous reliable data was generally difficult (60). Within these limitations the authors describe different patterns in brain activity for infants that required respiratory support and infants that transitioned independently. Also, aEEG was correlated with different cerebral oxygenation patterns. These findings are important as they pave the way for future studies.

Both studies analyzed brain activity by interrogating the aEEG mean minimum and mean maximum voltages. However, the aEEG trend alone is a high level summary measure of the EEG with poor time resolution due to compression in the aEEG algorithm, and it does not display the second by second activity of the brain; as a result, it is not optimal for application in the DR. Digital aEEG machines obtain one or two channels of EEG signal, which is then amplified and passed through an asymmetric bandpass filter that strongly attenuates activity less than 2 Hz and more than 15 Hz, to minimize artifacts. Additional processing includes semilogarithmic amplitude compression, rectification, and time compression (13). Heavy signal processing used in the aEEG algorithm eliminates much of the detail (e.g. frequency band content) available in the EEG, and many clinically important features are lost. Furthermore, there is no clear definition for aEEG, and most EEG machines implement different versions of the aEEG algorithm (71). The mean and maximum of the aEEG voltage need to be plotted and displayed for a number of minutes before any assessment of the overall baseline EEG activity can be made. In addition, it is well known that interpretation of the background aEEG pattern can be problematic due to baseline drift and other artifacts (72, 73). This is not optimal for DR EEG recording when real-time second by second information would be advantageous. For example, a recording of approximately 30 s duration alone using standard EEG would be enough to establish the presence of continuous EEG activity in a term newborn. This information would be hugely beneficial in the DR to help guide resuscitation and to determine the need for immediate passive cooling. Thoresen et al. coined the phrase "time is brain" in relation to the timing of cooling for neuroprotection (57), and we strongly believe that EEG in the DR could help identify those infants who would benefit most from early neuroprotective strategies.

Whether EEG could play a role in prognostication for infants requiring TH in the immediate newborn period is less clear. From clinical and preclinical studies, we know that recovery of

EEG activity during the first 24 h after hypoxia ischemia, after a period of prolonged (several hours) suppression, can be associated with normal outcome (74, 75), and little to no histological injury (76). However, we now know that infants with even mild HIE can have cognitive delays at 5 years (14). The prolonged suppression is an actively mediated response, at least partially mediated by neurosteroids such as pregnanes and adenosine, which are upregulated for hours after the insult (77, 78). Previous papers that reported normal outcomes in infants with an initial flat EEG trace that recovered quickly and had normal outcome were limited by small numbers and follow-up continued until 2 years of age (75). The authors even admit this themselves as they say that "a normal score in the early years cannot preclude later neurological, perceptual-motor, or cognitive abnormalities" (75). Therefore, we continue to recommend multichannel continuous EEG monitoring for such infants for the duration of TH.

Electroencephalography in its raw format (not a modified aEEG) can be assessed both qualitatively and quantitatively. Qualitative EEG analysis is mainly used for clinical purposes. It is based on visual interpretation of the EEG signal and describes background features such as amplitude, frequency, and continuity of the EEG, symmetry, synchrony, and sleep–wake cycling. Quantitative EEG analysis is a method predominantly used in research and includes time and frequency domain analysis. Neither study identified in our review analyzed the EEG in its raw format, either for qualitative or quantitative purposes.

However, we still have a way to go before EEG monitoring is routine in the DR. Signal interpretation is difficult, but huge advances have already been made in quantitative analysis of the neonatal EEG and we now have algorithms that can accurately grade the EEG in term and preterm newborns (70, 79–84). The feasibility of EEG recording is constantly improving and newer amplifiers with high common mode rejection ratios are now available that make EEG recording more possible and less susceptible to noise and other artifacts. We have seen that excellent quality EEGs are now possible for even extremely preterm infants in the NICU, as long as there is adequate setup and preparation (85). Multiple channels of EEG are not required to assess the grade of EEG baseline activity in the DR, one channel of good quality EEG is perfectly acceptable to assess amplitude, continuity, and frequency of the EEG. EEG sensors are constantly evolving, and newer disposable single application sensors are now available also making EEG electrode acquisition more feasible.

Electroencephalography has long been considered just too difficult to deploy in environments like the DR and NICU. There have been major recent advances to the adoption of EEG in the NICU primarily due to advances in technology (2). Modern machine learning techniques are also advancing rapidly and will soon be able to provide non-EEG experts with the help needed to assist in the interpretation of EEG patterns on a 24/7/365 basis. These difficulties should no longer be a barrier to the adoption of EEG in the DR.

In conclusion, the time is now right to advance the objective monitoring of neurological function of newborn infants in the DR, and urgent research is clearly warranted. More EEG studies from healthy term and preterm newborns in the DR to establish feasibility and normative reference ranges are clearly a priority. Advances in automated analysis of the baseline EEG will be hugely beneficial in this effort particularly if outputs are incorporated into standard patient monitors. We look forward to further studies in this area.

AUTHOR CONTRIBUTIONS

GB and ED conceived and designed the review. DF performed the literature search and drafted the initial manuscript. All the authors (DF, ED, and GB) critically revised the manuscript for important intellectual content, agreed on the final manuscript, and approved its submission for publication.

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SUPPLEMENTARY MATERIAL

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Review

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Optimising Intravenous Volume Resuscitation of the Newborn in the Delivery Room: Practical Considerations and Gaps in Knowledge

Daragh Finn[a, b] Charles C. Roehr[c, d] C. Anthony Ryan[a, b]
Eugene M. Dempsey[a, b]

[a]Department of Paediatrics and Child Health, Cork University Maternity Hospital and University College Cork, and [b]Irish Centre for Fetal and Neonatal Translational Research, University College Cork, Cork, Ireland; [c]University of Oxford, Department of Paediatrics, Newborn Services, John Radcliffe Hospital, Oxford University Hospitals, NHS Foundation Trust, Oxford, UK; [d]Department of Neonatology, Charité University Medical Center Berlin, Berlin, Germany

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Abstract
Volume resuscitation (VR) for the treatment of newborn shock is a rare but potentially lifesaving intervention. Conducting clinical studies to assess the effectiveness of VR in the delivery room during newborn stabilization is challenging. We review the available literature and current management guidelines to determine which infants will benefit from VR, the frequency of VR, and the choice of agents used. In addition, the potential role for placental transfusion in the prevention of newborn shock is explored.

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Introduction

The neonatal resuscitation section of the "2015 International Liaison Committee on Resuscitation (ILCOR) Recommendations" was recently published [1]. These recommendations provide updated evidence on a number of key areas of newborn management in the delivery room (DR), and there is now a sizable body of evidence supporting many aspects of support in the DR. However, a number of outstanding issues remain unresolved, outlined in the "2010 PICO Questions Not Reviewed" in the 2015 section of the above mentioned consensus document [1]. In particular, whilst up to 10% of newborns require assistance with breathing at birth, the use of chest compression, medication administration, and fluid bolus volume resuscitation (VR) occurs significantly less frequently and is not as well studied [2].

Prospective studies evaluating VR during newborn stabilization remain impracticable as the frequency of VR in this population is very low, and it may be challenging to withhold fluid as a control measure in such circumstances. Also, whilst short-term outcome measurements are possible, it is difficult to ascribe robust long-term outcome measures to a single intervention during DR stabilization. Unnecessary VR in the setting of asphyxia has the potential for harm. Nonetheless, the question of the adequacy of VR during stabilization of the newborn infant arises relatively frequently.

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E-Mail karger@karger.com
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Eugene M. Dempsey
Department of Paediatrics and Child Health, Cork University Maternity Hospital
University College Cork
Cork T12 YE02 (Ireland)
E-Mail g.dempsey@ucc.ie

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Table 1. Objective monitors for assessing newborn circulatory status in the DR

	Normative values established for term infants[1]	Normative values established for preterm infants[2]	Accuracy	Comments
Pulse oximetry HR	+	+	+	gold standard monitor for assessing HR in the DR; may be unreliable during CPR
ECG HR	+	+	+	quicker data acquisition than pulse oximetry but may require extra personnel
Doppler USHR	+	+	+	a novel method for accurate data acquisition but extra trained personnel required
BP	+	–	–	accurate measurements not feasible in the DR setting
ECHO-LVO/RVO	+	–	+	supplies valuable information but extra trained personnel required
NICOM-LVO	+	–	–	limited as only trends in CO can be appreciated; further studies advised

BP, blood pressure; CO, cardiac output; DR, delivery room; ECHO, echocardiogram; ECG, electrocardiogram; HR, heart rate; LVO, left ventricular output; RVO, right ventricular output; NICOM, non-invasive cardiac-output monitoring; US, ultrasound.
[1] In the immediate newborn period; [2] <32 weeks' gestation in the immediate newborn period.

We reviewed the current available literature on this important aspect of newborn care, in an effort to uncover the evidence to support the use of VR in the DR. We reviewed (1) how to determine which infants may benefit from VR, (2) the indication and frequency of VR in the DR, (3) which fluid should be used, and, lastly (4) whether there is a role for placental transfusion in such infants.

How to Determine Which Infants Require VR

In newborn term and preterm infants, the practice of VR is often considered to be beneficial, for instance, in severe arterial hypotension or severe metabolic acidosis in the context of neonatal shock [2, 3]. Shock is caused by an acute failure of circulatory function and is characterized by inadequate tissue and organ perfusion [4], and is most commonly caused by an asphyxial insult and/or hypovolaemia in newborn infants where there may/may not be obvious blood loss and also in the setting of sepsis.

VR can be lifesaving for newborn infants with hypovolaemic shock or sepsis. However, infants who sustain an acute perinatal asphyxial insult, not secondary to acute blood loss, are generally euvolaemic [2]. In cases of intrauterine hypoxia, there is often an increased blood volume [5, 6]. VR in such infants may lead to volume overload and worsen cardiovascular compromise in infants who may have impaired myocardial contractility [2, 7]. However, in a compromised term neonate in the DR, distinguishing an infant with hypovolaemic shock from a normovolaemic infant with asphyxia is challenging.

ILCOR advises clinical assessments of peripheral perfusion to differentiate between the normovolaemic and hypovolaemic state [1]. In the 2010 ILCOR report as well as in the 2015 European Resuscitation Committee (ERC) guidelines, the colour of the mucous membranes was said to be a useful clinical discriminator [8, 9]. In the case of hypovolaemic shock, these membranes will be pale, but in the case of asphyxia, they may have a "normal" colour [10]. However, assessments such as capillary refill time, colour, and palpation of peripheral pulses are subjective, and there can be significant inter-rater variability, as highlighted by several investigators [11, 12]. Assessments based on the colour of the mucous membranes, although specific if oxygen saturations are <70%, are still subjective, and are associated with a low sensitivity [13], making it difficult to clinically determine the underlying aetiology of newborn shock.

Objective measures of newborn circulatory status are an important component of assessing infants with shock in the DR, both for diagnosing circulatory failure and to monitor the response to treatment. We will discuss the

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methods used for heart rate (HR) and blood pressure (BP) assessment in the DR, and also newer modalities such as echocardiography (ECHO), perfusion index (PI), and non-invasive cardiac monitoring (NICOM) (Table 1).

Assessment of newborn HR has been the mainstay to assess effective newborn transition and to gauge the need for resuscitatory interventions in the DR [1]. Methodologies include assessment by stethoscope auscultation, palpation, pulse oximetry, electrocardiogram (ECG), and Doppler ultrasound. While the clinical assessment of HR by auscultation at the apex with a stethoscope is more accurate than the assessment of umbilical pulsations [14], these methodologies are often inaccurate compared with other objective methods, such as pulse oximetry and ECG [9]. A recent commentary has highlighted that a prolonged time period to auscultate may provide a more accurate HR [15].

Assessing HR from pulse oximetry readings provides real-time accurate information [16], but there can be delays in signal acquisition of between 1 and 2 min [17], and especially in low-perfusion states [18]. Whilst pulse oximetry is easy to apply by using a single probe, preferably on the right hand (pre-ductal) of the neonate, in depressed neonates with poor cardiac output, lack of signal may be confused with handling errors or device failure, and hence distract from managing the clinical state of the infant. In addition to the HR, pulse oximetry also provides oxygen saturation data on a continuous basis. Similarly to the abovementioned errors associated with obtaining oxygen saturation signals, pulse oximetry-derived HR can be adversely affected by improper application, movement artifact, or poor peripheral perfusion, and so may not be reliable while performing chest compressions [19].

Evaluation of the HR by means of ECG has been shown to provide more accurate HR values, in a shorter time than pulse oximetry HR in the DR, and it is less prone to movement artifact. Katheria et al. [20] reported median times for acquiring a signal from ECG and pulse oximetry of 4 and 32 s following application, respectively. However, obtaining an ECG requires the application of 3 chest leads; this may itself take up to 20s [20]. In practice, a baby's wet skin may also pose a challenge, as not all ECG leads stick well to a wet surface and so the task of applying the leads may require additional personnel. Furthermore, pulseless electrical activity can present with a visible ECG, but no cardiac output, even though this is an extremely rare occurrence in the newborn.

Hutchon [21] showed that measurement of the neonatal HR by Doppler ultrasound is possible, and can easily be seen as an extension of fetal HR monitoring until pulse oximetry readings are available. Measurements are accurate and comparable with ECG HR values [22]. This approach may be challenging, as clinical expertise is required for accurate ultrasound assessments and, at present, continuous measurements are not practical. In conclusion, the assessment of HR is important. To date, the accuracy of routinely applied methods varies, with palpation and auscultation being the least accurate and ECG being the most accurate [23].

Neonatal oscillometric BP monitoring is another objective methodology that has been investigated during neonatal transition, although not widely used clinically. A number of studies have shown that BP measurements are obtainable in the DR [24, 25]. However, such non-invasive BP measurements are not reliably consistent, especially in preterm neonates, and invasive BP monitoring is not practical in the DR setting [3]. Thus, BP acquisition and values obtained in the DR may not be clinically useful in assessing the circulatory status of newborn infants.

A recent review identified 4 studies of cardiac-output ECHO monitoring during term newborn stabilization [24]. These studies confirm that ECHO assessment of neonatal transition (ductal haemodynamics, and changes in right and left ventricular outputs) is feasible as an objective adjunct to determining newborn haemodynamic status [26–28]. Normative ECHO values for left ventricular output and stroke volume in the first 15 min of life have been determined [27, 29]. Therefore, in theory, ECHO could help distinguish between infants who present with low-output cardiac failure in the setting of hypovolaemic shock, and high-output failure in the setting of asphyxia. However, studies have yet to assess whether ECHO analysis could help in determining the aetiology of newborn shock or volume responsiveness in the newborn period, and whether this approach is indeed useful to guide clinical decision-making [30].

Weisz et al. [31] described a method which provides non-invasive continuous cardiac-output monitoring (NICOM). This technology is based on the assumption that changes in the resistance to electrical currents captured by electrodes on the thorax are directly related to changes in aortic volume during different stages of the cardiac cycle. NICOM measurements correlate well with timed ECHO measurements in neonates [31]. However, NICOM underestimates the actual cardiac-output value (47% error reported) [31]. Therefore, it may be more useful in monitoring trends in cardiac output. It is not designed to help in discriminating between causes of newborn shock or volume responsiveness in the newborn period, and a systematic review of NICOM confirmed that

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it is not accurate in determining volume responsiveness in paediatric patients [30]. Katheria et al. [32] documented increasing cardiac outputs on NICOM over the first 5 min of life in term infants during delayed umbilical-cord clamping, and, although feasible, at present, NICOM is not a valuable tool for assessing infants in the DR.

PI monitoring is a non-invasive method of assessing peripheral perfusion and provides continuous values. These values are derived from and displayed by a pulse oximeter, which utilizes an extra wavelength emission in its calculations to distinguish between the pulsatile and non-pulsatile components of arterial blood, and produces a real-time measure of peripheral perfusion [33]. The PI has been utilized to assess infants in a number of clinical domains in the NICU setting [34]. These include elective screening for congenital cardiac disease [35], predicting low systemic blood flow [36], and assessing perfusion following blood transfusion [37]. Values for PI are also easily obtained in the DR [38]. However, they are highly variable in the immediate newborn period, for both term and preterm infants, which limits the use of PI in assessing newborn circulatory status in the DR [38, 39].

Near-infrared spectrospcopy (NIRS) may be a useful adjunct, and there have been a number of recent DR-orientated studies addressing the use of NIRS [40, 41]. It is easy to apply and there is very little delay in signal acquisition. NIRS has been utilized to assess the adequacy of peripheral oxygenation [42]. Wardle et al. [43] evaluated oxygen delivery and consumption in the forearm of 30 preterm babies, 15 of whom were hypotensive by Watkins criteria. They identified a lower oxygen delivery and consumption in the hypotensive babies. However, NIRS has yet to demonstrate that its use results in improved outcomes for term and preterm infants.

In summary, there appears to be no single failsafe or reliable clinical or electronic modality that accurately delineates haemodynamic status in the healthy or sick neonate during transition. Objective HR assessment remains important. The typical description of acute blood loss or hypovolaemic circulation has been that "pallor of the mucous membranes and skin is nearly always present" [44, 45]. We contend that this clinical sign is a very poor discriminator between acute blood loss and asphyxia, and that the utilization of other objective parameters (BP, ECHO, NICOM, and PI) may allow for better discrimination between these 2 broad categories in the future. However, the sensitivity and specificity of these parameters, individually or collectively, remains to be determined.

The Frequency of VR in the DR

Although the incidence of neonatal shock remains unknown, <1% of newborn infants require advanced resuscitative measures, including chest compression, drug administration, and fluid boluses during newborn stabilization [46]. Wyckoff et al. [2] described a cohort of 37,972 infants of >34 weeks' gestation delivered over a 30-month period, 28 of whom (0.07%) received intensive CPR. This was defined as the need for >60 s of positive pressure ventilation and chest compressions, with or without the administration of medications. Five infants did not respond to these interventions (including VR in at least 4 of these cases) and died in the DR. Of the remaining 23 infants admitted to the NICU, 13 had received VR. Therefore, in this cohort of infants delivered at >34 weeks' gestation, only 0.04% (4.4/10,000) received VR in the DR. The authors compared the infants that had received VR ($n = 13$) with those who had not ($n = 10$). The patients who received volume were more likely to have low Apgar scores (Apgar <2 at 5 and 10 min), to have a lower cord pH, and to have received adrenaline in the DR and their mean resuscitation times were longer in duration (8 vs. 4 min). The mean BP on admission was lower (32 vs. 49 mm Hg) and initial haematocrit was also lower (41 vs. 54) in the group who received volume. In the 13 infants who received VR, the clinical indication for the initial use of volume was an inadequate HR despite CPR and adrenaline administration in 10 cases, and poor perfusion coupled with a clinical suspicion of acute blood loss in the other 3. It is difficult to tease out the underlying aetiology of shock from this retrospective study, other than to say that the majority of infants who received volume were hypotensive on arrival to the NICU, but the majority of those who did not receive volume were not. The aetiology of newborn shock is multifactorial, and determining the difference between acute blood loss and asphyxia based on BP values upon admission is challenging. From this retrospective study, one can conclude that sicker babies (lower Apgar score, lower cord pH, in receipt of adrenaline) are more likely to receive VR, which is consistent with current resuscitation guidelines.

Overall, there is rather limited information available and there are no comparative studies to assess variations in practice between neonatal centers. We know that VR is rare, but there is a paucity of available research to quantify just how often it occurs. Future resuscitation committees should reach a consensus on a definition for newborn shock if studies are to be of value. Without further data, it will be challenging to perform comparative studies or best-practice reviews on VR in the DR.

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Table 2. Volume resuscitation agents in hypovolaemic shock

	Availability	Efficacy	Risk	Cost	Recommendation
O-Rhesus-negative blood	centre-dependent	most efficacious	low	a valuable resource	gold standard treatment for hypovolaemic shock
Crystalloid (NaCl 0.9%)	readily	equal to albumin	none	–	first-line agent when whole blood is not available
Albumin	readily	equal to crystalloid and synthetic volume expander	low	+	not recommended
Synthetic volume expander	readily	equal to albumin	low	+	not recommended

What Agent Should Be Administered in Hypovolaemic Neonates?

International guidelines generally advise that, when hypovolaemic shock is suspected, emergency un-cross-matched O-Rhesus-negative blood should be administered whenever available (Table 2) [1]. If not, isotonic crystalloid fluids should be given. Colloid infusions such as albumin are no longer advised as a treatment option during DR stabilizations [9, 44]. However, the suggestion stems from extrapolation of data from studies on animal models and older children, as there is a paucity of neonatal or DR studies. The ideal amount to be transfused is unclear, but an initial 10–20 mL/kg may be appropriate, considering that DCC may result in an additional 30% blood transfer.

Whole blood provides volume, oxygen-carrying capacity, and colloids, and is the most rational agent to administer in the setting of acute blood loss. Transfusion of blood products carries a small risk of infectious transmission (in the order of viral contamination in 1/1–1.3 newborns) [47], which may be particularly harmful towards extremely-low-birth-weight infants who are already immunologically compromised and neurodevelopmentally vulnerable [48]. Haemolytic transfusion reactions are rare in newborn infants [49]. We recently reviewed our own practice (Medical Centre, University College Cork, Cork, Ireland) in relation to the administration of emergency un-cross-matched blood in the DR. Over a 5-year period, there were 42,657 births, and 6 infants (1.4/10,000 live births) received an emergency blood transfusion in the DR [50]. Neither delayed cord clamping nor milking was routinely practiced in our DR in this time frame. The indication for administration of whole blood was based on a non-response to intensive CPR and a history of possible blood loss (e.g., vasa previa, fetomaternal haemorrhage, or placental abruption). However, generally speaking, whole blood is not readily available and the administration of crystalloid occurs in the first instance. This figure is greater than the DR volume administration rate reported by Wyckoff et al. [2], where 3 infants received volume because of concerns about acute blood loss (0.8/10,000).

There is no data from DR resuscitations comparing the efficacy of crystalloid or colloid agents. Albumin is the most abundant protein in plasma, and, during normal homeostasis, is responsible for maintaining 60–80% of colloid osmotic pressure. Much of the data on crystalloid or colloid use has been derived from the management of preterm infants at risk of/with established hypotension [51]. Neonatal studies to date performed outside the DR setting have displayed no difference in efficacy between colloid and crystalloid infusions [52, 53], and crystalloids are generally the preferred agent for many practical reasons: they are readily available, cheaper, and carry a lower risk of infectious complications [45]. Synthetic colloid volume expanders are as effective as albumin, have no infectious risks, and are readily available [54]. However, they are also expensive compared to crystalloids, and concerns have been raised in the past regarding different solutions disturbing paediatric coagulation systems [55]. Therefore, when whole blood is not available, the administration of crystalloid volume is advised for the treatment of newborn hypovolaemic shock.

The volume to be infused and the rate of infusion have not been studied in neonates. However, it should be noted that there is animal data which raises a number of concerns related to the rapid administration of volume expanders [7, 56]. Wyckoff et al. [7] compared 5% albumin, normal saline, and no volume on the development

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of pulmonary oedema and the restoration of mean arterial pressure during the resuscitation of asphyxiated piglets. Volume administration in these animals did not improve mean arterial BP. The authors demonstrated an increased risk of pulmonary oedema in the piglets when albumin was administered compared to the control animals. Another study evaluated the effect of rapid volume administration on coagulation haemostasis in piglets, comparing 4 different fluids including normal saline and albumin [56]. These piglets were not hypovolaemic. All fluids administered caused a significant weakening of clot strength, suggesting that rapid volume administration can impact upon the coagulation profile. Therefore, the potential side effects of the rapid administration of crystalloids or colloids in the DR setting need to be carefully considered.

Is There a Role for Placental Transfusion in Compromised Infants?

The 2015 ILCOR and ERC guidelines advocate delayed cord clamping (DCC, for at least 1 min) in uncompromised term and preterm infants [1, 9]. This is based on a plethora of benefits outlined in recent Cochrane reviews for both term and preterm infants, such as reduced incidences of anemia, hypotension, and intraventricular haemorrhage following DCC [57, 58]. However, the authors advise that, until further evidence is available, placental transfusion should be discontinued in infants who are not breathing, so that resuscitation measures are not delayed [1]. They acknowledge that even though there is compelling physiological data from animal studies to suggest many benefits to resuscitating depressed newborns whilst on the cord, such a recommendation has not been formulated in the ILCOR or ERC guidelines due to the lack of human studies on the feasibility and safety of this approach [59, 60]. First-in-human studies are currently underway.

Newborns that require resuscitation at birth are at a higher risk of brain injury and death, and some commentators have argued that these infants may receive the greatest benefit from DCC [61]. In the setting of hypovolaemic shock, fresh whole blood which supplies volume expansion, colloid expansion, and oxygen-carrying capacity may be considered an ideal agent [62]. The benefits of DCC are thought to result from a number of physiological processes that include (1) the placental transfer of blood, (2) accommodating a more stable haemodynamic transition from fetal life, and (3) a transfer of stem cells.

The volume and rate of delivery of placental blood as a result of DCC was thought to be increased if the infant was placed in a superior position relative to the placenta when uterine contractions are present and if newborn respiration has commenced [63–65]. However, recent studies suggest that the position of the newborn may not have much influence on the volume of blood transfused [66, 67]. Placental transfusion can result in a direct intravascular transfusion of 30–40% of the total neonatal blood volume [63–65, 68]. For infants with hypovolaemic shock, DCC could be an important first step in their resuscitation, if early identification was possible [69]. For preterm infants (<32 weeks' gestaion), an increase in total blood volume results in higher BP and a reduced need for inotropic support, with no significant side effects [57]. Conversely, it is unknown whether asphyxiated infants will benefit from placental transfusion and whether DCC could be deleterious due to the potential for volume overload, polycythemia, and the possible delay in establishing positive pressure ventilation [70].

DCC may facilitate a more stable haemodynamic transition for compromised infants [61]. In preterm infants, it was associated with a 50% reduction in intraventricular haemorrhage (although not significant for grade 3 or 4), which can be explained by the increase in fluctuations of cardiac output which follow immediate cord clamping [57, 71, 72].

DCC also increases the transfer of haematopoietic stem cells, endothelial cell precursors, mesenchymal progenitors, and pluripotent lineage stem cells [73]. Stem cell therapies are under investigation for the early treatment of developmental brain injury, including perinatal asphyxia and preterm birth [74, 75]. The evidence to date supports that cord blood cells may provide neuro-protective benefits due to their actions on a range of complementary biochemical pathways that become dysregulated in response to perinatal asphyxia [76]. Autologous umbilical-cord blood mononuclear cells in asphyxiated newborn lamb and rat models restore normal brain metabolism, and reduce brain inflammation, astrogliosis, and neuronal apoptosis [74, 77, 78]. Studies to date have concentrated on autologous transfusions, and the placental transfusion of stem cells by DCC has yet to be studied in vivo. Therefore DCC for infants in need of resuscitation cannot be recommended based on the transfer of stem cells alone [76].

Strategies that allow for placental transfusions but do not delay resuscitative measures are currently under evaluation, as mentioned earlier. Newborn resuscitation at the bedside while the cord is still attached is now feasible

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with the introduction of mobile resuscitation trolleys [79]. Another strategy that allows for placental transfusion at birth and does not delay neonatal resuscitation is umbilical-cord milking, which has the advantage of transfusing similar volumes without delaying routine neonatal resuscitation [80]. Short-term benefits similar to those with DCC for preterm infants have been reported [81]. However, there is still a dearth of knowledge about umbilical-cord milking, with concerns that multiple stripping of the cord could release harmful cytokines or cellular debris into the infant's circulation so, at present, guidelines do not recommend it following term or preterm deliveries [61].

While DCC may be appropriate when haemorrhagic shock is presumed, the same difficulties in distinguishing such infants from other compromised infants remain. Further research on stem cell transplants, bedside resuscitation measures, and umbilical-cord milking are warranted.

Conclusion

In a setting with presumed or obvious blood loss such as placental abruption or fetal-to-maternal transfusion, VR therapy may indeed have an important role to play. However, for other clinical scenarios such as asphyxia, the current set of clinical and technical tools makes it difficult to differentiate the haemodynamically compromised infant who will benefit from volume therapy from the normovolaemic asphyxiated infant who may, potentially, be further compromised by volume therapy. When the decision to treat is made, fresh whole blood should be used if available, and crystalloid solutions if not. DCC remains the most obvious source for immediate transfusion in such infants but, currently, it is unknown if DCC is beneficial in the setting of haemorrhagic shock, and further work is needed to assess whether DCC with ventilatory support results in better outcomes for compromised infants at birth.

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Author Contributions

E.M.D. conceived and designed the review. D.F. drafted the initial manuscript. All authors critically revised the manuscript for important academic content, agreed on the final draft, and approved its submission for publication.

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