How to Monitor the Brain during Immediate Neonatal Transition and Resuscitation: A Systematic Qualitative Review of the Literature

Gerhard Pichler^{a–c} Po-Yin Cheung^{a, b} Khalid Aziz^{a, b} Berndt Urlsberger^c
Georg M. Schmölzer^{a–c}

^aDivision of Neonatology, Department of Pediatrics, University of Alberta, and ^bNeonatal Research Unit, Royal Alexandra Hospital, Alberta Health Services, Edmonton, Alta., Canada; ^cDivision of Neonatology, Department of Pediatrics, Medical University, Graz, Austria

Key Words

Neonates · Cerebral tissue oxygen saturation · Oxygenation · Perfusion · Cerebral activity · Near-infrared spectroscopy · Amplitude-integrated encephalogram · Doppler sonography

Abstract

Background: The brain is vulnerable to injury and dysfunction during transition after birth in neonates. Clinical assessment of the neurological status immediately following birth is difficult, especially during resuscitation. **Objective:** Our aim was to review physiological monitoring of the brain during immediate postnatal transition – the first 15 min after birth. **Methods:** A systematic search of PubMed and EMBASE was performed using the following terms: newborn, neonate, neonates, transition, after-birth, delivery room, cerebral, brain, monitoring, neurology, oxygenation, saturation, activity, imaging, perfusion, Doppler, and blood flow. Additional articles were identified by manual search of cited references. Only human studies describing cerebral changes during the first 15 min after birth were included. **Results:** Six studies were identified, which described sequential measurements of cerebral perfusion using Doppler sonography, one of these in combination with continuous monitoring of cerebral tissue oxygenation with near-infrared spectroscopy (NIRS). A further 15 studies were identified that used NIRS to

continuously monitor cerebral tissue oxygenation. In one study, cerebral activity was continuously monitored with an additional amplitude-integrated encephalogram. **Conclusion:** Monitoring the brain provides additional information during immediate transition and may help to guide resuscitation. Doppler sonography is technically challenging during resuscitation and is therefore of limited value. NIRS provides continuous monitoring and is feasible even in very-low-birth-weight infants. In the future, an amplitude-integrated encephalogram might give further information on the status of the brain, but before any of these modalities can routinely be recommended during neonatal resuscitation, clinical trials targeting stable brain function parameters are needed.

© 2014 S. Karger AG, Basel

Introduction

Fetal to neonatal transition (defined for this study as the first 15 min after birth) is a very complex physiological process. Disturbances are common with potential for long-term harm. Initial assessment of neonates is usually based on visual inspection, palpation and/or auscultation, and response to stimuli. Assessment includes evaluation of breathing, heart rate, skin color, muscle tone and reflexes using the Apgar score [1–4]. Unfortunately, clin-

Fig. 1. PRISMA flowchart of the search terms presented in the online supplementary Appendix.

Table 1. Cerebral monitoring immediately after birth

	Cerebral perfusion	Cerebral oxygenation	Cerebral activity
Monitoring	Doppler sonography	Near-infrared spectroscopy	Amplitude-integrated EEG
	Non-continuous	Continuous	Continuous
Study design	Observational	Observational	Observational
Human studies	6	15	1

ical assessment of the newborn has high interobserver variability leading to similar variability in Apgar scores, which are amplified when observers score preterm babies or babies in need of resuscitation [5–7]. The unreliability of clinical assessment has led to increased use of monitoring (e.g. arterial pulse oximetric oxygen saturation (SpO₂) and heart rate) to guide neonatal resuscitation [8–10]. In addition, respiratory function monitoring has been demonstrated to improve mask ventilation in neonates requiring breathing support [11]. Although there is increasing evidence regarding the potential benefits of monitoring during neonatal transition, no improvements in short- or long-term outcomes have been reported [10].

The brain is a vulnerable organ during fetal to neonatal transition. However, current routine monitoring using SpO₂ and heart rate does not provide information about cerebral oxygenation or perfusion or brain activity. Monitoring these parameters might influence interventions that affect survival as well as short- and long-term neurodevelopment outcomes. The aim of the review is to discuss the feasibility of currently available methods to mon-

itor cerebral transition in newborn infants during the immediate postnatal transition (arbitrarily defined as the first 15 min after birth) along with advantages and disadvantages of each method.

Search Strategy and Selection Criteria

Articles were identified using the stepwise approach specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [12].

Search Strategy

A systematic search was performed of PubMed and EMBASE to identify articles in English language published from January 1973 through October 2013. Studies had to address monitoring the brain in neonates during the first 15 min after birth. Search terms included: newborn, neonate, neonates, transition, after-birth, delivery room, cerebral, brain, monitoring, neurology, oxygenation, saturation, activity, imaging, perfusion, Doppler, and blood flow (see online suppl. Appendix 1, www.

Table 2. CBF velocity measured with Doppler sonography in neonates immediately after birth

Author/year	Gestation	Mode of delivery	Intubation for respiratory support	Artery	First measurement				
					time after birth, min	V _{max} , cm/s	V _{diast} , cm/s	V _{mean} , cm/s	course
Sonesson, 1987 [13]	term	CS	no	internal carotid artery	<15	33.7±6.7	8.8±4.6	–	decrease
Maesel, 1994 [14]	term	VD	no	medial cerebral artery	4 (2–6)	48.3±10	14.6±6	29.1±8	increase/decrease
Ipsiroglu, 1993 [15]	term	VD/CS	no	anterior cerebral artery	1–4	58±16	–	35±13	increase/decrease
Maesel, 1996 [16]	term	VD/CS	no	medial cerebral artery	11±4	–	–	29±8*– 34±10**	decrease
Noori, 2012 [17]	term	VD	no	medial cerebral artery	7	–	–	34.4±12.7	decrease
Jorch, 1993 [18]	preterm	CS	yes	anterior cerebral artery	1.25	29 (11–57)	1 (–1 to 25)	–	increase/decrease

CS = Cesarean section; VD = vaginal delivery; V_{max} = peak-systolic flow velocity; V_{diast} = end-diastolic flow velocity; V_{mean} = mean flow velocity.
 * Vaginal delivery, appropriate for gestational age term neonate. ** Cesarean section, appropriate for gestational age term neonate.

Table 3. Cerebral oxygenation monitored with NIRS in neonates immediately after birth

Author/year	Neonates	Delivery	Oxygen	Device	Position	Duration, min
Peebles, 1992 [19]	term	VD	no	/	scalp	9
Isobe, 2000 [20]	term	CS/VD	yes/no	IMUC 7000	frontal	15
Isobe, 2002 [21]	term	CS/VD	no	IMUC 7000	frontal	15
Fauchère, 2010 [22]	term	CS	no	NIRO 300	frontal right	13
Urlesberger, 2010 [23]	term	CS	no	INVOS 5100	frontal left	10
Urlesberger, 2011 [24]	term	CS/VD	no	INVOS 5100	frontal left	10
Fuchs, 2011 [28]	preterm	CS	yes	FORE-SIGHT	frontal	10
Kratky, 2012 [26]	term	VD	no	INVOS 5100	frontal left	15
Noori, 2012 [17]	term	VD	no	INVOS	frontal	20
Fuchs, 2012 [29]	preterm	CS/VD	yes/no	FORE-SIGHT	frontal	10
Binder, 2013 [30]	preterm	CS	yes/no	INVOS 5100	frontal left	15
Urlesberger, 2013 [27]	term	CS	no	INVOS 5100	frontal left	15
Pichler, 2013 [32]	term	CS	no	INVOS 5100	frontal left	15
Almaazmi, 2013 [25]	term	VD/CS	no	FORE-SIGHT	frontal right	10
Pichler, 2013 [31]	preterm/term	VD/CS	no	INVOS 5100	frontal left	15

karger.com/doi/10.1159/000357162). Additional published reports were identified through a manual search of references in retrieved articles and in review articles. Only human studies with brain monitoring within 15 min after birth were included. Studies starting brain monitoring 15 min after birth and animal studies were excluded.

Study Selection

Articles identified following literature review were evaluated independently by two authors (G.P., G.M.S.) for inclusion using title and abstract. Where uncertainty remained regarding eligibility for inclusion, the full text was reviewed. Two reviewers independently identified relevant abstracts and critically appraised the full text of

identified articles and assessed the methodological quality of included studies. Data were analyzed qualitatively. Data extraction included the characterization of study type, patient demographics, methods, and results.

Results

Our initial search identified 2,185 articles; after removal of duplicates and rejection (e.g. no monitoring in the first 15 min after birth in human neonates) (fig. 1), 20 studies fulfilled our inclusion criteria (table 1). No randomized controlled study was identified. All studies performed cerebral monitoring during the first 15 min after

birth. Six studies described sequential measurements of cerebral perfusion using Doppler sonography (table 2) [13–18], one of them using continuous monitoring of cerebral tissue oxygenation with near-infrared spectroscopy (NIRS) [17]. Fifteen studies described cerebral oxygenation during neonatal transition using NIRS (table 3) [17, 19–32]. One of these studies continuously monitored cerebral activity using amplitude-integrated electroencephalography (aEEG) [32].

Discussion

Fetal to neonatal transition is a complex event including respiratory, cardiovascular, and cerebral changes. Several methods have been described to monitor cerebral changes during fetal and neonatal transition, including Doppler sonography, NIRS, or aEEG.

Doppler Sonography

Sonesson et al. [13] described a decrease of up to 20% in systolic, diastolic, and mean cerebral blood flow (CBF) velocity from the first minutes to 30 min after birth in 20 healthy term newborns, although no change in arterial blood pressure or heart rate was observed. Assuming unchanged intracranial pressure after birth, a fall in CBF velocity and volumetric blood flow without any change in arterial pressure suggested an increase in intracranial vascular resistance in blood vessels distal to the site of measurement [13]. Similar to the previous finding, Maesel et al. [14] reported a decrease in peak-systolic (28%) and end-diastolic (44%) CBF velocities and an increase in the pulsatile index after cord clamping compared to fetal values. Similar observations in 17 out of 20 healthy term neonates were reported by Ipsiroglu et al. [15].

Although a small study reported higher initial CBF velocities in term infants after cesarean section versus vaginal delivery [15], Maesel et al. [16] were unable to observe any difference in CBF velocity in a larger cohort of neonates. Noori et al. [17] recently reported cardiac function, blood flow across the patent ductus arteriosus (PDA), and cerebral oxygenation in addition to CBF velocity in term infants. A reduction of 26% in CBF velocity after 7 min after birth was likely due to an increase in arterial oxygen content and/or shunting through the PDA, whereby changes in diameter of vessels were not ruled out [17]. In intubated preterm infants, a transient increase in CBF velocity was observed within the first 5 min with a decrease thereafter [18]. These neonates were intubated in the first

minutes after birth and thus the initial increase might be due to recovery (increase of heart rate) after intubation.

Although studies predominantly described a decrease of CBF velocity during the immediate transition period, clinical implications remain questionable, since comparison of studies is limited. Differences in CBF velocities between studies might be due to different cerebral arteries with different diameters, or to different insonation angles or due to different time points of measurements that might have influenced velocity. An advantage of Doppler sonography is the possibility of non-invasive monitoring of different regions of the brain. Further limitations of Doppler sonography during immediate transition period are: (i) CBF velocity is measured and not CBF, (ii) measurements are affected by movement of the infant, (iii) it is not continuously acquired, and (iv) it is technically difficult to perform during transition, especially during resuscitation.

Near-Infrared Spectroscopy

Recently there has been increasing interest in continuous monitoring of cerebral tissue oxygenation using NIRS during immediate transition. NIRS measures tissue oxygenation in the arteriolar, capillary and venular compartment. Thus, changes in tissue oxygenation might be due to changes in oxygen delivery and oxygen consumption. In 1992, Peebles et al. [19] described the first study of a term neonate using NIRS during immediate transition and reported a rapid increase of oxygenated hemoglobin and decrease of deoxygenated hemoglobin with initiation of respiration. Cerebral tissue oxygen saturation in neonates immediately after birth was first reported by Isobe et al. [20, 21]. In term neonates, cerebral tissue oxygen saturation achieved a plateau after 7–8 min, earlier than SpO₂ or peripheral tissue oxygen saturation [22, 23]. Cerebral fractional tissue oxygen extraction (FTOE) showed a similar time course to cerebral tissue oxygen saturation achieving a plateau earlier compared to peripheral FTOE [23]. These results demonstrate the potential for preferential oxygen delivery to the brain with increasing CBF in the first minutes after birth [14, 15, 18].

Cerebral tissue oxygen saturation is less affected by mode of delivery (e.g. vaginal delivery vs. cesarean section) [21, 24, 25], although significantly lower SpO₂ and heart rate values have been reported in infants born by cesarean section [24]. Interestingly, cerebral tissue oxygen saturation of vaginally delivered neonates shows a decrease of up to 10% in cerebral tissue oxygen saturation accompanied by an increase of FTOE after 8 min of age [17, 21, 26]. Despite a further increase in SpO₂, the changes in cerebral tissue oxygen saturation and FTOE might

be due to a decrease in CBF after 8 min of age [17]. Increases in arterial oxygen content and/or shunting through the PDA are most likely the cause for these observed CBF changes [17]. Term infants with a visible left-to-right shunt via the ductus arteriosus have a 7% higher cerebral tissue oxygen saturation 15 min after birth compared to infants without a visible shunt [27]. One explanation for the latter finding might be that in newborns where there is no left-to-right flow via the PDA there may be a period of reduced left ventricular output, which may result in impairment of CBF [27].

There is increasing evidence that cerebral tissue oxygenation is modified by resuscitation interventions in preterm infants [28–30]. In late preterm infants receiving respiratory support in the delivery room, cerebral tissue oxygen saturation values were significantly lower when compared to infants experiencing normal (unassisted) transition. In addition, cerebral FTOE values were significantly elevated over a longer period of time [30]. These elevated cerebral FTOE values in the respiratory support group suggest compensation for lower cerebral oxygen delivery [30]. In very-low-birth-weight (VLBW) infants receiving effective sustained inflation during resuscitation at birth, an increase in heart rate and cerebral tissue oxygen saturation was followed by a SpO₂ increase [28]. However, if the sustained inflation was not effective, no immediate increase in SpO₂, heart rate or cerebral tissue oxygen saturation was observed [28]. In a recent study, reference ranges of cerebral tissue oxygenation and cerebral FTOE in neonates requiring no medical support during transition immediately after birth were reported [31].

NIRS is feasible even in VLBW infants during immediate transition and resuscitation. The main limitation of NIRS is that different devices use different technologies and algorithms to measure tissue oxygenation. The most widely used NIRS devices in neonates during transition are the NIRO 300 and 200NX (Hamamatsu, Japan), the InvoTM Cerebral/Somatic Oximeter Monitor (Somanetics, USA) and the FORE-SIGHT (Casmed, USA). Differences in measured regional cerebral tissue oxygenation values between these devices are up to 10% after transition is complete. These differences have to be taken into account using reference ranges or limits. On the other hand, in lower cerebral tissue oxygenation ranges during the first minutes after birth, the difference between devices has been described to be within a range of 2–3% [25].

Amplitude-Integrated EEG

Pichler et al. [32] recently described the use of aEEG in addition to NIRS to monitor cerebral activity during im-

mediate transition. Increase in cerebral activity was associated with an increase in cerebral oxygenation in term infants without the need of resuscitation [32]. In comparison, infants requiring resuscitation had a different cerebral activity pattern compared to uncompromised neonates [32].

aEEG with the advantage of continuous, non-invasive recording is limited by the technical difficulties of sampling and interpretation of an oscillating signal that is prone to artefact.

Gaps in Knowledge

There are several observational studies describing both normative and pathological data on cerebral oxygenation using NIRS. Future studies should address combining SpO₂ and cerebral tissue oxygenation monitoring during neonatal transition to guide respiratory support, supplemental oxygen delivery, and hemodynamic support to maintain adequate cerebral oxygen delivery and avoid cerebral hypo- and hyperoxygenation. In addition, studies using cerebral monitoring during immediate transition in asphyxiated neonates and extremely low gestational age preterm neonates potentially share some light on how to reduce cerebral damage and impaired neurological outcome. Monitoring of cerebral activity with aEEG in addition to cerebral tissue oxygenation monitoring might improve our understanding on the cerebral status of newborn infants and might improve short- and long-term outcomes. Cerebral Doppler sonography is technically challenging during resuscitation and of limited value until newer, rapidly applicable technology is available.

Conclusion

Clinical neurological examination during assisted transition from intrauterine to extrauterine life is unreliable and a poor predictor of long-term outcome. Monitoring the brain provides additional information during immediate transition and may help to guide resuscitation. NIRS is at the moment the most promising method since it provides continuous data monitoring, rapid acquisition, and is feasible even in VLBW infants receiving resuscitation interventions. Clinical trials targeting stable brain function parameters proving beneficial effect on short- and long-term outcome are needed before any of these modalities can be routinely recommended during neonatal resuscitation.

Acknowledgement

G.M.S. is a recipient of a Banting Postdoctoral Fellowship, Canadian Institutes of Health Research and an Alberta Innovates – Health Solutions Clinical Fellowship.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

- 1 Apgar V: A proposal for a new method of evaluation of the newborn infant. *Curr Res Anesth Analg* 1953;32:260–267.
- 2 Thorngren-Jerneck K, Herbst A: Low 5-minute Apgar score: a population-based register study of 1 million term births. *Obstet Gynecol* 2001;98:65–70.
- 3 Moster D, Lie RT, Irgens LM, Bjerkedal T, Markestad T: The association of Apgar score with subsequent death and cerebral palsy: a population-based study in term infants. *J Pediatr* 2001;138:798–803.
- 4 Casey BM, McIntire DD, Leveno KJ: The continuing value of the Apgar score for the assessment of newborn infants. *N Engl J Med* 2001;344:467–471.
- 5 Jepsen HA, Talashek ML, Tichy AM: The Apgar score: evolution, limitations, and scoring guidelines. *Birth* 1991;18:83–92.
- 6 Bashambu MT, Whitehead H, Hibbs AM, Martin RJ, Bhola M: Evaluation of interobserver agreement of Apgar scoring in preterm infants. *Pediatrics* 2012;130:e982–e987.
- 7 O'Donnell CP, Kamlin CO, Davis PG, Carlin JB, Morley CJ: Interobserver variability of the 5-minute Apgar score. *J Pediatr* 2006;149:486–489.
- 8 Dawson JA, Kamlin CO, Vento M, Wong C, Cole TJ, Donath SM, Davis PG, Morley CJ: Defining the reference range for oxygen saturation for infants after birth. *Pediatrics* 2010;125:e1340–e1347.
- 9 Dawson JA, Kamlin CO, Wong C, te Pas AB, Vento M, Cole TJ, Donath SM, Hooper SB, Davis PG, Morley CJ: Changes in heart rate in the first minutes after birth. *Arch Dis Child Fetal Neonatal Ed* 2010;95:F177–F181.
- 10 Dawson JA, Morley CJ: Monitoring oxygen saturation and heart rate in the early neonatal period. *Semin Fetal Neonatal Med* 2010;15:203–207.
- 11 Schmölzer GM, Morley CJ, Wong C, Dawson JA, Kamlin CO, Donath SM, Hooper SB, Davis PG: Respiratory function monitor guidance of mask ventilation in the delivery room: a feasibility study. *J Pediatr* 2012;160:377–381.
- 12 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
- 13 Sonesson SE, Winberg P, Lundell BP: Early postnatal changes in intracranial arterial blood flow velocities in term infants. *Pediatr Res* 1987;22:461–464.
- 14 Maesel A, Sladkevicius P, Valentin L, Marsál K: Fetal cerebral blood flow velocity during labor and the early neonatal period. *Ultrasound Obstet Gynecol* 1994;4:372–376.
- 15 Ipsiroglu OS, Stöckler S, Häusler MC, Kainer F, Rosegger H, Weiss PA, Winter R: Cerebral blood flow velocities in the first minutes of life. *Eur J Pediatr* 1993;152:269–270.
- 16 Maesel A, Sladkevicius P, Gudmundsson S, Marsál K: Mode of delivery and perinatal cerebral blood flow. *Early Hum Dev* 1996;44:179–185.
- 17 Noori S, Wlodaver A, Gottipati V, McCoy M, Schultz D, Escobedo M: Transitional changes in cardiac and cerebral hemodynamics in term neonates at birth. *J Pediatr* 2012;160:943–948.
- 18 Jorch G, Rabe H, Michel E, Engels M, Schulz V, Hentschel R, Koch HG, Hultsch E: Resuscitation of the very immature infant: cerebral Doppler flow velocities in the first 20 minutes of life. *Biol Neonate* 1993;64:215–220.
- 19 Peebles DM, Edwards AD, Wyatt JS, Cope M, Delphy DT, Reynold EO: Changes in human fetal cerebral oxygenation and blood volume during delivery. *Am J Obstet Gynecol* 1992;167:1916–1917.
- 20 Isobe K, Kusaka T, Fujikawa Y, Kondo M, Kawada K, Yasuda S, Itoh S, Hirao K, Onishi S: Changes in cerebral hemoglobin concentration and oxygen saturation immediately after birth in the human neonate using full-spectrum near-infrared spectroscopy. *J Biomed Opt* 2000;5:283–286.
- 21 Isobe K, Kusaka T, Fujikawa Y, Okubo K, Nagano K, Yasuda S, Kondo M, Itoh S, Hirao K, Onishi S: Measurement of cerebral oxygenation in neonates after vaginal delivery and cesarean section using full-spectrum near-infrared spectroscopy. *Comp Biochem Physiol A Mol Integr Physiol* 2002;132:133–138.
- 22 Fauchère JC, Schulz G, Haensse D, Keller E, Ersch J, Bucher HU, Wolf M: Near-infrared spectroscopy measurements of cerebral oxygenation in newborns during immediate postnatal adaptation. *J Pediatr* 2010;156:372–376.
- 23 Urlesberger B, Grossauer K, Pocivalnik M, Avian A, Müller W, Pichler G: Regional oxygen saturation of the brain and peripheral tissue during birth transition of term infants. *J Pediatr* 2010;157:740–744.
- 24 Urlesberger B, Kratky E, Rehak T, Pocivalnik M, Avian A, Czihak J, Müller W, Pichler G: Regional oxygen saturation of the brain during birth transition of term infants: comparison between elective cesarean and vaginal deliveries. *J Pediatr* 2011;159:404–408.
- 25 Almaazmi M, Schmid MB, Havers S, Reister F, Lindner W, Mayer B, Hummler HD, Fuchs H: Cerebral near-infrared spectroscopy during transition of healthy term newborns. *Neonatology* 2013;103:246–251.
- 26 Kratky E, Pichler G, Rehak T, Avian A, Pocivalnik M, Müller W, Urlesberger B: Regional cerebral oxygen saturation in newborn infants in the first 15 min of life after vaginal delivery. *Physiol Meas* 2012;33:95–102.
- 27 Urlesberger B, Brandner A, Pocivalnik M, Koestenberger M, Morris N, Pichler G: A left-to-right shunt via the ductus arteriosus is associated with increased regional cerebral oxygen saturation during neonatal transition. *Neonatology* 2013;103:259–263.
- 28 Fuchs H, Lindner W, Buschko A, Trischberger T, Schmid M, Hummler HD: Cerebral oxygenation in very low birth weight infants supported with sustained lung inflations after birth. *Pediatr Res* 2011;70:176–180.
- 29 Fuchs H, Lindner W, Buschko A, Almazam M, Hummler HD, Schmid MB: Brain oxygenation monitoring during neonatal resuscitation of very low birth weight infants. *J Perinatol* 2012;32:356–362.
- 30 Binder C, Urlesberger B, Avian A, Pocivalnik M, Müller W, Pichler G: Cerebral and peripheral regional oxygen saturation during postnatal transition in preterm neonates. *J Pediatr* 2013;163:394–399.
- 31 Pichler G, Binder C, Avian A, Beckenbach E, Schmölzer GM, Urlesberger B: Reference ranges for regional cerebral tissue oxygen saturation and fractional oxygen extraction in neonates during immediate transition after birth. *J Pediatr* 2013;163:1558–1563.
- 32 Pichler G, Avian A, Binder C, Zotter H, Schmölzer GM, Morris N, Müller W, Urlesberger B: aEEG and NIRS during transition and resuscitation after birth: promising additional tools; an observational study. *Resuscitation* 2013;84:974–978.