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Arterial blood pressure and cerebral tissue oxygenation during immediate transition after birth in term and preterm neonates – a prospective pilot observational study

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1. Background

1.1 Clinical assessment immediately after birth

Evaluation of a newborn infant immediately after birth could be a challenge. To standardize the clinical assessment Virginia APGAR introduced 1953 the so-called APGAR-Score, which is still used routinely worldwide, to evaluate the neonates in the delivery room. (1).

1.2 Monitoring immediately after birth

The latest resuscitation guidelines recommend in addition to the clinical assessment to monitor arterial oxygen saturation (SpO2) and heart rate (HR) immediately after birth in neonates in need of support (2).

However, since 1953 beside SpO2 and HR monitoring, further methods and parameters, which could be monitored have been described during the immediate transition after birth that might help to assess the neonate in this crucial period. These methods include cardio-circulatory monitoring of blood pressure or cardiac output (3–5), respiratory function monitoring (6), transcutaneous monitoring of pCO2 (7) and cerebral monitoring with (a)EEG or near infrared spectroscopy (NIRS) (10, 11).

1.3 Cardio-circulatory monitoring during immediate transition

Blood pressure on the one hand is a routine monitoring in the NICU measured invasively or with the oscillometric method non-invasively. During immediate neonatal transition in the delivery room, the invasive measurement is not feasible, whereby the oscillometric method has already been proven to be feasible. (13). Meanwhile, reference ranges for non-invasively measured arterial blood pressure have been published for preterm and term neonates (14).

Cardiac output on the other hand can be measured with noninvasive, minimal invasive and invasive methods (18). The gold standard method would be the so-called thermodilution technic, which is gained through a pulmonary vain catheter that is, however, quite invasive (19, 20). Cardiac output measurements are therefore performed routinely with the echocardiography especially in severely ill neonates in the NICU. The advantage of the echocardiography is that it is a non-invasive method and the disadvantages are that the quality of the echocardiography depends on the experience of the examiner and evaluation is non-continuous. Furthermore, the measurement itself has its limitation concerning feasibility when performed during resuscitation (4, 21, 22).

A further method to measure cardiac output is the electrical velocimetry. This method is based on the different electrical conductivity of certain biological tissues. Due to impedance changes during a heartbeat, the stroke volume can be assessed, and the cardiac output calculated (8). Electrical velocimetry monitoring is a feasible new method to measure cardiac output during the immediate transition after birth (9). Noori et al. showed that electrical velocity monitoring has regarding the cardiac output comparable results to echocardiography (12).

1.4 Near-infrared spectroscopy (NIRS)

NIRS was first described and published by Jöbsis (23) in 1977. The basis of this technique are the physical properties of the organic tissue to light in the near infrared region. The light used has therefore a wavelength in the near infrared region (700-1000 nm) (11). This light is absorbed, scattered or reflected differently by different chromophores such as myoglobin, cytochrome oxidase, oxygenated or deoxygenated hemoglobin in the biological tissue. Due to this, it is possible to monitor continuously the tissue oxygenation that depends on oxygen supply as well as the consumption of different tissues such as brain, kidney, or muscles (11, 24, 25).

NIRS therefore is a continuous noninvasive monitoring of tissue oxygenation that reflects the tissue oxygen saturation in veins, capillaries, and arteries of the measured compartment (10, 25, 26).

With the knowledge of the SpO2 and the tissue oxygen saturation the fractional tissue oxygen extraction (FTOE) can be calculated (FTOE=(SpO2-tissue oxygenation/SpO2). FTOE reflects the oxygen extraction of a tissue from the vessels, which helps to assess the activity of certain biological tissues (25, 27).

1.5 Arterial blood pressure, cardiac output and cerebral oxygenation

The tissue oxygen saturation is not only depending on the SpO2 but also on the hemoglobin content of the blood, the perfusion and tissue oxygen consumption. Concerning the perfusion and considering the brain it would be the so-called cerebral blood flow (CBF), which depends on cerebral perfusion pressure (CPP). CPP is defined as the difference between intracranial pressure (ICP) and mean arterial blood pressure (MABP) (28–30). During immediate transition ICP measurement is not feasible due to the invasive technics through a catheter and ICP can be assumed to be constant during the transition period especially in preterm neonates where the sutures are not closed yet. In contrast to that, the MABP can easily be measured

even during the immediate transition non-invasively with an oscillometric method as discussed previously (13).

MABP itself depends mainly on CO and vascular resistance. In the peripheral tissue, i.e. muscle, an increase of the MABP correlates well with an increase of oxygenated hemoglobin. The correlation between the MABP and the cranial perfusion and oxygenation should be weaker, due to cerebrovascular response mechanism, known as cerebral autoregulation that should keep cerebral perfusion constant independently of MABP (31).

In sick neonates and in preterm neonates, however this autoregulation is not working as well as in healthy term infants (15, 17).

1.6 Physiological changes of the cardio—circulatory system during transition

The main difference of fetal cardio-circulation to the cardio-circulation after birth is that before birth the lungs are by-passed, and the oxygenated blood is provided by the placenta. The three bypasses are the ductus venosus (DV), a connection between the umbilical vein and the vena cava inferior, the ductus arteriosus (DA), a vessel between pulmonary artery and the aorta to avoid pulmonary circulation, and the foramen ovale (FO), a connection between the cardiac atria which also serves the purpose to bypass the pulmonary circulation.

Due to these described peculiarities the fetal circulation is a parallel circulation instead of a serial one (32, 33).

During transition, the pulmonary resistance drops, due to the lung aeration. This resistance-drop triggers an increase of the pulmonary blood-flow. Considering this new detour, depending on when the umbilical cord was clamped, the preload is reduced during the first minutes after birth. Furthermore, due to the cord clamping the low-resistance placenta circulation is yield, which leads to an increased afterload and the arterial pressure increases. As a result of reduced preload and initial-increased afterload, the cardiac output is reduced with clamping the cord.

Considering these changes, the cerebral blood-flow as well as the systemic blood flow and systemic blood pressure are initially increased whereby a drop occurs immediately after the initial increase due to the reduced cardiac output (34). Afterwards, the cardiac output continues to stay low until the pulmonary blood-flow increases with ventilation of the lungs (35). During this cardio-circulatory and pulmonary changes immediately after birth the cerebral auto-regulatory mechanisms should maintain the cerebral blood-flow constant. These autoregulatory mechanisms are not yet fully comprehensible especially in preterm neonates (36, 37).

In term neonates Baik et al have demonstrated that cFTOE as well as crSO2 are independent of MABP (38, 39). However, Baik's study (38) only investigated MABP in connection with crSO2 as well as cFTOE 15 minutes after birth. However, the question remains, if in term neonates MABP has some influence on cerebral oxygenation before minute 15 after birth when the lung is aerated, and most cardio-circulatory changes take place.

Furthermore, Baik's study (38) showed a significant negative correlation between MABP and cFTOE in preterm neonates which seems to suggest that in preterm infants the autoregulatory mechanism are less mature than in term neonates and that preterm neonates may benefit from blood pressure monitoring during immediate neonatal transition. These findings are in accordance with the animal model of Helou and Rhees observation in neonates (15–17). However again the question remains, if in preterm neonates MABP has more influence on cerebral oxygenation before minute 15 after birth when the lung is aerating and most cardio-circulatory changes take place.

2 Aims

2.1 Primary aim

The primary aim of the present study is therefore to investigate if there is an influence of blood pressure on cerebral oxygen saturation and cerebral oxygen extraction within the first minutes (within 15 minutes) after birth in term and preterm neonates, when most cardio-circulatory changes and aeration of the lung take place.

2.2 Secondary aim

Secondary aims are to investigate a possible influence of cardiac output on cerebral oxygen saturation and cerebral oxygen extraction within the first minutes after birth in term and preterm neonates and any possible differences between term and preterm neonates.

3. Hypotheses:

3.1 Primary Hypothesis I

Non-invasive measured blood pressure correlates with cerebral oxygen saturation and cerebral fractional oxygen extraction, whereby higher blood pressure is associated with higher cerebral

oxygen saturation and lower cerebral fractional oxygen extraction in term and preterm neonates within the first 15 minutes after birth.

3.2 Secondary Hypotheses II

Cardiac output correlates with cerebral oxygen saturation and cerebral fractional oxygen extraction, whereby higher cardiac output is associated with higher cerebral oxygen saturation and lower cerebral fractional oxygen extraction, whereby correlations are more pronounced in preterm neonates within the first 15 minutes after birth.

4 Patients and Methods

4.1 Patients

Term and preterm neonates observed routinely at the resuscitation desk at the Division of Neonatology, Department of Pediatrics, Medical University of Graz after caesarean section and/or who require respiratory support will be eligible for the study. CPAP and PPV with mask, if necessary, will be performed with Neopuff Infant Resuscitator (Fisher&Paykel Healthcare, New Zealand).

The total number of birth/year at the Department of Obstetrics and Gynecology, Medical University of Graz is approximately 3000 - of these are around 8-10% preterm neonates.

The antepartum medical history and birth history will be collected. Gestational age, birth weight, gender, Apgar score, ph of umbilical artery and postnatal blood gases (if routinely analyzed) will be documented in each neonate.

4.1.1 Inclusion criteria

- Term and preterm neonates observed routinely at the resuscitation desk
- Decision to conduct full life support
- Written informed consent

4.1.2 Exclusion criteria

- No decision to conduct full life support
- No written informed consent
- Congenital malformation

4.1.3 Patient groups

1. Preterm neonates (<37+0 weeks of gestation)

2. Term neonates (≥37+0 weeks of gestation)

5 Sample size

In preterm infants, it was found that the correlation between MABP, and cFTOE is r = -0.19 at 15 minutes after birth. Even lower correlations were found for crS02 and MABP and for term infants (38). Due to the bevor in 1.6. described changes during the immediate transition period, which lead to a decrease in cardiac preload and an increase in cardiac afterload the cardiac output is reduced. Considering these changes in the cerebral blood flow as well as the systemic blood flow and systemic blood pressure we expect to find higher correlations in the fifth and tenth minute after birth. According to our experience, it is feasible to include 50 infants in this study. If 50 infants are included and a drop-out rate of 10% is considered, 45 infants can be analyzed. Using these 45 infants the lower limit of Spearman's rank correlation coefficient's 95% CI will be 0.14 for a correlation coefficient of r = 0.40. This lower limit increases to 0.20, 0.26, 0.32 for r = .45, r = .50 and r= .55 respectively.

Therefore we aim for a sample size of 50 neonates in each group – prterm neonates and term neonates, resulting in a total sample size of 100 neonates

6 Study design

Prospective observational pilot study

7 Monitoring

7.1 Routine Monitoring

SpO_2, heart rate, and central temperature will be monitored routinely. In addition, if CPAP or PPV are required non-invasive respiratory-function monitoring and transcutaneous pCO2 as routine non-invasive monitoring will be performed in the first minutes of resuscitation.

<u>Routine monitoring:</u>

1) Pulse oximetry (MR7CDS1 Radical 7, Chemomedica, Austria / IntelliVue MP70, Philips, Netherland)
2) Peripheral and central temperature (IntelliVue MP70, Philips, Netherland)
3) Respiratory function monitor (Monivent)
4) pCO2 (TC Sensor 84, etC02 Sensor, Radiometer RSCH GmbH, Thalwil, Switzerland / IntelliVue MP70, Philips, Netherland)

7.2 Additional Monitoring

In addition during the first 15 minutes we will record: NIRS measurements, non-invasive blood pressure and cardiac output.

Additional Monitoring:

5) NIRS (t-NIRS, Hamamatsu, Japan)
6) Blood pressure measurement (IntelliVue MP70, Philips, Netherland)
7) Cardiac Output (Aesculon-EV-Monitor, Osypka, Berlin, Germany)

7. 3 NIRS - cerebral regional oxygen saturation- tissue oxygenation index

For NIRS measurements the t-NIRS device (Hamamatsu, Japan) will be used. This monitor uses a "time resolved" technique and measures non-invasively oxygenated, deoxygenated and total hemoglobin and tissue oxygenation index (TOI that corresponds to cerebral regional oxygen saturation).

Immediately after birth when the neonate is brought to the resuscitation desk, a sensor will be placed and fixed with a CPAP cap on the left forehead.

*7.4*Blood pressure

For non-invasive blood pressure measurements the IntelliVue MP50 monitor (Philips, Netherland) will be used. The pneumatic cuff will be placed around the left upper arm and blood pressure measurements will be performed during the first fifteen minutes after birth.

*7.5*Cardiac output Monitoring

For non-invasive cardiac-output measurements the Aesculon-Monitor (Osypka, Berlin, Germany) will be used. The monitor uses a new technique of thoracic bioimpedance. Four surface EKG electrodes are placed over the skin (forehead, left side of the neck, left hemithorax and left thigh).

8 Routine Interventions

Resuscitation will be according the "European Consensus Guidelines" on the management of neonatal respiratory distress syndrome (2).

9 Outcome measures

9.1 Primary

- Blood pressure minute 5, 10 and 15
- NIRS data measured with t-NIRS minute 5, 10 and 15
- FTOE minute 5, 10 and 15

9.2 Secondary

- Cardiac output minute 5,10 and 15
- Gestational age

9.3 Exploratory

- Respiratatory support during resuscitation
- SpO2 level at each minute
- HR level at each minute
- Temperature minute 5 and 15
- Monitoring parameters during the first 15minutes after birth:
  - Mean (SD) HR
  - Mean (SD) BP

10 Outcome assessment tools

- Monitoring during the first 15 minutes after birth
- Medical history
- Severe morbidities and all cause mortality will be recorded

11 Risks and benefits

Pulse oxymetry the recommended routine monitoring will be performed in all neonates and SpO_2 will be kept within normal ranges (10^{th}-90^{th} centile) (2) in all neoantes hypoxygenation and hyperoxygenation defined by the routine monitoring should be avoided. Blood measurements are routine in neonates in the NICU and well tolerated. Irritation of the skin due to the NIRS and the Aesculon-Monitor sensors is improbable, because of the short measurement period. Risks related to the manipulation of the patient during positing and re-positing of the sensors will be minimized by experience of research team. Neonates will always be under routine monitoring and observation by nurses and neonatologists.

12 Informed consent procedure

Parents of potential participants will be invited to enroll their preterm newborn, when possible, before delivery. The qualified physician will make contact and parents will be informed of the study and given the Parent information sheet. The parents will be given time to think and ask

questions, before a written informed consent can be obtained. Parents will be given a copy of the informed consent.

13 Data collection

NIRS data and other monitoring data (SpO_2, HR, tcpCO2, and temperature) will be collected in a polygraphic system (alpha-trace digital MM, B.E.S.T. Medical Systems, Austria). Blood pressure, demographic and medical history data will be anonymized and collected with a CRF.

14 Data analysis

Initially, all data will undergo a descriptive analysis to uncover any data anomalies and missing values that may impact the validity of the data analysis.

Demographic, NIRS and routine monitoring data will be presented as n (%), mean and standard deviation (SD), or median and interquartile range (IQR), as appropriate.

Comparisons of categorical characteristics between preterm and term infants will be performed using chi-square test and for continuous variables using t-test or Mann-Whitney U-test, as appropriate.

Correlation analyses will be performed to investigate, if there is a connection between crSO2, cFTOE and MAP in preterm and term infants at different time points, individually. Correlations will be performed using Spearman's rank correlation coefficient or Pearson's correlation when appropriate. A p-value < 0.05 will be considered statistical significant. The statistical analyses will be performed using IBM SPSS Statistics 22.0.0 (IBM Corporation; Armonk, USA).

Comparison of correlation analyses at different time points and in term and preterm neonates will be descriptive.Statistical analysis is planned to be performed in cooperation with the Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Austria.

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