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Cerebral tissue oxygenation index, cardiac output and superior vena cava flow in infants with birth weight less than 1250 grams in the first 48 hours of life

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ABSTRACT

Background: Near-infrared spectroscopy is a non-invasive method of assessing cerebral oxygenation. Functional echocardiography is increasingly used by neonatologists in the assessment of cardiovascular function.
Aims: To correlate cerebral tissue oxygenation index (cTOI) and cardiac output in infants less than 1250 g at 6, 12, 24 and 48 hours of age.
Study design: A prospective observational study.
Subjects: Newborns with birth weight < 1250 g.
Outcome measures: Serial assessments of superior vena cava (SVC) flow, right and left ventricular outputs, ductus arteriosus and cTOI were performed at 6, 12, 24 and 48 hours of age. Clinical parameters, including mean blood pressure, mean airway pressure, blood gas parameters and oxygen saturations were recorded.
Results: 22 neonates were enrolled following parental consent. The mean birth weight was 851 g (SD ± 201), mean gestational age was 25.9 weeks (SD ± 1.7). Mean SVC flow at 6 hours of age was 56.8 ml/kg/min and increased to 68.6 ml/kg/min at 48 hours of age. 9 infants (41%) had at least one measurement of low SVC flow (<41 ml/kg/min) in the first 48 hours. Mean cTOI was 65.2% at 6 hours of age, 63.9% at 12 hours of age, 68.8% at 24 hours of age and 67.2% at 48 hours of age. Cerebral fractional tissue oxygen extraction values were highest at 12 hours (0.31 ± 0.09). There was no correlation between SVC flow and cTOI values.
Conclusion: SVC flow, left and right ventricular output increased during first 48 hours of life. cTOI decreased at 12 hours of age with a concomitant increase in fractionated oxygen extraction. These changes reflect transitional changes in both cardiac and cerebral hemodynamics in extremely low gestational age newborns during the first 48 hours.

1. Introduction

Despite continued advances in neonatal intensive care very preterm and extremely preterm infants remain at risk of short and long term morbidity. Approximately one third are affected by cardiovascular insufficiency resulting in systemic hypoperfusion and ischemia of vital organs [1]. Periventricular/intraventricular haemorrhage and periventricular leucomalacia are major complications of cerebral ischemia [2]. The critical period remains the first 48 hours of life; however, the ability to recognize infants with systemic or cerebral hypoperfusion remains limited.

Near-infrared spectroscopy (NIRS) is a relatively non-invasive bedside method to measure tissue oxygenation continuously. Spatially resolved spectroscopy makes it possible to measure ratio of absolute oxygenated haemoglobin to total haemoglobin (tissue oxygenation index) and represents an average of arterial and venous blood oxygenation [3,4]. When measured in the brain this is referred to as the cerebral tissue oxygenation index (cTOI). A previous study has documented an increase in cTOI during the first 3 days of life in preterm infants [5].

Functional echocardiography is increasingly used by neonatologists in the assessment of cardiovascular status of the newborn in neonatal intensive care unit. It provides information on both heart structure and function. With Doppler techniques, it is possible to measure cardiac output, superior vena cava (SVC) flow and shunts, including the patent ductus arteriosus. It is estimated that approximately 80% of upper body blood flow goes to the brain [6], suggesting that SVC flow may be a surrogate marker of cerebral perfusion. Low SVC flow has been associated

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with an increased risk of peri/intraventricular haemorrhage in preterm neonates [1,7].

We previously identified a weak correlation between SVC flow and cTOI in very low birth weight infants on the day 1 of life [8]. The aim of this study was to validate these findings in a similar, but lower birth weight and more immature group, utilising serial measurement of cerebral oxygenation by near infrared spectroscopy and echocardiographically measured cardiac output and input at predefined times over the first 48 hrs of life.

2. Methods

We conducted a prospective observational study at a level III neonatal intensive care unit (Coombe Women and Infants University Hospital, Dublin, Ireland) between February and June 2010. The study was approved by research ethics committee of the hospital. Neonates with birth weight less than 1250 g admitted to neonatal intensive care unit were eligible for enrolment and informed parental consent was obtained. Patients with congenital heart disease (excluding patent ductus arteriosus and foramen ovale) or major congenital malformations were excluded. All echocardiography and NIRS measurements as well as physiological data were recorded at 6, 12, 24 and 48 hours of age. Attending physicians were blinded to data from the study and values obtained (SVC flow and cTOI measurements) were not used in the management of infants.

2.1. Echocardiography studies

Phillips HD11XE ultrasound machine with 5–8 MHz transducer incorporating colour flow and pulsed wave Doppler with adaptive Doppler technology was used. A complete two-dimensional echocardiography examination was performed and structural normality of the heart was established on the first measurement. Infants were in supine position and were not sedated. No angle correction was used for Doppler measurements. We used methods described previously in the literature [9,10]. All parameters were calculated as an average value of five consecutive heart cycles. Velocity time integrals of SVC flow are influenced by respiration. If obvious pattern of size or shape of velocity time integrals was seen, we calculated consecutive complexes to cover all shapes equally. SVC flow, left and right cardiac output (LVO, RVO) were calculated using formula: flow = (velocity time integral × (Π × (mean diameter^2/4) × heart rate)/birth weight. A single investigator [JS] performed all examinations. JS is experienced in targeted neonatal echocardiography and obtained formal training supervised by a paediatric cardiologist. All scans were recorded on the hard disk and values were calculated at a later stage. Low SVC flow was defined as flow less than 41 ml/kg/min [1,7].

2.2. Cranial ultrasound

We used a 7.5 MHz transducer for the cranial ultrasound, which was performed after all echocardiography examinations, then serially every 2 weeks and before discharge from the hospital. IVH was classified according to Papile grading [11] and PVL according to the definition by de Vries et al. [12].

2.3. NIRS

All measurements were done using the NIRO-200 machine (Hamamatsu Photonics, Hamamatsu City, Japan). The probe was secured on the fronto-parietal region and shaded against ambient light. Mean cTOI from the 30 min period prior the echocardiography was calculated. The sample time was one every 5 second. Cerebral fractional tissue oxygen extraction (cFTOE) was calculated as cFTOE = (periph. SaO_2 – cTOI)/periph. SaO_2.

2.4. Clinical parameters

Parameters of ventilation support (ventilation mode, mean airway pressure, fraction of inspired oxygen), invasive blood pressure (if invasive measurement was not available, non-invasive blood pressure with pressure cuff of appropriate size was used) and circulatory support (catecholamine, volumotherapy in 6 hours before examination) were recorded before echocardiography. Arterial blood gas or capillary sample was obtained at the time of echocardiography.

2.5. Statistical analyses

We analysed the data using a PC-based statistics package (StatsDirect version 2.7.8) using paired *t*-test, Mann–Whitney U test and Pearson correlation as appropriate, $p < 0.05$ was considered significant.

3. Results

The study population consisted of 22 preterm infants with mean birth weight 851 grams (SD ± 201 g) and mean gestation age 25.9 weeks (SD ± 1.7). There were 11 female infants and 11 infants were delivered by caesarean section. The mothers of 17 infants received at least one dose of antenatal corticosteroids. 13 neonates received conventional ventilation, 3 high frequency oscillation and 6 neonates were on non-invasive nasal continuous positive airway pressure support at the time of the echocardiography. There were 3 infants on inhaled nitric oxide during the first 48 hours. A bolus of normal saline was administered to 4 infants (18%) within 6 hours of birth and 4 infants (18%) were treated with catecholamine. 21 (95%) babies survived to discharge. There were 4 infants who developed an intracranial haemorrhage grade 2 or more (Table 1). There were no infants excluded from the study.

cTOI decreased at 12 hours of age followed by a statistically significant increase at 24 hours of age ($p = 0.008$) and remained stable at 48 hours of age; mean values (±SD) were 65.2% (±10.05) at 6 hours, 63.9% (±5.93) at 12 hours, 68.8% (±5.65) at 24 hours and 67.2% (±7.15) at 48 hours of life. This was accompanied by reciprocal changes in cFTOE values. There was a non significant increase from 6 to 12 hours followed by a statistically significantly decrease at 24 hours of age ($p = 0.05$) which remained stable at 48 hours (Table 2).

SVC flow increased during the study period; mean values (±SD) were 56.8 ml/kg/min (±26.1) at 6 hours, 61.8 ml/kg/min (±28.8) at 12 hours, 64.9 ml/kg/min (±19.1) at 24 hours and 68.6 ml/kg/min (±26.5) at 48 hours of life, however this did not reach statistical significance ($p = 0.07$). 9 infants (41%) had low SVC flow in at least one measurement, the majority [6] of whom (27%) had low SVC flow at 6 hours, 5 (23%) at 12 hours, 1 (5%) at 24 hours and 2 (9%) neonates had low SVC flow at 48 hours of age. One infant had three recordings of low SVC flow and 3 infants had low SVC flow in two consecutive measurements. SVC flow negatively correlated with cTOI at 6 hours (p-value 0.02, correlation coefficient $r = -0.49$) (Fig. 1). There was no statistically significant correlation between SVC flow and cTOI at 12, 24 and 48 hours of age.

Four infants in our cohort developed severe IVH. One with a grade IV haemorrhage had severe pulmonary hypertension treated by

Table 1
Demographic data.

	Mean	SD
Birth weight (g)	851.9	201.9
Gestational age (week)	25.9	1.7
Female no. (%)	11 (50)	
Antenatal steroids no. (%)	17 (77)	
Vaginal delivery no. (%)	11 (50)	
IVH ≥ grade 2 no. (%)	4 (18)	
Survival no. (%)	21 (95)	