Cerebral oxygen delivery is reduced in newborns with congenital heart disease

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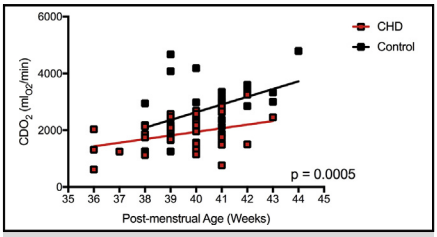
ABSTRACT

Objective: To investigate preoperative cerebral hemodynamics in newborns with congenital heart disease. We hypothesized that cerebral blood flow and oxygen delivery would be decreased in newborns with congenital heart disease compared with controls.

Methods: Using a ''feed-and-sleep'' approach to performing neonatal magnetic resonance imaging, we measured cerebral blood flow by using a slice prescription perpendicular to the right and left internal carotid arteries and basilar artery at the level of the clivus. We calculated brain volume by segmenting a 3-dimensional steady-state free procession acquisition of the whole brain, allowing quantification of cerebral blood flow indexed to brain volume. Cerebral oxygen delivery was calculated as the product of cerebral blood flow and preductal systemic arterial oxygen content obtained via a combination of conventional pulse oximetry and laboratory analysis of venous blood samples for hemoglobin concentration.

Results: A complete set of measurements were obtained in 32 newborns with heart disease and 31 controls. There was no difference in gestational age between the heart disease and control groups. There was no difference in cerebral blood flow compared with controls (103.5 ± 34.0 vs 119.7 ± 40.4 mL/min), whereas cerebral oxygen delivery was significantly lower in the congenital heart disease subjects (1881 ± 625.7 vs 2712 ± 915.7 mL_{O2}/min). Ten newborns with congenital heart disease had diffuse excessive high signal intensity in their white matter and 2 had white matter injury whereas another 5 had both.

Conclusions: Newborns with unrepaired cyanotic congenital heart disease have decreased cerebral oxygen delivery due to arterial desaturation. If brain growth and development are adversely affected through oxygen conformance, our findings could have clinical implications in terms of timing of surgical repair. (J Thorac Cardiovasc Surg 2016;152:1095-103)



Cerebral oxygen delivery is significantly diminished in congenital heart disease.

Central Message

In preoperative newborns with cyanotic congenital heart disease, cerebral blood flow is maintained whereas cerebral oxygen delivery is decreased through arterial desaturation.

Perspective

This paper investigates preoperative cerebral hemodynamics in congenital heart disease, exploring the impact of cyanosis on cerebral oxygen delivery, which could have implications for the timing of surgical repair.

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In recent decades, significant advances in cardiac surgical techniques have resulted in excellent survival rates for even the most complex forms of congenital heart disease (CHD). Despite improvements in intraoperative brain protection, however, the neurodevelopmental outcomes of the survivors remain a serious cause for concern, and quantitative brain magnetic resonance imaging (MRI) findings point to delayed brain development and white matter injury (WMI) resulting from chronic preoperative cerebral hypoxia as a possible cause.[1-5]

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Abbreviations and Acronyms

BA = basilar artery
BV = brain volume
CBF = cerebral blood flow
CDO_2 = cerebral oxygen delivery
CHD = congenital heart disease
CoA = coarctation of the aorta
DEHSI = diffuse excessive high signal intensity
Hct = hematocrit
Hgb = hemoglobin
MRI = magnetic resonance imaging
PC = phase contrast
PMA = postmenstrual age
SVP = single-ventricle physiology
TGA = transposition of the great arteries
VA = vertebral artery
WMI = white matter injury

Chronic hypoxia regulates cell metabolism through a mechanism known as oxygen conformance, whereby the cell protects itself against bioenergetic collapse by downregulating its oxygen requirement such that any reduction in oxygen delivery results in downstream effects on protein synthesis and cell cycling.[6] In a murine model, oxygen tension recently has been shown to impact postnatal myelination through hypoxia-inducible factor, which regulates angiogenesis and the maturation of oligodendrocyte precursor cells.[7] It is therefore possible that the rapid brain growth and development that normally occurs during early infancy could be adversely impacted by decreased cerebral oxygen delivery (CDO_2) that results from CHD, particularly in those lesions that require a palliative or delayed surgical approach.

Previous studies in which the authors used optical measurements of tissue oxygenation and the MRI arterial spin labeling method have suggested that CDO_2 and cerebral blood flow (CBF) are impaired in newborns with severe forms of CHD[8,9]; however, compensatory increases in CBF to maintain CDO_2 in the setting of hypoxia have been described in human and animal fetuses and adults.[10-12] A new approach to measuring CBF in newborns via the use of cine phase-contrast (PC) MRI has been described recently.[13] We were interested in applying this technique to newborns with CHD in combination with conventional methods for measuring the oxygen content of blood and estimating brain volume (BV) to investigate cerebral hemodynamics in newborns with unrepaired CHD.

METHODS

Subjects

The study design was a hospital research ethics board–approved, single-center prospective case control study conducted between June 2013 and April 2015 at The Hospital for Sick Children in Toronto. The parents of consecutive children born with single-ventricle physiology (SVP), transposition of the great arteries (TGA), and coarctation of the aorta (CoA) were invited to participate in the study. We defined subjects with SVP as those who were treated clinically on a palliative pathway to Fontan circulation. Preoperative imaging was arranged when the MRI was available and the clinical condition of the patient was suitable for an unsedated examination. Control subjects were drawn from a population of normal newborns born at Mount Sinai Hospital in Toronto during the same period.

Written consent was obtained from the parents of all subjects. We recruited 75 term newborns and all subjects were scanned in a 1.5-Tesla clinical MRI system (Siemens Avanto, Erlangen, Germany) before cardiac surgery at a mean age of 7.5 ± 11 days. The infants were fed and swaddled before imaging, and the scans were performed during sleep with no sedation or contrast medium using a 16-channel Siemens Pediatric Head Coil (Siemens Avanto, Erlangen, Germany).

CBF and CDO_2

CBF was measured according to a previously published technique consisting of a single cine PC acquisition prescribed perpendicular to both internal carotid arteries and the basilar artery (BA) at the level of the clivus.[13,14] The following scan parameters were used: echo time = 4.4 ms, field of view = 150 mm, matrix size = 150 × 112, slice thickness = 4 mm, temporal resolution = 14.3 ms, number of signal averages = 1, velocity encoding = 150 cm/s giving an in-plane resolution of 0.6 × 0.6 mm, and an acquisition time of 1 minute, 7 seconds. CBF volume was quantified with a commercial postprocessing tool (QFlow version 5.6; Medis, Leiden, The Netherlands).

In 14 patients, we obtained an additional PC acquisition in the neck, at the level of the larynx, which included imaging of the vertebral arteries (VAs) (Figure 1, *A*). Vessels were contoured manually by drawing points around the vessel circumference at each phase of the cardiac cycle and adjusted by the use of smoothing tools to yield vessel flows in mL/min. The arterial oxygen saturation was measured at the time of the PC acquisition by the use of conventional pulse oximetry with the probe applied to the right hand (model no. 2329; Masimo rainbow SET; Masimo Corp, Irvine, CA). The hemoglobin (Hgb) concentration was measured before MRI in all subjects with CHD, with samples obtained less than 8 days before imaging (mean interval 4 days). In control subjects, we were not permitted to obtain blood and used an estimated Hgb concentration of 17 g/dL based on well-established reference data[15,16] to calculate CDO_2 as follows:

$$CDO_2 = SaO_2 \times [Hgb] \times 1.36 \times CBF \quad [16]$$

where 1.36 is the amount of oxygen bound per gram of Hgb at 1 atmosphere.

BV and Brain Maturation

To index net CBF and CDO_2 measurements, BV was measured by segmenting the brain from a 3-dimensional steady-state free procession acquisition of the whole head (echo time = 2.0 ms, repetition time = 4.5 ms, field of view = 200, matrix size = 192 × 192, slice thickness = 0.9 mm, number of signal averages = 1, parallel imaging factor = 1, scan time = 37 seconds), with the use of Mimics (Materialize, Leuven, Belgium), where brain tissue was isolated from cerebral spinal fluid within the ventricular system and around the brain in the extra-axial cerebrospinal fluid space by the use of thresholding and fine edited by the use of slice selection tools (Figure 1, *B*). BV was converted to brain weight with a conversion factor of 1.04.[17] To assess WMI, diffuse excessive high signal intensity (DEHSI) in cerebral white matter was determined subjectively by a neuroradiologist in all subjects with CHD. Note was also made of any focal WMI or other abnormality. Furthermore, a total maturation score was evaluated by 2 observers (J.L., B.S.) blinded to