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Elevated cranial ultrasound resistive indices are associated with improved neurodevelopmental outcomes one year after pediatric cardiac surgery: A single center pilot study

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A B S T R A C T

Objective: To determine if a non-invasive, repeatable test can be used to predict neurodevelopmental outcomes in patients with congenital heart disease.
Methods: This was a prospective study of pediatric patients less than two months of age undergoing congenital heart surgery at the Children's Health Children's Medical Center at Dallas. Multichannel near-infrared spectroscopy (NIRS) was utilized during the surgery, and ultrasound (US) resistive indices (RI) of the major cranial vessels were obtained prior to surgery, immediately post-operatively, and prior to discharge. Pearson's correlation, Fischer exact *t* test, and Fischer r to z transformation were used where appropriate.
Results: A total of 16 patients were enrolled. All had US data. Of the sixteen patients, two died prior to the neurodevelopmental testing, six did not return for the neurodevelopmental testing, and eight patients completed the neurodevelopmental testing. There were no significant correlations between the prior to surgery and prior to discharge US RI and neurodevelopmental outcomes. The immediate post-operative US RI demonstrated a strong positive correlation with standardized neurodevelopmental outcome measures. We were able to demonstrate qualitative differences using multichannel NIRS during surgery, but experienced significant technical difficulties implementing consistent monitoring.
Conclusions: A higher resistive index in the major cerebral blood vessels following cardiac surgery in the neonatal period is associated with improved neurological outcomes one year after surgery. Obtaining an ultrasound with resistive indices of the major cerebral vessels prior to and after surgery may yield information that is predictive of neurodevelopmental outcomes.

Abbreviations: ACA, anterior cerebral artery; Bayley III, Bayley scales of infant and toddler development—third edition; CC, cross clamp; CPB, cardiopulmonary bypass; DHCA, deep hypothermic cardiac arrest; HLHS, hypoplastic left heart syndrome; L MCA, left middle cerebral artery; NIRS, near-infrared spectroscopy; R MCA, right middle cerebral artery; RI, resistive indices; SCP, selective cerebral perfusion; TGA, transposition of the great vessels; US, ultrasound; Vineland II, Vineland adaptive behavior scales—second edition.

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Introduction

Neonatal and pediatric patients with congenital heart disease are at high risk for developing neurologic abnormalities.[1] The factors influencing this risk are multiple and include pre-operative, intraoperative, and post-operative events.[1] In the past decade, the focus has shifted in the care of the children with congenital heart disease from survival to optimizing neurologic outcomes. Prevention and early recognition of neurologic injury is the key to improving outcomes – it is important for parents as well as providers to understand the risks associated with surgery for congenital heart conditions in infants.[2]

While many patients with congenital heart disease are at risk for poor neurodevelopmental outcomes, there are currently no good predictors of outcome. The use of ultrasound (US) technology to forecast neurodevelopmental outcomes in the neonatal population would be ideal as it is portable, repeatable, non-invasive, and its relatively low cost when compared to other imaging modalities.[3] It does not require anesthesia which has recently been shown to be deleterious to neurologic outcomes.[4] The majority of studies comparing neurologic outcome and ultrasound technology relate to perinatal hypoxic ischemic injury. In some studies, the resistive indices (RI) of large proximal anterior and middle cerebral arteries have correlated well with neurological outcomes,[5–7] but evidence in patients with congenital heart disease is lacking.[8,9] Another possible non-invasive method for monitoring patients during congenital heart surgery is the use of near-infrared spectroscopy (NIRS). Single channel NIRS measurements have been shown to correlate with cerebral blood flow in animal models, but evaluation of selective cerebral perfusion (SCP) with multi-site-detector NIRS has not been performed, as such it remains unknown if there are regional oxygenation differences.[10,11]

In this pilot study, the first aim was to use a repeatable, inexpensive screening tool to determine if any prediction could be made as to neurodevelopmental outcomes 1 year after pediatric cardiac surgery. A secondary aim was to use an experimental multi-site-detector NIRS to evaluate cerebral blood flow, and cerebral oxygenation.

Methods

This was a prospective study between the years of 2011 and 2013 of pediatric patients less than 2 months of age with congenital heart disease at Children's Health Children's Medical Center in Dallas, TX. The Institutional Review Boards of both Children's Health Children's Medical Center in Dallas and the University of Texas Southwestern Medical Center granted approval for this study. Informed consent was obtained from the parents for each of the participants. All infants (up to 2 months) with congenital heart disease who required congenital heart surgery were eligible for enrollment. Depending on the clinical scenario, some infants received SCP and some did not. We did not obtain data on anesthesia exposure, blood gas data, blood pressure measurements, or inotropic scores.

All patients received a pre-operative (in the pediatric cardiac intensive care unit), immediate post-operative (within 24 h of returning to the pediatric cardiac intensive care unit), and a prior to discharge cranial US with RI of the major intracranial vessels (anterior cerebral artery and both middle cerebral arteries). All studies were performed on the Philips iU22 ultrasound system (Philips Healthcare) by experienced radiology ultrasound technologists utilizing a standard protocol for transfontanelle pulsed wave and color doppler identification and interrogation of the middle and anterior cerebral arteries. Transcranial Doppler studies were performed according to the American Institute for Ultrasound in Medicine Practice Parameter for Performance of Transcranial Doppler Ultrasound Examination for Adults and Children (AIUM 2012). This included appropriate selection of transducer, color gain and Doppler settings to maximize vessel wall identification in order to obtain the highest velocities for reliable determination of RI. The formula used in the RI calculation was peak systolic velocity − end diastolic velocity/peak systolic velocity. RI is a dimensionless ratio and an index that is independent of the variations in arterial velocity values due to differences in the angle of insonation of the ultrasound probe. RI is thus a robust measure useful in serial assessment of cerebral vascular resistance.

All patients underwent multichannel NIRS. A continuous-wave NIRS system (CW-6, TechEn Inc.) was used to monitor the changes in cerebral perfusion and oxygenation throughout the surgery in the operating room only. The CW-6 system has lasers at two wavelengths (690 nm and 830 nm) as light sources. Each laser is modulated to a frequency between 6.4 and 12.6 kHz, and the received light by the detectors is demodulated and dampened to 25 Hz. When the data was processed later, the changes of oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (Hb) in cerebral perfusion were calculated based on the modified Beer-Lambert Law.[12] Two additional parameters were further derived as: $HbD = HbO_2 - Hb$ and $HbT = HbO_2 + Hb$. These two parameters have been previously described[13,14]: HbD reflects the changes in cerebral intravascular oxygenation, and HbT reflects the change of total hemoglobin concentration, which is proportional to the change of blood volume in the tissue. All of these hemodynamic parameters (HbO_2, Hb, HbD and HbT) are relative concentration changes (dConc) in a unit of micromole/liter or μM.

Neurodevelopmental status was assessed at a follow-up visit approximately 12 months following surgery. Assessments were completed by a pediatric neuropsychologist or a trained neuropsychology technician. This visit included administration of the Bayley Scales of Infant and Toddler Development–Third Edition (Bayley III)[15] and the Vineland Adaptive Behavior Scales–Second Edition, Survey Interview Form (Vineland II).[16] The Bayley III directly assesses a wide range of functions, including cognition, language, and motor-control. These are assessed through tasks administered by an examiner in which the child is presented with a variety of stimuli, asked to participate in various activities, and asked to follow various commands. This test is well-standardized, and its scale has been shown to have sound evidence of validity and reliability.[15] The Vineland II is a semi-structured interview assessing an individual's adaptive behaviors based on a caregiver's report in four broad domains: Communication, Daily Living Skills, Socialization, and Motor Skills. The Vineland II has been shown to have a high degree of test-retest reliability, and the subdomains have demonstrated acceptable levels of internal consistency.[16] The written communication subdomain scores were not included in our analyses, as this subscale is only applicable for children 3 years of age and older.

Continuous variables were evaluated with Pearson product-moment correlation using the Graphpad Prism 7 software package. The 95% confidence interval (CI) for the continuous variables were calculated based off the confidence interval of rho, based on the Fischer r-to-z transformation. Categorical variables were evaluated with the Fischer *t* test to determine the *p* value between the different groups. For neurodevelopmental outcomes data, the US RI data was not separated by SCP vs non-SCP so that we could evaluate the US RI to the outcome measurement. Because of the problems with the multi-site-channel NIRS, no statistics were performed on the NIRS data. For purposes of this study, the difference was considered statistically significant if the *p* value was 0.05 or less. For purposes of the magnitude of correlation, an R greater than 0.7 (or lower than −0.7) was considered to have a strong correlation. The