Time to surgery and preoperative cerebral hemodynamics predict postoperative white matter injury in neonates with hypoplastic left heart syndrome

Jennifer M. Lynch, PhD,[a] Erin M. Buckley, PhD,[a,b,c] Peter J. Schwab, BS,[c] Ann L. McCarthy, BBA,[c] Madeline E. Winters, BA,[c] David R. Busch, PhD,[c] Rui Xiao, PhD,[d] Donna A. Goff, MD, MS,[e] Susan C. Nicolson, MD,[f] Lisa M. Montenegro, MD,[f] Stephanie Fuller, MD,[g] J. William Gaynor, MD,[g] Thomas L. Spray, MD,[g] Arjun G. Yodh, PhD,[a] Maryam Y. Naim, MD,[h] and Daniel J. Licht, MD[c]

Objective: Hypoxic-ischemic white mater brain injury commonly occurs in neonates with hypoplastic left heart syndrome (HLHS). Approximately one half of HLHS survivors will exhibit neurobehavioral symptoms believed to be associated with this injury, although the exact timing of the injury is unknown.

Methods: Neonates with HLHS were recruited for pre- and postoperative monitoring of cerebral oxygen saturation, cerebral oxygen extraction fraction, and cerebral blood flow using 2 noninvasive optical-based techniques: diffuse optical spectroscopy and diffuse correlation spectroscopy. Anatomic magnetic resonance imaging was performed before and approximately 1 week after surgery to quantify the extent and timing of the acquired white matter injury. The risk factors for developing new or worsened white matter injury were assessed using uni- and multivariate logistic regression.

Results: A total of 37 neonates with HLHS were studied. On univariate analysis, neonates who developed a large volume of new, or worsened, postoperative white matter injury had a significantly longer time to surgery ($P = .0003$). In a multivariate model, a longer time between birth and surgery, delayed sternal closure, and greater preoperative cerebral blood flow were predictors of postoperative white matter injury. Additionally, a longer time to surgery and greater preoperative cerebral blood flow on the morning of surgery correlated with lower cerebral oxygen saturation ($P = .03$ and $P = .05$, respectively) and greater oxygen extraction fraction ($P = .05$ for both).

Conclusions: A longer time to surgery was associated with new postoperative white matter injury in otherwise healthy neonates with HLHS. The results suggest that earlier Norwood palliation might decrease the likelihood of acquiring postoperative white matter injury. (J Thorac Cardiovasc Surg 2014;148:2181-8)

See related commentary on pages 2188-9.

Approximately 30,000 children annually are born in the United States with congenital heart disease (CHD). Nearly one third of these patients with CHD require cardiac surgery in their first year of life.[1] With most of these patients now reaching school age,[2] the focus of research has shifted to addressing the neurodevelopment disabilities seen among survivors of these early heart surgeries. Nearly 50% of the school-age survivors exhibit neurobehavioral symptoms, such as inattention, hyperactivity, and impaired executive function.[3-5]

Neonatal imaging and neuropathologic studies of patients with complex CHD undergoing infant surgical intervention have revealed a high prevalence of periventricular leukomalacia (PVL).[6] PVL is a specific form of hypoxic-ischemic white matter injury that commonly occurs in a vascular watershed zone near the lateral ventricles. It is most often observed in preterm neonates, who have had neurodevelopmental outcomes remarkably similar to those of term patients with CHD. Studies have shown that PVL is related to neurodevelopmental delays in preterm infants.[7-9]

To date, clinical investigations of CHD neonates have focused on identifying the pre-, peri-, and postoperative risk factors linked to PVL to mitigate or prevent this injury.[10-12] However, uncertainties about its exact cause and timing remain.[10-12] These previous studies have

From the Department of Physics and Astronomy,[a] University of Pennsylvania, Philadelphia, Pa; Athinoula A. Martinos Center for Biomedical Imaging,[b] Optics Division, Massachusetts General Hospital, Charlestown, Mass; Division of Neurology,[c] The Children's Hospital of Philadelphia, Philadelphia, Pa; Department of Biostatistics and Epidemiology,[d] University of Pennsylvania, Philadelphia, Pa; Division of Pediatric Cardiology,[e] Loma Linda University Children's Hospital, Loma Linda, Calif; Division of Cardiothoracic Anesthesia,[f] The Children's Hospital of Philadelphia, Philadelphia, Pa; Division of Cardiothoracic Surgery,[g] The Children's Hospital of Philadelphia, Philadelphia, Pa; and Division of Critical Care Medicine,[h] The Hospital of Philadelphia, Philadelphia, Pa.

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Address for reprints: Jennifer M. Lynch, PhD, Department of Physics and Astronomy, University of Pennsylvania, 209 South 33rd St, Philadelphia, PA 19104 (E-mail: jenlynch@alumni.upenn.edu).

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Abbreviations and Acronyms

BFI = blood flow index
CBF = cerebral blood flow
CHD = congenital heart disease
CICU = cardiac intensive care unit
$CMRO_2$ = cerebral metabolic rate of oxygen
DCS = diffuse correlation spectroscopy
DHCA = deep hypothermic circulatory arrest
DOS = diffuse optical spectroscopy
[Hb] = deoxyhemoglobin
$[HbO_2]$ = oxyhemoglobin
HLHS = hypoplastic left heart syndrome
MRI = magnetic resonance imaging
OEF = cerebral oxygen extraction fraction
PVL = periventricular leukomalacia
ScO_2 = cerebral tissue oxygen saturation
THC = total hemoglobin concentration
TMS = total maturation score

identified possible risk factors for this injury such as brain immaturity, the duration of deep hypothermic circulatory arrest (DHCA), and postoperative cerebral oxy-genation.[12-14] However, most previous studies have been of mixed populations of neonates with various forms of CHD. We investigated a homogeneous cohort of neonates with hypoplastic left heart syndrome (HLHS). We used diffuse optical and diffuse correlation spectroscopy (DOS and DCS, respectively) for noninvasive bedside quantification of the pre- and postoperative cerebral hemodynamics.[15,16] Also, we explored the relationship of these parameters and other preoperative, operative, and postoperative variables with new or worsened PVL seen 1 week after surgical intervention.

METHODS

Patient Population

All term (37-42 weeks' gestation) newborns with pre- or postnatally diagnosed HLHS who had been admitted to the cardiac intensive care unit (CICU) at The Children's Hospital of Philadelphia were screened for study inclusion and approached for participation in the present prospective study. The exclusion criteria included birth weight <2 kg, a history of neonatal depression (ie, 5-minute APGAR of <5 or cord pH of <7.0), perinatal seizures, evidence of end-organ injury, preoperative cardiac arrest, and/or significant preoperative intracerebral hemorrhage such as grade 3 or 4 intraventricular hemorrhage.

Study Protocol

The institutional review board approved all procedures. The patients' demographic data were recorded. A study timeline is presented in Figure 1 and has been described previously.[17-20] On the morning of surgery, all patients received general endotracheal anesthesia (fentanyl 5-10 μg/kg, pancuronium 0.2 mg/kg). Subsequently, they underwent brain magnetic resonance imaging (MRI) for preoperative injury assessment. Preoperative DOS and DCS measurements of cerebral oxygenation (ScO_2), oxygen extraction (OEF), and cerebral blood flow (CBF) were also taken at this time.

After MRI, the patients underwent cardiopulmonary bypass with DHCA for their stage I palliation. Antegrade cerebral perfusion was not used. The operations were performed by 1 of 4 cardiac surgeons. pH-stat blood gas management was used. To achieve DHCA, the patients underwent core and surface cooling to a nasopharyngeal temperature of 18°C. Commercial cerebral oximetry was not used to guide intra- or postoperative management. Patients received either a Blalock-Taussig shunt or a right ventricle to pulmonary artery shunt (Sano). The surgical strategy included sternal closure where tolerated. Patients born with an intact atrial septum underwent balloon atrial septostomy soon after birth and before surgery.

After surgery, the patients were transported back to the CICU. The postoperative ScO_2, OEF, and CBF were quantified every 2 hours for the first 12 hours during recovery. Approximately 1 week after surgery, the patients underwent a postoperative follow-up MRI scan to assess the development and/or progression of brain injury.

Brain MRI

All images were acquired using a 1.5T Avanto MRI system (Siemens Medical Systems, Malvern, Pa) using a 12-channel head coil. The studies included T_1-weighted magnetization-prepared rapid acquisition gradient echo and T_2-weighted sampling perfection with application-optimized contrasts using different flip angle evolution sequences acquired in the axial plane. The images were later reconstructed in the sagittal and coronal planes. Susceptibility and diffusion weighted sequences were also acquired. The presence of PVL was assessed from the T_1-weighted sequences in conjunction with diffusion weighted imaging on both the pre- and postoperative scans. Manual segmentation of the T_1-weighted hyperintense lesions was performed using ITK-SNAP[21] (available at: http://www.itksnap.org/) and used to calculate the PVL volumes. New or worsened PVL was calculated by the difference in the PVL volume between the post- and preoperative scans. Additionally, 2 independent observers, who were unaware of the clinical data, evaluated the total brain maturation score (TMS) using axial T_1- and T_2-weighted images.[22,23]

DOS and DCS Measurements

DOS and DCS use near-infrared light to noninvasively probe the static and dynamic properties of cortical brain tissue. Our custom-made optical instrument combines these 2 techniques on a mobile cart that can be used in the MRI suite and operating room and at the bedside during recovery.[17,18,24]

DOS (also known as near-infrared spectroscopy) is a widely accepted method for quantifying tissue oxygenation. Multiseparation frequency domain DOS, used in the present study, is capable of accurate quantification of ScO_2 (ie, in contrast to commercial oximeters, which use continuous-wave near-infrared spectroscopy to monitor trends in saturation). DOS uses the photon diffusion theory to relate the measured amplitude attenuation and phase shift of modulated and multiply scattered light detected on the tissue surface to the wavelength-dependent tissue absorption (μ_a) and scattering (μ_s') properties. The wavelength- and time-dependent absorption coefficient, $\mu_a(\lambda, t)$, depends linearly on the oxy- ($[HbO_2]$) and deoxyhemoglobin ([Hb]) concentration; thus measurements at multiple wavelengths yields these 2 parameters. From $[HbO_2]$ and [Hb], we can derive the total hemoglobin concentration (THC) (THC = $[HbO_2]$ + [Hb]) and ScO_2 (ScO_2 = $[HbO_2]$/THC). The OEF can be calculated from the ScO_2 and arterial oxygen saturation measured clinically from an arterial blood gas sample.[17] The cerebral blood volume (mL/100 g of tissue) can be calculated from the THC.[25] The DOS device used in the present study (Imagent, ISS Inc, Champaign, Ill) is amplitude modulated at 110 MHz and uses source lasers at 2 wavelengths, λ = 688 and 830 nm.

DCS uses near-infrared light to noninvasively monitor the CBF. DCS measures the temporal fluctuations of the reflected light intensity at the tissue surface, which are primarily caused by moving red blood cells.[15,26,27]