CONG

Increasing cumulative exposure to volatile anesthetic agents is associated with poorer neurodevelopmental outcomes in children with hypoplastic left heart syndrome

Laura K. Diaz, MD,[a] J. William Gaynor, MD,[b] Shannon J. Koh, BA,[b] Richard F. Ittenbach, PhD,[c] Marsha Gerdes, PhD,[d] Judy C. Bernbaum, MD,[d] Elaine H. Zackai, MD,[d] Robert R. Clancy, MD,[d] Mohamed A. Rehman, MD,[a] Jeffrey W. Pennington, BS,[e] Nancy Burnham, MSN,[b] Thomas L. Spray, MD,[b] and Susan C. Nicolson, MD[a]

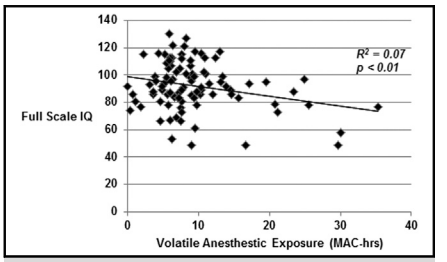
ABSTRACT

Objectives: Despite improved survival in children with hypoplastic left heart syndrome (HLHS), significant concern persists regarding their neurodevelopmental (ND) outcomes. Previous studies have identified patient factors, such as prematurity and genetic syndromes, to be associated with worse ND outcomes. However, no consistent relationships have been identified among modifiable management factors, including cardiopulmonary bypass strategies, and ND outcomes after cardiac surgery in infancy. Studies in immature animals, including primates, have demonstrated neurodegeneration and apoptosis in the brain after certain levels and extended durations of anesthetic exposure. Retrospective human studies have also suggested relationships between adverse ND effects and anesthetic exposure.

Methods: Cumulative minimum alveolar concentration hours (MAC-hrs) of exposure to volatile anesthetic agents (VAA) (desflurane, halothane, isoflurane, and sevoflurane) were collected from an anesthetic database and medical record review for 96 patients with HLHS or variants. ND testing was performed between ages 4 and 5 years, including full-scale IQ, verbal IQ, performance IQ, and processing speed. Four generalized linear modes were hypothesized a priori and tested using a Gaussian (normal) distribution with an identity link.

Results: Cumulative VAA exposure ranged from 0 to 35.3 MAC-hrs (median 7.5 hours). Using specified covariates identified previously as significant predictors of ND outcomes, statistically significant relationships were identified between total MAC-hrs exposure and worse full-scale IQ and verbal IQ scores (P's < .05) alone and after adjusting for relevant covariates.

Conclusions: Increased cumulative MAC-hrs exposure to VAA is associated with worse ND outcomes in certain domains in children with HLHS and variants. (J Thorac Cardiovasc Surg 2016;152:482-9)



Increasing exposure to volatile anesthetic agents is associated with lower full-scale IQ.

Central Message

This study shows that greater exposure to volatile anesthetic agents is correlated with worse neurodevelopmental outcomes for patients with hypoplastic left heart syndrome.

Perspective

Studies in immature animals have documented neurotoxic effects of common anesthetic agents. Studies in children have shown associations between anesthetic exposure and increased likelihood of developmental disabilities. This study shows that in children with hypoplastic left heart syndrome, increasing exposure to volatile anesthetic agents (VAAs) is associated with worse neurodevelopmental outcomes, suggesting that VAA exposure may be a modifiable risk factor.

See Editorial Commentary page 490.

From the Departments of [a]Anesthesia and Critical Care Medicine, and [d]Pediatrics, [b]Division of Pediatric Cardiothoracic Surgery, and [c]Center for Biomedical Informatics, The Children's Hospital of Philadelphia, Perelman School of Medicine at The University of Pennsylvania, Philadelphia, Pa; and [c]Division of Biostatistics and Epidemiology, Cincinnati Children's Medical Center, University of Cincinnati School of Medicine, Cincinnati, Ohio.

This research was supported by a grant from the Fannie E. Rippel Foundation; American Heart Association National Grant-in-Aid (9950480N); Grant HL071834 from the National Institutes of Health; support from The Cardiac Center at The Children's Hospital of Philadelphia, the Alice Langdon Warner Endowed Chair in Pediatric Cardiothoracic Surgery and the Daniel M. Tabas Endowed Chair in Pediatric Cardiothoracic Surgery at The Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania.

Received for publication Oct 1, 2015; revisions received March 3, 2016; accepted for publication March 17, 2016; available ahead of print May 13, 2016.

Address for reprints: J. William Gaynor, MD, Pediatric Cardiothoracic Surgery, The Children's Hospital of Philadelphia, Perelman School of Medicine at The University of Pennsylvania, 3400 Civic Center Boulevard, Ninth Floor, Main Building, Philadelphia, PA 19104 (E-mail: gaynor@email.chop.edu).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2016.03.095

Abbreviations and Acronyms

AIMS = Anesthesia Information Management System
APOE = Apolipoprotein E
AUC = area-under-the-curve
BSID-II = Bayley Scales of Infant Development-II
CHD = congenital heart defects
CNS = central nervous system
CPB = cardiopulmonary bypass
DHCA = deep hypothermic circulatory arrest
FSIQ = full-scale IQ
GA = general anesthesia
HC = head circumference
HLHS = hypoplastic left heart syndrome
ICU = intensive care unit
LOS = length of stay
MAC-hrs = minimum alveolar concentration hours
ND = neurodevelopmental
NP = nasopharyngeal
PIQ = performance IQ
SES = socioeconomic status
VAA = volatile anesthetic agents
VIQ = verbal IQ
WPPSI-III = Wechsler Preschool and Primary Scale of Intelligence, 3rd edition

Scanning this QR code will take you to the article title page.

Each year approximately 10,000 neonates and infants receive general anesthesia (GA) for repair of congenital heart defects (CHDs).[1] Neurodevelopmental (ND) disability occurs in many survivors, resulting in an increasing focus on prevention of adverse ND outcomes.[2] There is increasing evidence of congenital and acquired preoperative central nervous system (CNS) abnormalities in infants with CHD.[3,4] Although some studies have implicated perioperative factors such as the use of CPB with or without deep hypothermic circulatory arrest (DHCA) and postoperative length of stay (LOS), these findings are not consistent.[5,6] Instead, patient-specific factors, such as birth weight, ethnicity, and presence of a genetic syndrome, have been identified as the strongest predictors of ND outcomes in infants undergoing cardiac surgery, including those with hypoplastic left heart syndrome (HLHS).[7,8]

Over the past decade, studies in immature animal models, including primates, have documented neurotoxic effects on the developing brain following exposure to all anesthetic and sedative medications commonly administered to infants and children.[9,10] Retrospective studies in humans have shown associations between exposure to GA in early childhood and increased likelihood of subsequent behavioral or developmental disabilities.[11,12] Two recent studies have reported a potential relationship between anesthetic exposure and ND outcomes in children with CHD, but with conflicting results.[13,14] Significant questions remain regarding the period of maximal vulnerability to anesthetic exposure in neonates and infants, the role specific anesthetic agents may play with respect to ND outcomes, and the effects of duration of anesthetic exposure and cumulative dose. No previous study has evaluated the potential ND effects of VAA using a homogeneous sample of preschool children with CHD with (1) repetitive exposure to anesthetic agents beginning in infancy, (2) precise quantification of the cumulative anesthetic exposure, and (3) formal evaluation of intelligence.

Our previous analysis of ND outcomes in a patient cohort with single-ventricle CHD, consisting primarily of children with HLHS, found that patient factors were more important predictors than operative management variables, but anesthetic exposure was not assessed.[15] The current study was undertaken to build on these findings and evaluate the potential impact of increasing cumulative exposure to VAA, a modifiable management factor, on ND in preschool children with HLHS or variants.

MATERIALS AND METHODS

Sample

This study constitutes of a subgroup analysis of patients enrolled in a prospective study evaluating the effects of apolipoprotein E (*APOE*) gene polymorphisms on ND outcome after cardiac surgery requiring CPB in infants 6 months of age or younger.[16] Exclusion criteria for the overall study were (1) presence of multiple congenital anomalies, (2) recognized genetic or phenotypic syndrome other than chromosome 22q11 microdeletion, and (3) language other than English spoken in the home. Premature and low birth weight infants were enrolled. The current study evaluated a subgroup of infants with HLHS or variants from the time of initial anesthetic exposure to the time of ND follow-up between the ages of 4 and 5 years. All exposures to VAA at our institution during the time period from initial admission to the 4- to 5-year ND evaluation were collected retrospectively. The institutional review board at The Children's Hospital of Philadelphia approved the study and written informed consent was obtained for the primary study from a parent or guardian.

Data Collection

Demographic and preoperative factors including gestational age, birth weight and head circumference (HC), Apgar scores, and preoperative intubation were obtained from birth and hospital records. For all operative encounters, weight, age at operation, and type of operation were recorded. For cardiac surgeries using CPB, perfusion data, including aortic cross-clamp time, CPB time, duration of DHCA, total support time (CPB time plus