animal studies and exploring possible pharmacologic therapy for children with CHD. Going forward, further integration with neuroscience research will be helpful in designing experiments to determine the complex cellular events underlying brain injury. Hopefully, the knowledge gained will lead to treatment to protect immature brains during pediatric cardiac surgery. As the present report and recent studies indicate,^{8,9} animal studies show great promise in elucidating the cellular etiologies of disturbed brain development in the CHD population and establishing new approaches for improvement of neurologic development.

References

1. Wake H, Moorhouse AJ, Miyamoto A, Nabekura J. Microglia: actively surveying and shaping neuronal circuit structure and function. *Trends Neurosci.* 2013;36:209-17.
2. Korotcova L, Kumar S, Agematsu K, Morton PD, Jonas RA, Ishibashi N. Prolonged white matter inflammation after cardiopulmonary bypass and circulatory arrest in a juvenile porcine model. *Ann Thorac Surg.* 2015;100:1030-7.
3. Kajimoto M, Nuri M, Sleasman JR, Charette K, Nelson BR, Portman MA. Inhaled nitric oxide reduces injury and microglia activation in porcine hippocampus after deep hypothermic circulatory arrest. *J Thorac Cardiovasc Surg.* 2021;161:e485-98.
4. James C, Millar J, Horton S, Brizard C, Molesworth C, Butt W. Nitric oxide administration during paediatric cardiopulmonary bypass: a randomised controlled trial. *Intensive Care Med.* 2016;42:1744-52.
5. Checchia PA, Bronicki RA, Muenzer JT, Dixon D, Raithel S, Gandhi SK, et al. Nitric oxide delivery during cardiopulmonary bypass reduces postoperative morbidity in children—a randomized trial. *J Thorac Cardiovasc Surg.* 2013;146:530-6.
6. Hiramatsu T, Jonas RA, Miura T, duPlessis A, Tanji M, Forbess JM, et al. Cerebral metabolic recovery from deep hypothermic circulatory arrest after treatment with arginine and nitro-arginine methyl ester. *J Thorac Cardiovasc Surg.* 1996;112:698-707.
7. Morton PD, Ishibashi N, Jonas RA. Neurodevelopmental abnormalities and congenital heart disease: insights into altered brain maturation. *Circ Res.* 2017;120:960-77.
8. Lawrence KM, McGovern PE, Mejaddam A, Rossidis AC, Baumgarten H, Kim AG, et al. Prenatal hypoxemia alters microglial morphology in fetal sheep. *J Thorac Cardiovasc Surg.* January 6, 2020 [Epub ahead of print].
9. Leonetti C, Back SA, Gallo V, Ishibashi N. Cortical dysmaturation in congenital heart disease. *Trends Neurosci.* 2019;42:192-204.

See Article page e485.

Commentary: A miracle product, applied early and often

David Bichell, MD

Publications about nitric oxide (NO) topped 6000 per year through the early 2000s, describing actions in cardiovascular biology, cancer, immunology, and neurology. NO-mediated endothelial dysfunction underlies a broad array of diseases, and NO is a putative miracle product to the rescue.¹ As some applications of NO in congenital heart surgery are maturing toward standard-of-care status, new clinical applications are emerging, some effective and some remaining good news only for piglets and rats.

David P. Bichell, MD

CENTRAL MESSAGE

Mitigating microglia-mediated brain damage may be among reasons for administering nitric oxide at reperfusion from cardiopulmonary bypass, but clinical relevance remains unproven.

Checchia and colleagues² showed a reduction in serum inflammatory markers and myocardial injury and shorter mechanical ventilation and intensive care unit stay in pediatric patients undergoing tetralogy of Fallot repair who had NO delivered to the CPB circuit. A randomized prospective trial of children undergoing cardiopulmonary bypass (CPB) at

From the Department of Cardiac Surgery, Monroe Carell, Jr, Children's Hospital, Vanderbilt University Medical Center, Nashville, Tenn.

Disclosures: Author has nothing to disclose with regard to commercial support.

Received for publication Dec 21, 2019; accepted for publication Dec 23, 2019; available ahead of print Jan 11, 2020.

Address for reprints: David P. Bichell, MD, Department of Cardiac Surgery, Monroe Carell, Jr, Children's Hospital, Vanderbilt University Medical Center, 5247 Doctors' Office Tower, 2200 Children's Way, Nashville, TN 37232-9292 (E-mail: david.bichell@vumc.org).

J Thorac Cardiovasc Surg 2021;161:e500-1

0022-5223/\$36.00

Copyright © 2020 Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2019.12.084>

moderate hypothermia shows that NO administered to the oxygenator during pediatric CPB reduces low cardiac output postoperatively by attenuating ischemia reperfusion injury, mitigating the generation of oxygen-free radicals.³

In the brain, microglia are involved with vascular morphogenesis and maintenance and neuroprotection but also neurodestruction and apoptosis. Much remains unknown about the responsible signaling pathways.⁴ Kajimoto and colleagues,⁵ in this issue of the *Journal*, explore NO, CPB, and the brain, showing a significant reduction of degenerating and apoptotic hippocampal neurons in the NO group compared with untreated piglets, in a model of 30 minutes of deep hypothermic circulatory arrest. Spectacular 3-dimensional images of a reduction in activated microglia with NO administration accompany the data to tell a compelling story of microglia standing down from an otherwise-destructive stance.

Hypothermia itself contributes to the magnitude of the inflammatory response to CPB in the brain.^{6,7} Cerebrovascular autoregulation is normal at normothermia, impaired at moderate hypothermia, and absent at deep hypothermia, at which point autoregulation is pressure-passive.⁸ Deep hypothermia is associated with hippocampal damage from deranged cerebrovascular autoregulation, damage felt to occur largely during reperfusion and rewarming. Further, the degree of hypothermia during CPB is correlated with an increase in circulating glial fibrillary acidic protein, a biomarker of brain injury and a predictor of neurodevelopmental abnormalities.⁹ Most current practices use little or no deep hypothermia.

Kajimoto and colleagues⁵ add enthusiasm for NO applied early and often, and more evidence that what is good for the

extracranial organs is good for the brain. Compelling as these data are to the piglet under conditions of deep hypothermia, they may or may not translate to clinical validity. There are several established reasons for administering NO during CPB, and mitigating microglia-mediated brain damage may be among them, but the idea will be more compelling if the data uphold relevance at modest hypothermia or normothermia, the climate of modern clinical practice.

References

1. Yetik-Anacak G, Catravas JD. Nitric oxide and the endothelium: history and impact on cardiovascular disease. *Vasc Pharmacol*. 2006;45:268-76.
2. Checchia PA, Bronicki RA, Muenzer JT, Dixon D, Raithel S, Gandhi SK, et al. Nitric oxide delivery during cardiopulmonary bypass reduces postoperative morbidity in children—a randomized trial. *J Thorac Cardiovasc Surg*. 2013;146:530-6.
3. James C, Millar J, Horton S, Brizard C, Molesworth C, Butt W. Nitric oxide administration during paediatric cardiopulmonary bypass: a randomised controlled trial. *Intensive Care Med*. 2016;42:1744-52.
4. Zhao X, Eyo UB, Murugan M, Wu L-J. Microglial interactions with the neurovascular system in physiology and pathology. *Dev Neurobiol*. 2018;78: 604-17.
5. Kajimoto M, Nuri M, Sleasman JR, Charette K, Nelson BR, Portman MA. Inhaled nitric oxide reduces injury and microglia activation in porcine hippocampus after deep hypothermic circulatory arrest. *J Thorac Cardiovasc Surg*. 2021;161: e485-98.
6. Eggum R, Ueland T, Mollnes TE, Videm V, Aukrust P, Fiane AE, et al. Effect of perfusion temperature on the inflammatory response during pediatric cardiac surgery. *Ann Thorac Surg*. 2008;85:611-7.
7. Heltne JK, Bert J, Lund T, Koller ME, Farstad M, Rynning SE, et al. Temperature-related fluid extravasation during cardiopulmonary bypass: an analysis of filtration coefficients and transcapillary pressures. *Acta Anaesthesiol Scand*. 2002;46:51-6.
8. Taylor RH, Burrows FA, Bissonnette B. Cerebral pressure-flow velocity relationship during hypothermic cardiopulmonary bypass in neonates and infants. *Anesth Analg*. 1992;74:636-42.
9. Vedovelli L, Padalino M, D'Aronco S, Stellin G, Ori C, Carnielli VP, et al. Corrigendum to: "Glial fibrillary acidic protein plasma levels are correlated with degree of hypothermia during cardiopulmonary bypass in congenital heart disease surgery" [*Interact Cardiovasc Thorac Surg* 2017]. *Interact Cardiovasc Thorac Surg*. 2017;25:164.