Patent ductus arteriosus (PDA), in which the ductus arteriosus fails to close after birth, is a common congenital heart defect in premature infants. The optimal management of a hemodynamically significant PDA, in terms of the indications for closure, timing of closure, and role of surgery, has been debated for decades. Although diastolic runoff and left-to-right shunting in the presence of a significant PDA have been postulated to compromise blood flow to the immature brain and other structures, resulting in increased morbidity and mortality, some studies have shown that surgical PDA closure may contribute to perioperative hemodynamic instability, neurosensory complications, and even increased risk for worse neurodevelopmental outcome.

In this issue of Pediatrics, Lemmers et al. present a retrospective comparison of cerebral oxygenation, as measured by near-infrared spectroscopy (NIRS), and MRI-assessed regional brain volume and myelination in 3 groups of premature infants. One group underwent successful early closure of a PDA with 1 or 2 doses of indomethacin; pharmacological closure failed in the second group, and they underwent surgical ligation; and the third group of matched controls did not have a PDA. Their findings confirm that a hemodynamically significant PDA is associated with reduced regional cerebral oxygenation saturation (rS\textsubscript{O}2) and that the infants who needed surgery had significantly lower rS\textsubscript{O}2 before ductal closure than those who did not. They also observed a time-dependent fall in rS\textsubscript{O}2 that was obviously most common in the infants who underwent surgery, often crossing a widely accepted critical threshold of 40%. However, despite dramatic associations between the presence and duration of significant PDA and cerebral hypoxia, there was only a soft association between a lower rS\textsubscript{O}2 and reduced cerebellar volume on MRI, but otherwise no association with regional brain volumes or brain maturation at term-equivalent age.

This study has reinforced the potential utility of NIRS monitoring in the preterm population, in assisting clinicians in decision-making about the management of hemodynamically significant PDA. The lack of significant relationships between presence of a PDA, rS\textsubscript{O}2, and brain volumes and maturity may initially appear surprising, and it conflicts with studies from other investigators. However, the aggressive approach to early intervention on the PDA may distinguish this study population from others. As the authors themselves state, their routine management after detection of a significant PDA is to intervene in a stepwise fashion until the duct is closed, typically starting at ~4 days of postnatal age. The relative sparing of the brain volumes and lack of impact on brain maturity in the PDA groups could indeed be interpreted as a positive and may refute a more conservative approach.
Although the perennial debate about the short- and long-term benefits of PDA closure continue, this debate has traditionally focused on the development of chronic lung disease rather than on the relationship between the PDA and neurodevelopmental outcome. Numerous studies have reported that PDA leads to lower cerebral oxygenation, and Lemmers et al. previously reported that infants with PDA had mean arterial blood pressure and regional cerebral oxygen saturation that were significantly lower than those of control infants (mean arterial blood pressure, 33 ± 5 mm Hg vs 38 ± 6 mm Hg; regional cerebral oxygen saturation, 62% ± 9% vs 72% ± 10%, for PDA and controls, respectively). Although lower cerebral oxygenation has been shown to be associated with worse neurodevelopmental outcome in term infants undergoing surgery for congenital heart disease, this relationship is not addressed in the current article. In preterm infants, lower cerebral volume, specifically decreased total brain volume and deep nuclear gray matter volume, is known to be associated with worse cognitive and motor development and a higher incidence of cerebral palsy. This current study did not demonstrate a difference in total brain volumes and maturation between the 3 study groups, and the significance of the observation of lower cerebellar volumes of the surgical group is not known.

This article provides us with some interesting food for thought. It adds to the debate about the optimal treatment of premature infants with a significant PDA, in terms of the indications for closure, potential benefits of closure, and optimal timing for closure. Proponents of early closure would interpret the findings as supporting this approach and proceed to surgery without significant delay when medical therapy has failed. However, those favoring more conservative management, which may be less aggressive with respect to timing or to whether to proceed with surgery if medical management fails, could reasonably argue that the MRI data were at best inconclusive and that without data about postclosure NIRS, and more importantly neurodevelopmental outcome, the implications of the study can only be speculative and should therefore be interpreted with caution.

Despite these limitations, Lemmers’ findings provide some new input to a sound question with conflicting data and seem to support early PDA closure in premature infants. Additionally, their results should stimulate additional investigations into early, protocolized surgical PDA closure and its impact on neurodevelopment in this patient population.

ABBREVIATIONS
NIRS: near-infrared spectroscopy
PDA: patent ductus arteriosus
rSO2: regional cerebral oxygenation saturation

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Patent Ductus Arteriosus and the Immature Brain: Is Early Intervention Protective?
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DOI: 10.1542/peds.2015-4659 originally published online March 30, 2016;

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