Hey, Doctor, Leave the PDA Alone

William E. Benitz, MD

At a meeting of the Section of Pediatrics of the Royal Society of Medicine in October 1958, Dr Burnard[1] reported the first observation that prematurity is associated with persistence of the murmur of patent ductus arteriosus (PDA), and that the latter is associated with dyspnea. Reinforced by subsequent confirmation, the concept developed that prolonged ductal patency in preterm infants is pathologic and therefore requires treatment. The hypothesis that left-to-right ductal shunting associated with persistent PDA is a direct cause of the various adverse outcomes overrepresented in preterm infants with PDA has become deeply ingrained in theory and practice, despite absence of supporting evidence. Randomized controlled trials over 4 decades have demonstrated that early, routine intervention to close the PDA in preterm infants fails to ameliorate risk of those outcomes, casting doubt on this hypothesis.[2] The pervasive conviction that it is correct, however, resulted in open-label treatment of at least some control subjects in most treatment trials and in nearly all recent case series of observational management. The available data, therefore, cannot entirely exclude the possibility that a select group of preterm infants with PDA might benefit from medical, surgical, or interventional catheter closure of the PDA. In addition, available evidence only demonstrates absence of benefit with respect to outcomes that have been measured, and cannot exclude other potential benefits, such as reduction in the rate or severity of pulmonary hypertension associated with bronchopulmonary dysplasia, avoidance of late pulmonary venous stenosis, or some other outcome that has not been considered in trials done to date.

The report in this issue,[3] from 2 institutions in Europe, adds substantial new information to this conversation. With due respect to the limitations imposed by the retrospective observational study design, this is the first description of the natural history of ductal closure in preterm infants from more than a single center, the largest such series to date, and the only series in which serial echocardiography was performed for all subjects for the duration of hospitalization. In this cohort of 280 very low birth weight (VLBW) infants managed without interventions to close the PDA, spontaneous closure occurred before discharge in 237 (85%). Rates of intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and necrotizing enterocolitis in the entire VLBW birth cohort (368 infants) compared favorably to contemporaneous data from Vermont-Oxford Neonatal Network centers, supporting the argument that noninterventional management is, at a minimum, relatively safe, and suggesting that development of sequelae is not simply a function of the duration of left-to-right ductal shunting. These conclusions must be tempered by recognition that 17 (6%) of the 297 eligible infants were treated to close the PDA, so this study cannot permit conclusions about safety of truly universal nonintervention. The criteria for treatment in those cases are not stated, so this report also cannot guide selection of infants who might benefit from treatment. The results reported by Sung et al,[4] in which there was no apparent excess mortality or morbidity in 97 infants

Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford, California

DOI: https://doi.org/10.1542/peds.2017-0566

Accepted for publication Apr 25, 2017

Address correspondence to William E. Benitz, MD, Division of Neonatal and Developmental Medicine, Stanford University, 750 Welch Rd, Suite 315, Palo Alto, CA 94304. E-mail: benitzwe@stanford.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: Dr Benitz received honoraria for speaking on this topic at academic meetings.

FUNDING: Supported by the Philip Sunshine Professorship in Neonatology of Stanford University.

POTENTIAL CONFLICT OF INTEREST: The author has indicated he has no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2016-4258.

To cite: Benitz WE. Hey, Doctor, Leave the PDA Alone. *Pediatrics*. 2017;140(2):e20170566

managed without resort to medical or surgical treatment, may have similar implications.

Taken together, these reports imply that the proportion of preterm infants with PDA who might benefit from treatment to close the ductus must be small. Unfortunately, we still do not know how or at what age to identify those infants, or even if they exist. Closing the knowledge gap on these matters will require carefully designed and executed clinical trials. There must be explicit and precise specification of the adverse outcomes to be prevented by treatment, not simply a broad primary and numerous secondary end points, preferably supplemented by long-term surveillance for unexpected outcomes. Selection of subjects will demand development of predictive tools (perhaps echocardiographic or biomarker measurements) that reflect the magnitude of ductal shunting and are strongly predictive of the outcomes of interest, allowing focus on a small subset of high-risk VLBW infants with PDA. Open label treatment in the control group should be prohibited or governed by strict failure criteria that can then delimit the characteristics of infants who may benefit from treatment. Such trials should either demonstrate that intervention to close the ductus alters the incidence of a particular adverse outcome or extend the range of preterm infants for whom treatment to close the ductus is known to be ineffective. For the large majority of preterm infants with PDA, the utility of measures designed to minimize consequences of left-to-right ductal shunting (such as fluid restriction, distending airway pressure, or red blood cell transfusion) should also be systematically evaluated. The work of Semberova et al[3] should provide motivation for pursuit of those goals, even as treatment to close the PDA becomes much more selectively used.

ABBREVIATIONS

PDA: patent ductus arteriosus
VLBW: very low birth weight

REFERENCES

1. Burnard ED. A murmur that may arise from the ductus arteriosus in the human baby. *Proc R Soc Med.* 1959;52(1):77–78
2. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? *J Perinatol.* 2010;30(4):241–252
3. Semberova J, Sirc J, Miletin J,et al. Spontaneous closure of patent ductus arteriosus in infants ≤1500 g. *Pediatrics.* 2017;140(2):e20164258
4. Sung SI, Chang YS, Chun JY, et al. Mandatory closure versus nonintervention for patent ductus arteriosus in very preterm infants. *J Pediatr.* 2016;177:66–71.e1

Hey, Doctor, Leave the PDA Alone

William E. Benitz

Pediatrics 2017;140;
DOI: 10.1542/peds.2017-0566 originally published online July 12, 2017;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Hey, Doctor, Leave the PDA Alone

William E. Benitz

Pediatrics 2017;140;
DOI: 10.1542/peds.2017-0566 originally published online July 12, 2017;