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Treatment and Nontreatment of the Patent Ductus Arteriosus: Identifying Their Roles in Neonatal Morbidity

In this volume of *The Journal*, Bixler et al report their study of 61 520 infants (delivered before 31 weeks' gestation) in the Pediatrix Clinical Data Warehouse; they found that both the incidence of patent ductus arteriosus (PDA) reported and the number of infants receiving PDA treatment (either medical or surgical) declined significantly between 2006 and 2015.[1] Their findings are similar to the results reported by Lokku et al from the Canadian Neonatal Network and by Hagadorn et al from the Pediatric Hospital Information System database.[2,3] Although these studies demonstrate that there has been a decline in both the desire to in-

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BPD	Bronchopulmonary dysplasia
PDA	Patent ductus arteriosus
RCT	Randomized controlled trial

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vestigate the presence of a PDA, as well as to treat it when present, they cannot tell us whether this trend toward nontreatment (or conservative management) has been applied primarily to infants with small, insignificant left-to-right PDA shunts or whether infants with moderate/large PDA shunts also have been included in this approach. This is an important consideration. Although there is no association between the presence of small PDA shunts and neonatal morbidity, there is evidence for a direct association between moderate/large shunts and serious morbidities.[4] The heterogeneity in shunt size among the infants included in these studies makes it impossible to tell whether nontreatment of infants with moderate/large PDA shunts has had a positive or negative impact on neonatal morbidity.

The trend toward nontreatment of the PDA appears to be driven by the belief that treatment to induce PDA closure does not improve long-term neonatal outcomes.[5,6] The evidence to support this claim comes from controlled clinical trials that compared infants who received treatment to close the PDA with those who received no treatment. However, interpreting the results of these clinical trials requires that one recognize the basic assumptions behind the clinical trial study design. If these are not appreciated, the study results can be misinterpreted. For example, although we may question whether a moderate/large PDA shunt is responsible for specific neonatal morbidities, there is no question that a moderate/large PDA shunt has significant hemodynamic consequences for the infant. A moderate/large left-to-right PDA shunt causes a decrease in systemic blood pressure, a reduction in blood flow to the systemic organs, an increase in pulmonary blood pressure and flow, an increase in lung water, and a decrease in lung compliance.[7-18] Every infant with a moderate/large PDA shunt is challenged by these hemodynamic changes. How an infant adapts to these hemodynamic changes determines how clinicians respond to the infant. Any study that compares treatment (to close the PDA) with no treatment of the PDA has to include the recognition that "other" treatment modalities are being used to offset the hemodynamic consequences of the PDA (eg, inotropic support, fluid restriction, or increased end-expiratory pressure).[19-22] Therefore, if morbidities are found in the no-treatment arm of these studies, one has to ask the following: Are they due to the persistent PDA shunt itself, or are they due to the "other" treatments used to stabilize the infants while awaiting spontaneous closure? Although most trials describe in detail what is being done to infants in the treatment arm, virtually no study describes the "other" treatments used to deal with the PDA's hemodynamic effects in the no-treatment arm of the study. The outcomes of these trials depend as much (or even more so) on the "other" treatments used in the no-treatment arm as they do on those used in the treatment arm. Stated another way, the treatment vs no- treatment trials do not really tell us about the morbid effects of the PDA on the newborn, they just tell us about 2 different treatment choices: one designed to close the ductus and one designed to treat its hemodynamic consequences.

There is probably no better example to illustrate this point than to consider the question: should infants with a moderate/large PDA shunt be ligated within the first 2 weeks after birth? Consider first the seminal randomized controlled trial (RCT) of early surgical closure vs no treatment reported by Cotton et al in 1978.[23] In this study, ventilated infants born preterm were randomized at the end of the first week to either surgical PDA ligation or no treatment. Despite the fact that performing a surgical ligation increases the risk for pulmonary morbidity, the authors found that infants in the surgical treatment arm had a lower incidence of pulmonary morbidity than infants with a persistent PDA in the no-treatment arm of the study.[24-33]

In contrast to the findings of Cotton et al, recent controlled clinical trials report the opposite results, namely, less morbidity in the no-treatment arm compared with the arm that underwent early surgical closure.[23,34,35] The beneficial effects of no treatment appeared to be attributable to the elimination of ligation from the no-treatment arm of the study because the difference between the study arms disappeared when the analyses were adjusted for the different ligation rates.[32]

So, what's the difference between the earlier study of Cotton et al and the more recent studies? In both studies, the investigators had 2 choices: either to close the ductus itself (treatment) or to mitigate its hemodynamic effects (no treatment). In the study of Cotton et al, the no treatment group received long-term, high-volume, and high-pressure mechanical ventilation, which was the prevalent form of ventilation in the 1970s, to control PDA-induced pulmonary edema.[23,36] One needs to ask: were the pulmonary morbidities in the no-treatment arm due to the persistent PDA itself, or were they due to the treatments used to stabilize the infants while awaiting spontaneous closure?[23,36]

In contrast, the more recent surgical closure trials managed infants in the no-treatment group with a "gentler" ventilator approach, which avoided intubation and tolerated hypercarbia. With this type of respiratory management, there is no evidence that early surgical PDA closure prevents the evolution of BPD.[24,34,37-39] In fact, many morbidities associated with ligation (postligation hypotension, vocal cord paralysis, bronchopulmonary dysplasia [BPD], and abnormal neurocognitive development) appear to be reduced when ligation is delayed for at least several weeks.[24,31-33,40] At this point in time, avoiding surgical ligation or delaying it until late in the neonatal course appears to be preferable to ligating the PDA within the first 2-3 weeks. Unfortunately, there is no information to determine which infants are most likely to benefit from later surgical ligation and which infants might best be left untreated.

Let's turn now to the trials that used indomethacin or ibuprofen to study the effects of pharmacologic PDA closure on neonatal morbidity. Although more than 30 placebo-controlled RCTs have examined this question, the evidence for long-term benefits from pharmacologic PDA closure still appears to be in doubt.[11,41-46] Most of these trials were performed more than 17 years ago, and as with the surgical treatment trials, interpreting the results of the pharmacologic RCTs requires an understanding of how infants in the no-treatment arm were handled.