Association between Hemodynamically Significant Patent Ductus Arteriosus and Bronchopulmonary Dysplasia

Federico Schena, MD, Gaia Francescato, MD, PhD, Alessia Cappelleri, MD, Irene Picciolli, MD, Alessandra Mayer, MD, Fabio Mosca, MD, and Monica Fumagalli, MD

Objective To assess whether the duration and magnitude of the shunt with patent ductus arteriosus (PDA) are related to a higher incidence of bronchopulmonary dysplasia (BPD) or death.

Study design A total of 242 infants ≤28 weeks gestational age were evaluated retrospectively between 2007 and 2012; 105 (43.3%) developed BPD or died (group 1) and 137 (56.6%) did not (group 2). A review of all echocardiographic evaluations performed from birth up to 36 weeks of postconceptional age or final ductal closure was carried out, to detect the presence of PDA, and estimate the severity of ductal shunt through the "PDA staging system" proposed by McNamara and Sehgal.

Results Group 1 presented with a hemodynamically significant ductus arteriosus (DA) (E3 and/or E4-PDA) for a longer period of time vs group 2: 4.8 vs 2.3 days, respectively ($P < .001$). Persistence of a nonsignificant DA (E2) was not associated with development of BPD ($P = .16$). Each week of a hemodynamically significant DA represented an added risk for BPD (OR 1.7), and the duration of a small, nonsignificant DA (E2) did not. Surgical ligation of PDA itself was not found to be an independent risk factor for BPD. In the subgroup of patients who received ligation, a later ligation (33 vs 23 days) and a prolonged PDA were the only factors associated to BPD or death.

Conclusions A shared scoring system of the severity of ductal shunt is helpful to correctly evaluate the association between PDA morbidities, to compare scientific studies, and to guide treatment. *(J Pediatr 2015;166:1488-92)*.

Patent ductus arteriosus (PDA) occurs in up to 70% of preterm infants born before 28 weeks gestation. Its frequency depends on the population, timing of investigation and diagnostic criteria, and it is inversely related to gestational age. The persistency of a ductus arteriosus (DA) in premature infants can cause pulmonary hyperemia and edema, and a decrease in renal, mesenteric and cerebral perfusion. It has been associated with mortality[1] and severe morbidity, including intraventricular hemorrhage,[2] necrotizing enterocolitis,[3] and retinopathy of prematurity.[4]

PDA has been related to pulmonary function impairment, prolonged ventilator dependency,[5] and development of bronchopulmonary dysplasia (BPD), either independently[6] or as an additional risk factor together with sepsis, low birth weight, and respiratory distress syndrome (RDS).[6,7] However, this association with BPD is not proven to be causal. In fact, it is unclear whether such morbidity must be considered to be related to the potential negative effects of the ductal shunt itself, or indirectly to the treatments, the choice of which has become controversial over time.

Recent randomized controlled trials[8,9] were designed to assess the relationship between timing and type of treatment and the success of PDA closure and the development of morbidities. Although nonsteroidal anti-inflammatory drugs such as indomethacin and ibuprofen have been shown to be effective in producing ductal closure,[8,10] and, therefore, have become a substitute for surgical ligation, the long-term benefits of these interventions on BPD, necrotizing enterocolitis, or survival have yet to be established. There is a high likelihood of spontaneous closure during the neonatal period, and evidence that preterm infants with mild signs of PDA do not necessarily benefit from early pharmacologic treatment if compared with a more conservative management.[9] Later or selective surgical ligation appears to be associated with a lower occurrence of neonatal morbidity and development of BPD,[11] retinopathy of prematurity, and neurodevelopmental impairment.[12]

Uncertainty over the efficacy of currently used treatments in reducing mortality and morbidity and their potential adverse effects has led some authors to propose PDA as an "innocent physiological bystander" and to suggest a more conservative approach.[13]

Ao	Aortic
BPD	Bronchopulmonary dysplasia
DA	Ductus arteriosus
E/A	Early passive to late atrial contractile phase of transmitral filling ratio
FiO_2	Fraction of inspired oxygen
HSDA	Hemodynamically significant ductus arteriosus
LA	Left atrium
PDA	Patent ductus arteriosus
RDS	Respiratory distress syndrome

From the Neonatology and Neonatal Intensive Care Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

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Most trials have not focused enough attention on the degree or magnitude of hemodynamic significance. PDA is not the same as a hemodynamically significant DA (HSDA). The lack of a standardized approach to define hemodynamic significance of PDA makes its clinical impact and contribution to neonatal morbidities difficult to define. Echocardiographic documentation of an important left-to-right transductal shunt, with measurable hemodynamically effects, leading to clinical instability, is the basis for identification of HSDA. The traditional approach takes into consideration its size, considering it significant when it exceeds the diameter of 1.5 mm, as proposed by Evans.[14] In 2007, McNamara et al proposed a classification that recognizes HSDA as a clinical continuum in which the spectrum of disease ranges from mild to severe, depending on the magnitude of the ductal shunt.[15] Few have considered all of these variables together in determining the effect of a PDA or its treatment on neonatal morbidity.[16,17] The aim of this study is to assess whether the duration and magnitude of the ductal shunt are related to a higher incidence of BPD or death.

Methods

This observational, retrospective study was conducted at the neonatal intensive care unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan between January 2007 and December 2012. The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed. Infants ≤28 weeks gestational age were included in the study. Exclusion criteria were outborn babies, major malformations, congenital heart disease, and early death (in the first 72 hours of life).

Clinical and demographic data were collected by reviewing medical records of enrolled patients. The infants who developed BPD or died were compared with infants without BPD. The following neonatal characteristics and morbidities were collected and compared between the 2 groups: gestational age, sex, twin pregnancy, intrauterine growth retardation, the use of antenatal corticosteroids, premature rupture of membranes, clinical chorioamnionitis, birth weight, Apgar score, severity of RDS based upon radiologic evaluation of severity, grading 0 to 4 as defined by Wolfson et al,[18] maximum oxygen requirement (maximum fraction of inspired oxygen [FiO_2]) in the first 72 hours, pneumothorax, pulmonary hypertension, need for inotropic drugs in the first 72 hours, and early (in the first 7 days of life) or late (after 7 days of life) proven sepsis (with positive blood culture). BPD was defined according to the criteria proposed in 2001 by Jobe and Bancalari.[19]

Every premature infant underwent an echocardiographic examination during the first 24 hours of life to exclude a congenital heart disease. Additional ultrasound examinations were performed by a cardiologist or a trained neonatologist, according to the severity of the clinical condition, presence of a ductal shunt, and need for treatment. Decision over treatment was based upon a specific written procedure available in our unit, but they were also discussed collegially taking into consideration clinical, ultrasonographic, and biochemical evaluations. Possible contraindications to treatment were carefully examined.

A systematic review of all echocardiographic examinations performed from birth up to 36 weeks of postconceptional age or final ductal closure was then carried out, evaluating the presence of PDA and estimating the severity of the ductal shunt through the "PDA staging system" proposed by McNamara and Sehgal.[15] Each staging grade corresponds to echocardiographic features that assess the size of the ductus, the pattern of ductal flow with color Doppler, the left atrial size (expressed as left atrium [LA] to aortic [Ao] ratio), the absence or reversal of end-diastolic flow in the superior mesenteric artery, the filling pressure of the left ventricle (expressed as the early passive to late atrial contractile phase of transmitral filling ratio [E/A]) or isovolumic relaxation time. A score for increasing severity has been created: E1 (no evidence of ductal flow); E2 (small and nonsignificant DA with the following features: transductal diameter <1.5 mm, restrictive continuous transductal flow, no signs of left heart pressure loading, no signs of left heart pressure loading is repeated twice, normal superior mesenteric arterial diastolic flow); E3 (moderate HSDA with the following features: transductal diameter 1.5-3.0 mm, unrestrictive pulsatile transductal flow, LA:Ao 1.5-2:1, mild-moderate left heart pressure loading, decreased or absent diastolic flow in superior mesenteric artery); and E4 (large HSDA with the following features: transductal diameter >3.0 mm, unrestrictive pulsatile transductal flow, LA:Ao >2:1, mitral regurgitant jet >2.0 m/s, severe left heart pressure loading, reversal of end diastolic flow in the superior mesenteric artery).

The duration of any ductal patency (E2 + E3 + E4) and the duration of HSDA (E3 + E4) was calculated and expressed in days. In the case of contrasting echocardiographic measures demonstrating two different degrees of severity of PDA, it was arbitrarily decided to assign the highest score. Echocardiographic examinations were not performed on a daily basis (mean number of days among 2 examinations: 1.9 days; median: 2 days). Therefore, in-between days were assigned partly (50%) to the stage detected by the first examination and partly (50%) to the stage detected on the second examination (ie, if a stage 2 was detected on day 4 of life, no ultrasound was performed until day 7 when a stage 3 was detected, in-between days 5 and 6 were registered as stage 2 and 3, respectively).

Strict ultrasonographic monitoring of patients with PDA allowed us to take into account the failure or success of medical therapy. Late re-openings were considered as separate events (eg, if a clinical evaluation led to a diagnosis of a reopening 8 days after documented ductal closure, we did not take into account that elapsed time).

Statistical Analyses

Univariate and multivariate analysis was performed to assess the association between PDA measures and the onset of BPD or death at 36 weeks postmenstrual age, adjusted for the main