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EDITORIAL COMMENT

Ductus arteriosus: The coming of age of a fetal vessel

Canal arterial: o amadurecimento de um vaso fetal

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''Nature's destruction of fetal structures that are superfluous in the adult seems to me something much greater than her original creation of those structures''

Galen of Pergamun (AD 129-200)

The ductus arteriosus (DA) is a unique, dynamic vascular structure functioning as a prenatal bypass between pulmonary artery and aorta. Intimal thickening together with O_2-dependent constriction functionally closes the DA during the first hours after birth. While in healthy term newborns, the DA) presents a spontaneous functional closure of almost 100% within 72 hours of life,[1] in premature neonates, the closure of the PDA may occur later or not at all. It is influenced by several factors, including gestational age (GA), prenatal corticosteroid administration, hyaline membrane disease, mechanical ventilation, fluid intake in the first week of life, infection and genetic factors.[2,3]

Persistent ductus arteriosus (PDA) is, therefore, a frequent occurrence in preterm infants requiring intensive care, with an incidence inversely proportional to GA, of around 30% in extremely low birth weight newborns ($\leq$28 weeks).[3] On account of the hemodynamic changes that occur after birth, PDA leads to shunting of the blood from the systemic to the pulmonary circulation. The clinical and hemodynamic impact depends on the magnitude of the shunt and the compensation capacity of the preterm myocardium to maintain effective systemic blood flow.

A large shunt volume through the PDA may cause a significant increase in pulmonary blood flow, congestive heart failure (HF) and decreased systemic blood flow. Pulmonary hyperperfusion may lead to pulmonary edema and hemorrhage, which usually manifest itself by the second day of life, respiratory deterioration, increased need for mechanical ventilation and increased risk of bronchopulmonary dysplasia (BPD).[4] The phenomenon of systemic ''circulatory steal'' seems to be related to acidosis and systemic hypoperfusion and/or hypotension, which is more evident in the first hours of life and may put several organs at risk of ischemia. Indeed, several Döppler and NIRS studies have shown decreased cerebral, coronary, abdominal aorta, superior mesenteric and renal blood flow in RNPT PDAs, suggesting a potential role for the PDA in the pathogenesis of inotropic-resistant hypotension, intraperiventricular hemorrhage, periventricular leukomalacia, cerebral palsy, necrotizing enterocolitis, and renal dysfunction.

The hemodynamic changes resulting from the PDA and the epidemiological association of PDAs with increased morbidity and mortality in preterm infants[4] have meant that for decades PDAs have been considered a pathological condi-

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tion requiring active closure therapy. However, and despite six decades of research, there is still no conclusive evidence of a causal relationship between the hemodynamic changes resulting from PDA and neonatal morbidity and mortality, or of the long-term benefit of the various strategies for PDA closure. It is not clear whether the morbidity and mortality associated with PDA result from the volume of ductal shunt, the adverse effects of treatment or are merely consequences of prematurity.

The management of PDA in preterm infants consists of three different methods: conservative management with supportive therapy alone, pharmacologic closure, and surgical ligation.[5,6] Several pharmacological strategies have been tried, mainly with cyclooxygenase (COX) inhibitors, and more recently with paracetamol. COX inhibitors, such as indomethacin and ibuprofen, work by reducing the production of prostaglandin. Although these therapeutic strategies have proved effective in closing the DA, especially if started early, there is no evidence of benefits from the various therapeutic strategies on long-term neonatal morbidity, especially BPD, retinopathy of prematurity (ROP), neurosensory deficit, death and combined results of death or BPD and death or neurosensory deficit. The exception to this being the significant reduction in severe HIPV and severe pulmonary hemorrhage in the first week of life with prophylactic indomethacin, and the significant reduction of NEC with prophylactic surgical ligation.[5–8]

On the other hand, in clinical practice, not all PDAs respond to the different pharmacological treatments, and not without being associated with significant adverse effects, such as increased ventilation days and supplemental oxygen and increased risk of BPD with indomethacin, ibuprofen and prophylactic surgical closure; increased risk of gastrointestinal perforation, especially with the association of indomethacin or ibuprofen with perinatal corticosteroids; increased gastrointestinal bleeding with ibuprofen; renal adverse effects with early indomethacin and ibuprofen and ROP, neurodevelopmental impairment, left vocal cord paralysis, diaphragmatic paresis or eventration, chylothorax and scoliosis, with surgical closure. These aspects, associated with the possibility of spontaneous closure of the DA, have led many centers in recent years to advocate a less aggressive approach to PDA.

Although the evidence suggests that routine treatment for DA closure has no demonstrable long-term benefit, the perception that large shunts may put some preterm infants at risk of pulmonary edema and hemorrhage, congestive HF, and systemic hypoperfusion has led to a growing trend toward an individualized therapeutic approach, which considers the individual variability of the new-born. Hence, the active treatment for PDA closure is suggested for newborns who may benefit most from treatment, i.e., the most premature, without prenatal corticoids, with severe respiratory disease, ventilated, with spontaneous DA constriction failure and a ''growing'' or ''pulsatile'' ductal flow pattern in the first hours of life.

It is therefore not surprising that several groups have dedicated their efforts to the search for markers to identify patients who are more likely to respond to pharmacologic treatment.[9]

In this issue of the journal, Santos et al.[10] present the results of an eight-year retrospective observational study, which included all preterm infants with a GA between 23 and 32 weeks with a diagnosis of PDA, admitted to the Neonatology Department of a large Portuguese Hospital Center. Their aim was to identify predictive factors of response to medical treatment, to enable better stratification of the provision of care to preterm newborns with hemodynamically significant PDA. The closure rate with ibuprofen was within the margins reported by previous studies, with approximately 62% responding to one cycle of treatment and 80% after a second cycle. Not surprisingly, statistically significant differences were identified for the type of delivery (eutocic), GA, the mean weight and length (more premature, smaller, and lighter), the mean platelet count (and need for platelet transfusion), need for invasive mechanical ventilation, the treatment with diuretics (furosemide). These variables were all associated with a worse response to ibuprofen treatment. A logistic regression model was developed that considered the effect of the variables GA, type of delivery and need for diuretic treatment and transfusion on response to ibuprofen therapy, with a positive predictive value of 89% and a negative predictive value of 88.8%.

These results, although relevant for the personalized approach to these patients, should be seen in the light of the limitations inherent to its retrospective nature, and of having been carried out at only one center, with a small sample (81 preterm infants). These data emphasize the need to define a personalized approach to preterm infants with hemodynamically significant PDA, to improve the individual approach to this very vulnerable group of patients, helping to identify a subgroup in whom active pharmacologic closure treatment is more likely to be beneficial. This would prevent unnecessary exposure to drugs and considering surgical ligation early during therapy. Further studies will be needed in order to improve the predictive model.

Conflicts of interest

The author has no conflicts of interest to declare.

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