

Letter to the editor

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Ductal closure in neonates: a developmental perspective on platelet–endothelial interactions

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Platelet–vasculature interactions are well known to play an important role in normal hemostasis and atherosclerosis in adults [1]. However, the impact of platelet–endothelial interactions on human development and neonatal disease is less well understood. Recently, Echtler *et al.* [2] published their investigations on the role of platelets in the closure of the ductus arteriosus. *In utero*, the ductus arteriosus serves to divert blood flow away from the lungs and toward the placenta by connecting the pulmonary artery to the aorta. A patent ductus arteriosus (PDA) in the first 3 days of life is a physiologic shunt in healthy term and preterm infants. However, a persistently patent ductus arteriosus in preterm infants, which occurs in approximately 60% of all infants born after less than 28 weeks of gestation [3], can lead to clinical complications depending on the degree of left-to-right shunting. The increase in pulmonary blood flow, especially in very immature infants (<1000 g), can cause left ventricular volume overload, pulmonary edema, loss of lung compliance, and subsequent cardiopulmonary deterioration, ultimately leading to chronic lung disease (CLD) [4]. Therefore, the understanding of the mechanisms underlying ductus arteriosus closure is of pivotal clinical importance especially for preterm infants.

Echtler *et al.* provide new and intriguing insights into the mechanisms of definite ductal closure: initial ductus arteriosus constriction, which is triggered by factors such as oxygen and decreasing prostaglandin levels [3,4], appears to be followed by platelet-triggered ductal sealing and subsequent vascular remodeling [2]. The authors show by means of intravital confocal microscopy that, following birth, platelets are recruited to the endothelium of the murine ductus arteriosus. Induced dysfunction of platelet adhesion and aggregation or defective platelet formation (*Nfe-1/–* mice) are demonstrated to cause persistent ductus arteriosus. Echtler *et al.* [2] also performed a retrospective study in preterm infants born at 24–30 weeks gestation and reported mild thrombocyto-

penia (platelet counts 101 000–140 000 per μ l) to be a significant risk factor for failure of ductus arteriosus closure in this population. However, two very recent retrospective studies from Japan [5] and the United States [6] did not find such an association between thrombocytopenia and failure of PDA closure. While ethnic differences and different gender distribution in the cohorts studied may explain some of the ambiguous findings [7], clearly, prospective studies are needed to shed light on the current controversy.

In addition to platelet number, we believe that platelet dysfunction in preterm neonates might also play an important role in the pathogenesis of PDA. In that regard, Echtler *et al.* [2] did not find differences in the expression levels of platelet surface molecules involved in platelet adhesion (including CD41, CD61 and GPVI) between murine neonatal and adult platelets. Studies of these receptors in human neonatal and adult platelets have yielded similar results, although some authors have reported lower CD61 expression levels in platelets of very immature preterm infants (<30 weeks gestation) [8]. However, substantial functional differences between human neonatal and adult platelets have been documented, including decreased agonist-induced granule secretion and exposure of the fibrinogen binding site on the GPIIb–IIIa complex and decreased aggregation in response to most platelet agonists (such as collagen, epinephrine, ADP and thrombin). The mechanisms responsible for these differences include a decreased number of α 2-adrenergic receptors, decreased calcium mobilization, and impaired signal transduction in neonatal platelets [9].

The hemostatic system in neonates is different from that of adults in many aspects and, in healthy full-term infants, the overall result is a delicate hemostatic balance. In fact, whole blood tests of primary hemostasis (such as the bleeding time and the PFA-100) have revealed more effective primary hemostasis in healthy full-term neonates than in healthy adults, as demonstrated by shorter bleeding and closure times. This has been attributed to the presence of higher hematocrits, higher MCVs, and higher concentrations of large vWF multimers in neonates compared to adults, all factors that enhance primary hemostasis and compensate for the impaired platelet function [10].

In neonates born very prematurely (<30 weeks gestation), however, platelet function is more substantially impaired than in full-term infants, and is insufficiently compensated for by other factors. Thus, compared to full-term neonates, extremely preterm neonates have

lower levels of CD62P (P-selectin) expression on resting platelets [11], lower levels of P-selectin and PAC-1 expression following stimulation [8], decreased platelet adhesion under flow conditions [12], and longer bleeding times and closure times by PFA-100 [10,13]. Importantly, this population with the most significant evidence of platelet dysfunction also has the highest incidences of intraventricular hemorrhage and of PDA [4,14]. In fact, although the study by Echtler *et al.* [2] identified mild thrombocytopenia as a significant risk factor for PDA in preterm neonates, a higher incidence of PDA has not been reported among otherwise healthy full-term neonates with severe alloimmune or autoimmune thrombocytopenia (platelet counts <50 000 per μ l) [15].

On the basis of these findings, we propose that the recent recognition of the important role of platelets in the process of postnatal closure of the ductus arteriosus raises the possibility that platelet dysfunction in extremely preterm infants (which is exacerbated during illness [16]) might be a previously unrecognized developmental factor contributing to the higher incidence of PDA among the most immature infants. Further studies will be necessary to test this hypothesis.

In conclusion, Echtler *et al.* demonstrated for the first time platelet-induced vascular obliteration and subsequent remodeling in neonatal health and disease. These findings should encourage further investigations on the role of platelets in conditions such as neonatal intraventricular hemorrhage, persistent pulmonary hypertension of the newborn and neonatal thrombosis and stroke, among others. We suggest that developmental differences in platelet function between term and preterm neonates, children, and adults play a key role in the pathobiology of these diseases and should constitute an essential part of future research efforts.

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