Path Toward Proactive Therapy for Patent Ductus Arteriosus

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Management of patent ductus arteriosus (PDA) in newborns is challenging. Options are in particular restricted by risk–benefit considerations. Severe forms of ductus malfunction, causing circulatory failure, require heart surgery or vascular intervention to correct the structural defect. Development of lower-risk alternatives is warranted. Deconvolution of underlying pathobiology would inform proactive promotion of innate ductus closure with the prospect of identifying druggable targets that address a current unmet need in vulnerable populations.

PDA
Cardiac congenital anomalies affect 1% of live births or 40,000 babies annually in the United States and are the leading cause of morbidity and mortality associated with congenital defects. Particularly common is PDA, found in 0.3–0.8% of term infants. In contrast with other cardiac anomalies, PDA is the only known congenital condition in which pharmacotherapy may successfully salvage underlying disease. However, therapeutic protocols vary among healthcare providers. A call for action to optimize therapeutic regimens and address the significant portion of nonresponders to existing management options has been issued, prompted by a recent systematic analysis of 4,800 infants with PDA. Accordingly, the present perspective summarizes PDA pathobiology–informed advances that aim to enhance the success rate in potentially responsive preterm infants and to seek alternatives for cohorts not responding to current strategies.

Ductus arteriosus (or “ductus Botalli”) is a vital fetal conduit enabling intrauterine life by directly connecting the pulmonary with the systemic circulation to bypass nonfunctioning lungs (Figure 1). With the first breath at birth and the establishment of functioning lungs, the ductus becomes obsolete and spontaneously closes before converting into a fibrotic remnant (“ligamentum arteriosus”). Persistent ductus patency, i.e., PDA, provokes pathological shunting predisposing to cardiopulmonary complications and systemic adversity. Timely treatment protects the heart from decompensation and contributes to longitudinal physical fitness and social wellness. Failure to complete normal development in utero typically relegates traditional congenital cardiac defects to anatomical correction of an already-florid disease state. Conversely, the remnant destiny of PDA, i.e., the failure to withdraw from a fetal structure, offers the unique opportunity to rescue a still-nascent culprit pathway at the point of diagnosis.

The mechanisms of perinatal ductus regulation are complex and at present not fully understood. Natural closure is triggered by the transition at birth from the intrauterine to the extraterrestrial environment (Figure 1). The surge in blood oxygen tension and the concomitant drop in placenta-produced/lung-metabolized prostaglandins are mediators of ductus smooth muscle contraction. Moreover, the postnatal rapid decline in pulmonary vascular resistance promotes collapse of the ductus cavity. The squeezed ductus, with trapped blood clot, cuts the flow within hours to days after birth. Fibrotic remodeling ensues and culminates within months after birth, completing the transition to a ductus-independent postnatal circulation.

Multiple causes of ductus malfunction can lead to PDA. They encompass defective metabolic pathways and associated sensing, and/or aberrant processes of functional/structural closure. Clinical risk factors precipitating disease prevalence include gestational age, along with confounding chromosomal anomalies. Indeed, more than 250 genetic disorders have been linked to PDA, in particular trisomy 21 or Down syndrome, where PDA is integral to a syndromic presentation. Manifestation of PDA can range from a silent to an overt condition, depending on the severity of the patency-associated shunt.

TREATMENT GAPS
Vulnerable pediatric populations demand rigorous benefit–risk assessment in clinical decision making. Echocardiography is the first-line modality to quantify PDA-associated shunt and its impact on the cardiopulmonary system. Patients with PDA with hemodynamic overload and organ failure symptomatology face the prospect of a poor outcome, requiring implementation of consensus-based advanced therapy. In premature babies with no contraindications, an attempt to close a symptomatic PDA is initiated using pharmacotherapy with prostaglandin inhibitors that modulate ductus contraction.

Yet, the average 68% success rate of 14 widely used clinical protocols mandates escalation in therapy through invasive correction or additional rounds of treatment in initial nonresponders that could result from an inadequate management regimen and/or a diverse recalcitrant disease pathobiology. Pharmacotherapy for preterm PDA relies on 5 decades of clinical experience yet has not reached standardization. Selection of most effective timing, best agent, dose, and delivery means have all been central to the quest for best practice.

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Clinical experience indicates an age-dependent response to pharmacological ductus closure. There is consensus that prostaglandin inhibitors are contraindicated for PDA in babies born at full term. The principle of “do no harm” in the setting of full-term PDA was established more than 3 decades ago, and further clinical trials have been discouraged. Nonpharmacological management, i.e., catheter-based PDA occlusion or surgical ligation necessitating thoracotomy, is the standard of care for full-term PDA. Prophylactic PDA closure is not supported by ongoing clinical studies. Accordingly, nonsymptomatic PDA, which may or may not be diagnosed during infancy, is conservatively managed until disease progression qualifies for invasive closure. This “wait for surgery” schedule contributes to the growing number of adults with PDA, estimated at a quarter of a million living Americans. Thus, development of alternative therapeutic strategies aimed at early rescue is warranted, capturing the disease process in its evolution.

**Toward Proactive Strategy**

Traditional approaches in PDA management, based on prostaglandin inhibitors and interventional ductus closure, are reactive approaches. New treatment options should be ideally proactive, targeting endogenous ductus regulators, and be applicable in broader PDA subpopulations with bona fide long-term benefit documenting not only validation (i.e., safety and efficacy) but also utility (i.e., favorable outcomes; Figure 2).

To date, more than 100 genes associated with defective morphogenesis, abnormal sensing, and inefficient contraction/sealing of the ductus arteriosus have been identified and considered in principle druggable, potentially qualifying for early-stage theranostics screening. This growing list consists of prostaglandin receptors and related enzymes; adenosine triphosphate–sensitive potassium channels that regulate vascular tone by linking energetic demand and membrane electrical activity (Cantú syndrome); *TFAP2B* and *TBX1* transcription factors that are essential for neural crest development and cause Char syndrome and DiGeorge syndrome, respectively; and histone modifier *PRDM6*, regulating vascular smooth muscle differentiation, development, and remodeling. An example of multifunctional targeting is directed on the dynamin-related protein 1, which contributes to oxygen sensing, subsequent ductus constriction, and cell proliferation finalizing anatomical closure. In the context of diverse triggering mechanisms recognized in securing the multistep execution of ductus closure, a strategy that would pinpoint a common prerequisite—namely, vascular remodeling—is yet to be explored.

PDA-causing pathways have been studied mainly in the setting of natural, physiological ductus arteriosus closure or as part of syndromic disorders involving multiple development defects and premature birth. Further investigation of isolated PDA at full term, the largest subgroup that does not respond to prostaglandin antagonists, is needed to unmask possible pathways favorable for targeted therapy. Moreover, PDA cohorts associated with chromosome rearrangements or aneuploidy, such as Down syndrome, merit particular attention, as the number of affected babies has increased by 30% while their average lifespan has doubled in the last 2 decades.

Disease models serve a pivotal role in identifying underlying pathobiology and advancing therapeutic options that need to be developed and validated across the translational axis, from proof of concept to preclinical testing prior to regulatory approval for clinical assessment (Figure 2). Transgenic PDA models typically die early after birth, underscoring a pronounced pathogenicity associated with ductus failure. Establishing a surviving surrogate of clinical PDA would enable longitudinal, long-term testing of safety and efficacy of candidate (bio)therapies, a critical step in the clinical development process. The small size of the ductus arteriosus, i.e., a 200-μm diameter over a 500-μm length...
in a 1-day-old mouse, has also profoundly limited initial translational studies. In the absence of reproducible human-size models, the recognized bottlenecks in smaller animals are increasingly addressed, leveraging emerging technologies, e.g., low-input RNA sequencing, cutting-edge transgenesis, and high-resolution imaging. These advances collectively expand the reach of preclinical research in PDA needed for clinical advancements.

In parallel with ongoing efforts in decoding disease pathogenesis and developing targeted proactive therapies, new PDA options must carefully address issues associated with pediatric populations. These include assessment of age-dependent pharmacokinetics and pharmacodynamics profiles, special considerations in deploying optimal trial designs, avoidance of risk for mother and fetus in case of intrauterine treatment, and securing broader parent approval for infant enrollment to expand the currently available body of evidence. Tissue-specific delivery during infancy, while often challenging, is attractive in the context of overlapping with the natural time course of spontaneous ductus closure. The intimate ductus adaptation at birth contains nontraditional putative drug targets, including transcription factors and cell cycle regulators, as well as opportunities for epigenomic regulation, which may require advanced therapy medicinal products designation. The growing experience from ongoing investigation in the setting of cancer therapy provides a valuable blueprint for progressing toward a causative therapy for PDA.

OUTLOOK

In conclusion, PDA is a common cardiac anomaly with newly acquired knowledge expanding the understanding of underlying disease mechanisms. The ensuing development of proactive therapeutic approaches that target identified pathways, specific to the diseased neonatal organ system, would benefit vulnerable populations with PDA, in particular those in whom current pharmacological options are ineffective or contraindicated. Science-informed therapy at birth is at the vanguard of next-generation solutions in childcare. This evolving landscape heralds an evolution in pediatric clinical pharmacology that integrates the young patient within a causative care regimen.

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CONFLICT OF INTEREST

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