Received: 3 September 2018 | Accepted: 16 October 2018

DOI: 10.1111/chd.12714

SPECIAL ISSUE ARTICLE

WILEY Congenital Heart Disease

Molecular and mechanical factors contributing to ductus arteriosus patency and closure

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Funding information
National Institutes of Health, Grant/Award Number: HL109199, HL128386 and HL132805.

Abstract

Regulation of the ductus arteriosus, an essential fetal vessel connecting the pulmonary artery and aorta, is complex. Failure of this vessel to close after birth may result in a persistent left-to-right shunt through the patent ductus arteriosus, a condition associated with significant morbidities. Numerous factors contribute to the shift from fetal ductus patency to postnatal closure, requiring precise coordination of molecular cues with biomechanical forces and underlying genetic influences. Despite significant advances, questions remain regarding signaling dynamics and the natural time course of ductus closure, particularly in preterm neonates. This review highlights the contributions of early investigators and more recent clinician scientists to our understanding of the molecular and mechanical factors that mediate ductus patency and closure.

KEYWORDS
ductus arteriosus, oxygen, patent ductus arteriosus, prostaglandins

1 | INTRODUCTION

The ductus arteriosus (DA) is a muscular fetal artery connecting the pulmonary and systemic circulations. In utero, elevated pulmonary vascular resistance coupled with relatively low systemic resistance promotes right-to-left blood flow through the DA, allowing blood oxygenated by the placenta to bypass the developing lungs.[1] Postnatally, the DA must close to allow appropriate perfusion of the newly inflated lungs. Failure of this vessel to close within the first few days of life results in a persistent left-to-right shunt termed patent ductus arteriosus (PDA). PDA disproportionately affects premature infants (with a reported incidence of up to 80% in infants < 1000 grams)[2] and accounts for 5%-10% of all congenital heart defects in term infants.[3] Consequences of prolonged DA patency include: (1) overcirculation of the lungs due to excessive left-to-right shunt; (2) left-sided heart enlargement due to the increased blood volume returning from the lungs; and (3) ductus "steal" phenomenon resulting in decreased perfusion of peripheral organs. Therefore, PDA is associated with significant morbidities, including congestive heart failure, necrotizing enterocolitis, spontaneous intestinal perforation, neurodevelopmental impairment, intraventricular hemorrhage, respiratory distress syndrome, and chronic lung disease.[4]

The DA is a deceptively complex vessel that has challenged clinicians and basic scientists for centuries. Anatomical descriptions of the ductus date back to the second century AD,[5] however, the first illustrations of the DA didn't appear until the mid-1600s. The English physician, Sir William Harvey recognized its importance in fetal circulation and more accurately described the fetal DA as two roots of the great artery stemming from the heart that withers after birth.[6] Over the next three centuries, seminal studies by Jager and Wollenman, Cassels, Gittenberger-de Groot, and many others provided a detailed analysis of the DA's distinct histological structure.[7-9] Their observations describe the fetal DA as a muscular artery with a "looser" structure than the aorta or pulmonary artery, containing an internal elastic lamina but devoid of elastic fibers in the tunica media. In contrast, the mature DA poised for closure is said to contain spiral arrangements of smooth muscle fibers, a fragmented internal elastic lamina, and increasing numbers of intimal cushions composed of medial cells protruding into the vessel lumen, while a persistently patent term-gestation vessel contains thickened intact elastic laminae and/or ectopic elastic fibers and lack intimal cushions.[10,11] Similarly, hallmark studies by Coceani and Olley,[12] Elliott,[13] Sharpe,[14] Kennedy and Clark,[15] and Clyman[16] among others gave us the first mechanistic insights into the role of prostaglandins and oxygen in regulation

of DA tone. And yet, even with the aid of cutting-edge molecular biology techniques and major advances in diagnostics and patient management, the DA remains somewhat of a developmental enigma and questions regarding the genetic predisposition to PDA or its treatments, the timing of spontaneous closure, and best pharmacologic strategies for the persistently patent DA still remain.[17]

2 | FACTORS REGULATING DUCTUS TONE IN UTERO

The fetal DA has intrinsic tone and requires dilating factors to counteract competing vasoconstrictive agents in order to maintain patency in utero (Figure 1). Patency of the preterm DA is maintained by nitric oxide (NO) signaling, while that burden shifts to prostaglandin E_2 (PGE_2) later in development.[18] NO signaling relaxes the DA by activating cGMP/PKG signaling. PGE_2, working primarily through the EP4 receptor, induces DA dilation via activation of cAMP/PKA. While NO and PGE_2 are typically considered the primary mediators of DA dilation, other factors clearly play a role. Adenosine[19] and atrial naturetic peptide[20] have both been shown to dilate the DA via up-regulation of cAMP and cGMP signaling, respectively. Moreover, the gasotransmitter carbon monoxide (CO) also acts as a cGMP-mediated vasodilator[21] and elevated levels of endogenously produced CO (as measured by end-tidal CO, corrected for CO in ambient air) has been associated with symptomatic PDA in preterm infants.[22] In addition, voltage-gated potassium channels (Kv1.5, Kv 1.2, Kv2.1), ATP-gated potassium (K_{ATP}) channels, and larger-conductance voltage-dependent and calcium-activated potassium (BK_{Ca}) channels are enriched in the DA and act as vasodilators upon activation.[23,24]

3 | FACTORS MEDIATING DUCTUS CONTRACTION AFTER BIRTH

Over the years, many hypotheses have been put forth to explain the mechanism of postnatal DA closure. Early investigators postulated

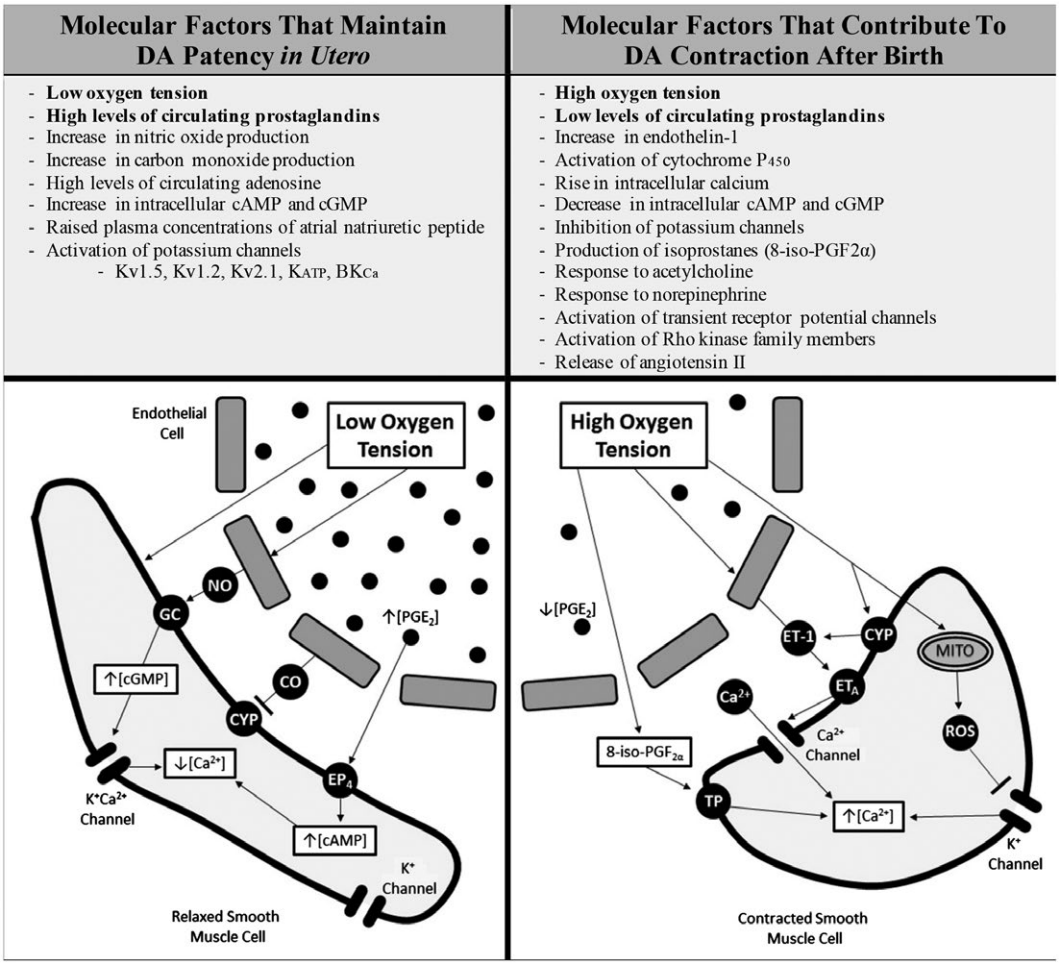

FIGURE 1 Factors affecting fetal DA patency and postnatal DA closure. The fetal DA is actively maintained in a relaxed state by overlapping mechanisms. Postnatal DA constriction is accomplished by reversal of low oxygen tension and high prostaglandin tone, and activation of multiple signaling pathways. Source: Figure adapted with permission from Hermes-DeSantis and Clyman.[49] Abbreviations: 8-iso-PGF2α, 8-iso prostaglandin F2α; Ca^{2+}, calcium; cAMP, cyclic adenosine monophosphate; cGMP, guanosine 3',5'-cyclic monophosphate; CO, carbon monoxide; CYP, cytochrome P450; EP4, prostaglandin E2 receptor 4; ET-1, endothelin-1; ETA, endothelin receptor type A; GC, guanylate cyclase; K^+, potassium; MITO, mitochondria; NO, nitric oxide; PGE_2, prostaglandin E2, ROS, reactive oxygen species; TP, thromboxane receptor

that the DA became kinked, compressed, or elongated to the point of vessel collapse after birth, resulting in an interruption of blood flow and thrombus formation.[6] However, these suppositions were all based on examination of postmortem tissue. Later histological studies suggested closure by active muscular contraction.[8] Our current understanding of postnatal DA constriction is that smooth muscle cell contraction is triggered by two major events: a precipitous decrease in PGE_2 levels and the onset of ventilation (Figure 1). Prostaglandin-induced DA relaxation is interrupted by umbilical cord clamping and removal of the placenta, thereby eliminating a major source of circulating prostaglandins. In addition, the onset of postnatal respiration reduces pulmonary vascular resistance and increases blood flow to the lungs (Figure 2), where prostaglandins are metabolized by 15-hydroxyprostaglandin dehydrogenase, further precipitating their decline.

DA closure is simultaneously initiated by the onset of respiration. A neonate's first few breaths serve to drive out fetal lung liquid from the alveolar space, allowing pulmonary gas exchange to commence, resulting in increased oxygen tension.[25] Crying (in which a large inspiration is followed by a forced expiration) immediately after birth has been hypothesized to aid in liquid clearance from the lung and cardiovascular transition.[26] Indeed, one study found that infants who cried more often within the first 10 minutes after birth had a lower DA flow ratio (right-to-left:left-to-right) and increased left ventricular output, signifying a faster neonatal transition.[27] Appreciating the relationship between respiration and DA constriction, Kennedy and Clark performed some of the earliest mechanistic studies in the early 1940s, noting that oxygen, but not nitrogen, could induce DA closure.[15] Moreover, Born et al demonstrated that ventilation of pregnant sheep with 100% oxygen caused increased fetal carotid oxygen saturation and corresponding DA constriction.[28]

Several mechanisms have been proposed to explain the DA's exceptional ability to sense and respond to oxygen. Three frequently invoked pathways include cytochrome P450-mediated induction

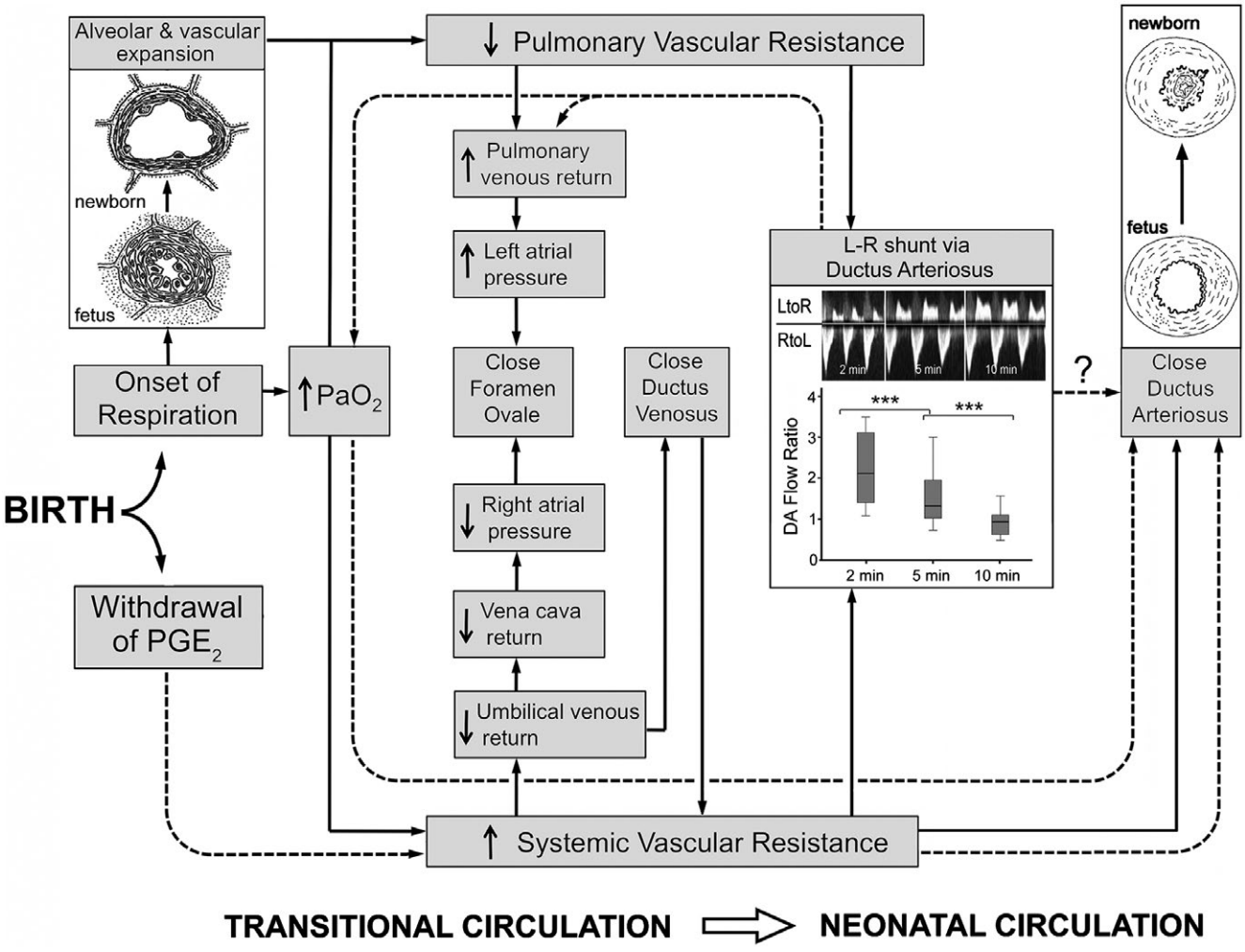

FIGURE 2 Physiological changes at birth leading to closure of the DA. At birth, PGE_2 levels fall while the onset of breathing results in alveolar expansion, physical stretch of pulmonary capillaries, and flow-mediated dilation (diagram adapted with permission from Lakshminrusimha and Steinhorn[50]). Sequential events lead to closure of the foramen ovale, ductus venosus, and reversal of flow in the ductus arteriosus soon after birth (diagram adapted with permission from van Vonderen, te Pas, Kolster-Bijdevaate, et al[33]), culminating in ductus constriction and eventual closure (diagram adapted with permission from Gittenberger-de Groot[7]). Source: Overall figure adapted from Nelson.[51]

of endothelin-1, production of "constrictor" isoprostanes (8-iso-PGF2α), and mitochondrial-mediated reactive oxygen species inhibition of Kv1.5 and Kv2.1.[4] Oxygen can also inhibit K_{ATP} channels resulting in membrane depolarization and activation of voltage-dependent calcium channels.[29] Other factors including the transient receptor potential channel, TRPM3,[30] angiotensin II, and Rho kinase family members (RhoA/B, Rock1/2) also promote DA constriction (Figure 1). In addition, the DA is innervated with cholinergic and adrenergic nerves that mediate constriction in response to acetylcholine and norepinephrine.[19] Despite their diversity, all of these pathways eventually converge on Ca^{2+}-mediated phosphorylation of myosin light chain, leading to actin/myosin interaction and ultimately DA smooth muscle cell contraction.[4,19]

4 | DUCTUS HEMODYNAMICS AND TIMING OF CLOSURE

The DA experiences unique hemodynamic alterations during the fetal-to-neonatal transition. In utero, blood flows through the DA in a right-to-left pattern. Within the first 10 minutes after birth, concomitant with the fall in pulmonary vascular resistance, flow across the DA becomes bidirectional and then exclusively left-to-right which decreases until the point of vessel closure and complete cessation of flow, a process which takes approximately 48 hours in healthy term neonates.[31-33] The preterm DA is less likely to spontaneously close, resulting in prolonged left-to-right shunting. Even in cases where the preterm duct does close without intervention, the time to closure is inversely proportional to gestational age at birth, with some very low birth weight infants requiring months or even years to achieve closure.[34,35] Given that prolonged left-to-right shunting has been associated with multiple morbidities, a more comprehensive understanding of factors that regulate the timing of DA closure (beyond oxygen and prostaglandins) and the molecular consequences of altered hemodynamic forces is needed to resolve which PDAs require intervention and which ones can safely be left to close on their own.[24]

While persistence of flow through the DA lumen is a strong predictor for development of a symptomatic PDA,[36] flow-mediated dilation, shear stress, and stretch forces are understudied aspects of DA regulation. Like other vessels, the endothelium and smooth muscle cells of the DA are studded with multiple factors known to sense and respond to biomechanical stimuli including transmembrane ion channels and receptors, extracellular components like the glycocalyx, primary cilia, adhesion molecules, and cytoskeletal proteins. Others have shown that biomechanical forces regulate the expression of vasoactive factors. For instance, endothelial cells up-regulate vasodilators (nitric oxide synthase, prostacyclin)[37,38] and are less likely to proliferate[39] in response to laminar shear stress. Conversely, under turbulent conditions (oscillatory or low flow), endothelial cells become more proliferative and up-regulate the expression of vasoconstrictors (endothelin 1) and adhesion molecules (VCAM-1, ICAM-1).[40,41] In addition, circumferential stretch induces phenotypic switching in vascular smooth muscle cells (from contractile to synthetic), which in turn causes increased rates of cell proliferation and migration.[42] Moreover, stretch induces endothelial release of angiotensin II[43] and smooth muscle cell production of matrix metalloproteinases (MMP2, MMP9),[44,45] leading to vasoconstriction and extracellular matrix remodeling, respectively. Of note, matrix remodeling and smooth muscle cell migration are essential components of intimal cushion formation and DA closure.[46,47] In addition, leukocyte adherence to the ductus lumen via VCAM-1 is necessary for intimal cushion expansion and permanent vessel occlusion.[48] Furthermore, DA endothelial and smooth muscle cells experience significant changes in shear stress and longitudinal/circumferential stretch forces as the postnatal ductus constricts. Therefore, it is reasonable to suggest that mechanosensors embedded in the DA can sense these biomechanical changes and interpret them as developmental cues that help coordinate the timing of vessel closure and remodeling.

5 | CONCLUSION

Persistent patency of the DA has been recognized for nearly two millennia. The longstanding association of PDA with adverse neonatal outcomes has led physicians to seek curative treatments to induce DA closure. Understanding the molecular and biomechanical forces that maintain relaxation of the fetal DA and orchestrate its closure after birth will support the development of novel treatments or provide a rational basis for tolerating its ongoing patency when conservative management strategies might be optimal.

ACKNOWLEDGMENTS

Supported in part by NIH grants HL128386, HL109199, and HL132805.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Stacey L. Crockett contributed to concept/design, creation of figures, drafting and critical revision, and approval. Courtney D. Berger contributed to concept/design, drafting and critical revision, and approval. Elaine L. Shelton contributed to concept/design, creation of figures, drafting and critical revision, funding, and approval. Jeff Reese contributed to concept/design, creation of figures, drafting and critical revision, funding, and approval.

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How to cite this article: Crockett SL, Berger CD, Shelton EL, Reese J. Molecular and mechanical factors contributing to ductus arteriosus patency and closure. *Congenital Heart Disease*. 2019;14:15–20. https://doi.org/10.1111/chd.12714