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Patent ductus arteriosus: The physiology of transition

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ABSTRACT

The transition from intrauterine to extrauterine life represents a critical phase of physiological adaptation which impacts many organ systems, most notably the heart and the lungs. The majority of term neonates complete this transition without complications; however, dysregulation of normal postnatal adaptation may lead to acute cardiopulmonary instability, necessitating advanced intensive care support. Although not as well appreciated as changes in vascular resistances, the shunt across the DA plays a crucial physiologic role in the adaptive processes related to normal transitional circulation. Further, we describe key differences in the behavior of the ductal shunt during transition in preterm neonates and we postulate mechanisms through which the DA may modulate major hemodynamic complications during this vulnerable period. Finally, we describe the conditions in which preservation of ductal patency is a desired clinical goal and we discuss clinical factors that may determine adequate balance between pulmonary and systemic circulation.

1. Introduction

The transition from intrauterine to extrauterine life represents a critical phase of physiological adaptation which impacts many organ systems, most notably the heart and the lungs. The majority of term neonates complete this transition without complications; however, dysregulation of normal postnatal adaptation may lead to acute cardiopulmonary instability, necessitating advanced intensive care support [1]. In some situations, death or adverse neurosensory impairment may ensue [2,3]. Invasive animal experiments have confirmed a progressive fall in pulmonary vascular resistance (PVR) over the first 48–72 hours after birth in response to lung recruitment and increased alveolar oxygen concentration [4]. As the PVR falls, the direction of flow across the ductus arteriosus (DA) and foramen ovale (FO) becomes increasingly left to right (i.e. shunting from the systemic to pulmonary circulation). This is soon followed by the closure of the DA in most infants, ductus venosus in many and lastly FO. With the help of intermittent application of non-invasive techniques such as echocardiography, these changes have also been well documented in human neonates [5–7]; however, their specific relationship with time after birth has not been firmly established. Although not as well appreciated as changes in vascular resistances, the shunt across the DA plays a crucial physiologic role in normal transition circulation, as highlighted in the following section. Subsequently, we describe key differences in the behavior of ductal shunt during transition in preterm neonates and, derived from the clues provided by previous physiological and epidemiological observations, we postulate mechanisms through which the DA shunt may modulate major hemodynamic complications during this vulnerable period. Lastly, in brief, we describe conditions in which preservation of ductal patency is a desired clinical goal and we discuss clinical factors that may determine adequate balance between pulmonary and systemic blood flow.

2. Postnatal transition and ductus arteriosus in healthy term neonates

Birth is a unique physiological event characterized by complex and sudden changes affecting several organ systems, most notably the respiratory and cardiovascular system [8]. Fetal life is characterized by the non-participation of lungs and dependence on placental circulation for gas exchange, along with its other metabolic functions. Fetal circulation is arranged in series, which differs from the postnatal situation. The majority of venous return coming from the placenta bypasses the hepatic circulation via the ductus venosus, reaching the inferior vena cava just before its entry into the right atrium [9]. Enabled by the anatomical location of the inferior vena cava and the high volume of umbilical venous return, most oxygenated blood crosses to the left atrium through the foramen ovale (FO), which is kept widely open by the

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higher right atrial pressure compared to the left. Of the remaining blood pumped into the pulmonary artery by the fetal right ventricle, a large proportion joins the systemic circulation without passing through the pulmonary vascular bed via the ductus arteriosus (DA); as a consequence, only 10–20% of total biventricular cardiac output enters the lungs during fetal life. This, however, increases to ~30% by late gestation, secondary to the increase in reactivity of the fetal pulmonary vasculature during the third trimester [10]. In addition to these anatomical factors, the unique fetal circulatory phenotype is made possible by the high PVR of the fluid-filled fetal lungs and low systemic vascular resistance (SVR) in the fetus secondary to its attachment to placental circulation. Maintenance of fetal circulation as well as its rapid adaptation after birth to a parallel circulation, where almost the entire cardiac output must pass through the lungs for oxygenation, is a result of a cascade of concurrent, interconnected but not completely understood mechanical, biochemical, and hormonal factors [11–14].

The sentinel event which triggers this dramatic circulatory adaptation at birth is the onset of ventilation [15]. Sudden and rhythmic distension of the lungs with air, aided by the high negative pressure of the first few breaths taken by the newly born, cause displacement of lung fluid from alveolar to interstitial space. This results in establishment of an air–liquid interface in the ventilated alveoli and a large initial drop in PVR. Although the specific mechanism(s) by which ventilation alone reduces PVR are not yet confirmed, the following factors are postulated to play key roles: (i) straightening of airways and untwisting of pulmonary vessels due to alveolar expansion; (ii) recruitment of intra-acinar arteries; (iii) increased capillary diameter caused by an increase in the transmural pressure across alveolar–capillary interface secondary to the newly developed surface tension inside the alveoli; and (iv) improvement in ventilation–perfusion matching caused by the vasodilatory effects of increased alveolar oxygen and the production of nitric oxide [12,14].

Coinciding with this rapid fall in PVR immediately after birth following ventilation, is the sudden increase in SVR secondary to removal of the placenta from the systemic circulation. As an instant result of the rapid shift in the PVR: SVR ratio, the directionality of blood flow across the DA changes from a purely right-to-left shunt (i.e. shunting from pulmonary to systemic) to a bidirectional pattern or perhaps exclusive left-to-right flow in some. This sudden onset of systemic-to-pulmonary ductal shunting, facilitated by the change in transductal resistance gradient, is thought to trigger the rise in pulmonary blood flow seen shortly after birth. The resultant abrupt gush of blood into the pulmonary vascular bed exposes the endothelium to increased shearing forces which, in addition to an increase in oxygen tension, induces production of vasodilatory mediators (e.g. nitric oxide, bradykinin, prostacyclin) and inactivates production of vasoconstrictor mediators (e.g. thromboxane, endothelin, leukotrienes) [13]. Contributory changes are also observed in pulmonary vascular smooth muscle cells, which undergo remodeling and progressive thinning starting shortly after birth. In terms of the cardiac shunts, an acute rise in pulmonary blood flow causes a significant increase in left heart preload and rise in left atrial pressure which, along with a reduction in volume and force of venous return from the inferior vena cava and lowering of right atrial pressure, results in contraction of the FO. The increase in arterial oxygen concentration, bradykinin production and reduction in circulating levels of prostaglandins induce constriction of the DA, followed by its functional closure within a couple of days. Absence of flow across the ductus venosus following removal of the placental circulation initially results in the constriction of its sphincter, followed by its complete closure.

Our knowledge of the transitional physiology as highlighted above is mostly derived from animal experiments; however, with the development and increasing use of echocardiography by neonatal clinicians, more transitional hemodynamic data are being published from human neonates [16,17]. Although these recent studies confirm the previous human and animal model observations, sequential time-specific changes in human neonates during the period of postnatal transition are still not firmly documented. Although it is known for some time that the DA closes functionally by 48 hours of age in most healthy term neonates, the natural history of patterns of ductal shunting normal trajectory was only recently described. In a prospective study of 50 healthy term neonates born at our institution, we performed sequential echocardiograms at day 1 and day 2 of age for each neonate, and confirmed that no transductal flow was seen in, 28 (56%) patients at 12–18 hours and 48 (96%) neonates at 30–40 hours of age respectively [18]. In the remaining infants, the DA was still open but demonstrated a small, restrictive, left-to-right shunt. No study participant had a bidirectional or unrestricted left-to-right shunt at either time point. On the other hand, flow could be clearly seen across the FO in 41 (82%) and 37 (74%) neonates at the first and second scan time respectively. When seen, the shunt across the FO was also only left to right. These findings were confirmed in a prospective observational study of 15 healthy term infants (Table 1, unpublished data). These data suggest that evidence of right-to-left flow beyond 8–12 hours of life is unusual for full-term healthy neonate. How these parameters change with various factors that are known to interfere with normal transition and whether the timing of these changes may have a diagnostic utility need further evaluation. The impact of delayed cord clamping on our understanding of 'standard' postnatal transition is further evolving [19]. In preterm neonates, the practice of delayed cord clamping does not seem to be associated with any change in the incidence of patent ductus arteriosus (PDA) [20].

Table 1
Flow characteristics of shunting of blood across ductal arteriosus and foramen ovale during the first day of life.[a]

Characteristic	Scan 1	Scan 2	Scan 3	Scan 4
Age (h)	0.4 ± 0.1	2.7 ± 0.2	8.2 ± 0.6	22.7 ± 0.7
Ductus arteriosus				
Closed	0	0	3 (20%)	10 (67%)
Small restrictive with left-to-right shunt	0	3 (20%)	7 (47%)	5 (33%)
Bidirectional shunt	15 (100%)	5 (33%)	1 (7%)	0
Growing shunt[b]	0	7 (47%)	4 (27%)	0
Percentage duration of right-to-left shunt in bidirectional shunts[c] (mean (SD; range))	32% (5; 22–40)	24% (5; 17–30)	23% (only one bidirectional shunt)	–
Foramen ovale				
No flow visualized	5 (33%)	4 (26%)	2 (13%)	2 (13%)
Right-to-left shunt	1 (6%)	0	0	0
Bidirectional shunt	1 (6%)	1 (6%)	1 (6%)	0
Left-to-right shunt	8 (53%)	10 (67%)	12 (80%)	13 (87%)

SD, standard deviation.

[a] Data obtained prospectively from 15 healthy human neonates using sequential echocardiography assessments.

[b] Growing shunt was defined as shunt pattern which is almost entirely left to right but had a small right-to-left component at end-diastole.

[c] Duration of right-to-left shunt/total shunt duration) × 100. No patient had unrestrictive left-to-right shunt across patent ductus arteriosus.

3. Ductus arteriosus during transition in premature neonates

The role of the DA during transition in preterm neonates has been a subject of much research and discussion [21–23]. This is likely due to failure of the normal biologic processes which modulate closure and the known association with several prematurity-related complications [24–28]. Lately, fueled by the failure of therapeutic randomized control trials and related meta-analyses to show an improvement in clinical outcomes, the feasibility of modifying patent DA-associated morbidities