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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

has been questioned, leading to further debate and controversy, as discussed elsewhere [23,29–31]. It is a well-established fact that preterm DA is less likely to close spontaneously as part of the transition to extrauterine life and that the incidence of patent DA is inversely related to gestational age at birth [28,32]. The preterm ductus is less muscular and thin-walled compared to the term ductus, which is developmentally designed for spontaneous closure following birth. Presence of systemic inflammatory mediators such as tumor necrosis factor alpha may result in increased circulating prostaglandins and reactive oxygen species, which contribute to the failure of spontaneous closure [33]. Additionally, a complex interplay of factors such as increased sensitivity of the preterm smooth muscle cells to the vasodilatory effect of circulating prostaglandins and nitric oxide [34], early adrenal insufficiency [35], thrombocytopenia [36–38], and impaired platelet function [39] may also play a role in prolonged ductal patency.

Other contributory factors that may warrant consideration relate to the resuscitation techniques. In particular, the unintended negative impact of exposure to positive pressure ventilation, oxygen, and artificial surfactant may include a more rapid fall in PVR. Indeed, physiological observations obtained using functional echocardiography, pre- and post-treatment in neonates $< 32$ weeks, reported an association of surfactant administration with an increase in the right ventricular output and absolute ductal diameter [40]. Interestingly, in all neonates, post surfactant treatment, DA flow became exclusively left to right and was unrestrictive. These measurements were performed at a mean age of 0.5 hours. This type of shunt pattern is likely to persist, as suggested by other studies reporting an unrestrictive and exclusively left-to-right shunt at the level of the DA in the majority of preterm infants when assessed as early as 5 hours of age [41,42]. This is in stark contrast to the DA flow pattern observed in healthy term neonates at a similar age, as highlighted above. Even in cases where preterm DA undergoes spontaneous closure, it does not occur till after several days of age, which is again inversely proportional to the gestational age at birth. In a retrospective study of 280 preterm infants who did not receive active medical or surgical therapy directed at closing the ductus, the median time to DA closure was 71, 13, 8, and 6 days in infants born at $< 26$, $26^{+0}$ to $27^{+6}$, $28^{+0}$ to $29^{+6}$, and $\geq 30$ weeks respectively [43]. Together these observations suggest that in the absence of interventions such as prophylactic indomethacin, a majority of extreme preterm neonates will be exposed to a systemic-to-pulmonary shunting of blood across the DA, at least for a period of time. The clinical significance of this exposure during the transitional and early postnatal period as well as its role in the pathophysiology of complications has not yet been completely elicited.

Patent DA in preterm neonates has been reported to be associated with increased mortality as well as several major short-term complications [24,27,28,44–47]. In this section, however, we focus on the relevant complications known to occur during the immediate transitional period in premature infants, namely intraventricular hemorrhage (IVH) and pulmonary hemorrhage (PH) [48–50]. To establish causality and mechanisms though which the DA may contribute to these complications requires an ability to continuously monitor the hemodynamic profile of the DA and then relate it to the timing of IVH/PH. This is not feasible in contemporary clinical practice for obvious reasons; however, physiological and epidemiological investigations have provided several hints. First, the timing of the peak incidence of these hemodynamic complications raises suspicion, as it closely relates to the time when left-to-right shunt across DA is progressively increasing in its volume [50]. Second, the interventions that have been shown to reduce the incidence of IVH and/or PH, such as antenatal steroids and prophylactic indomethacin, are also associated with reduction in the frequency of patent DA [51,52]. Whether this is a coincidence or an unrelated therapeutic effect is not known. A pre–post retrospective cohort study demonstrated a reduction in the incidence of IVH with implementation of standardized practice of early screening and targeted treatment of patent DA in preterm neonates; however, the sample size in this study was small [53]. A recent randomized control trial of ductal treatment including 92 neonates showed that screening and initiation of targeted treatment for neonates with a large DA before 12 hours of age is associated with reduction in the frequency of PH; however, no other difference was noted in the measured outcomes [54]. This trial, however, stopped before completion of intended recruitment due to lack of availability of indomethacin. Another recent report from a large population-based cohort from France reported an association between the practice of echocardiographic evaluation and treatment for patent DA before 3 days of age in preterm neonates with lower mortality and incidence of PH [55].

Although definitive mechanistic studies are still awaited, painstakingly conducted sequential echocardiography studies in relatively large cohorts of extreme preterm neonates have provided invaluable insights [41,46,48]. A strong association has been noted between low superior vena cava flow during the early hours after birth in preterm neonates and subsequent development or progress to higher grade IVH [41]. Interestingly, the low superior vena cava flow at 5 hours of age was directly related to the observed ductal diameter and the use of higher mean airway pressure, presumably due to their negative effect on systemic vascular resistance and systemic venous return respectively. Another prospective physiological study found that lower cardiac output, ventricular function and cerebral blood flow during the first 12 hours of age and their subsequent increase precede development of high-grade IVH in extreme preterm neonates [56]. These observations are consistent with the recognized ischemia–reperfusion theory for occurrence of IVH and suggest a link with the left-to-right shunt across the DA.

We propose an interaction between the immature preterm myocardium and exposure to an unrestrictive DA shunt during postnatal transition as an important contributor to the pathophysiology governing occurrence of IVH and PH in preterm neonates. The preterm myocardium is inherently less contractile, perhaps owing to fewer contractile units, increased water content and immature sarcoplasmic reticulum [57–59]. Clinically this translates into a higher dependency of the myocardial function, and a delay in adapting to changes in loading conditions. So, when the flow pattern of a DA shunt becomes left to right shortly after birth, it results in a sudden increase in pulmonary blood flow, pulmonary venous return and left heart preload, which “the stiff” premature left ventricle may not tolerate well. Failure of the compensatory increase in left ventricular relaxation, filling, and output may lead to increased left atrial pressure and pulmonary venous hypertension, predisposing the infant to PH. The coincidental association of this physiological disturbance with the onset and timing of PH on day 1 to day 2 of postnatal life is noteworthy [49].

In addition, the systemic impact of a sustained unrestrictive left-to-right shunting DA includes lower post-ductal vascular resistance, resulting in a preferential ‘sucking’ blood downstream, away from the cerebral circulation. In the absence of the compensatory increase in left ventricular output, it may result in a relative state of cerebral hypoperfusion, especially if it exceeds the infant's cerebral autoregulation capacity (Fig. 1A). As the left ventricle adapts to changes in loading conditions, it responds by increasing its output, first to normal range and subsequently even higher, if the left-to-right ductal shunt continues to persist and increase in volume. As the cerebral vascular bed is preductal, theoretically it is exposed to this sudden restoration/increase in blood flow, creating an ischemia–reperfusion pathophysiology, which may predispose to IVH (Fig. 1B).

This association, however, may involve many layers of interaction between the host and disease (Fig. 2), which poses a major challenge to prove such a link in the clinical setting. For instance, in one group of patients, the severity of pre-existing hypoperfusion may be such that a ‘normal’ reperfusion state is enough to lead to IVH with no contribution from DA shunt, whereas in others it may be a combination of both. On the other hand, in some patients, the extent of the DA shunt may itself be high enough to supersede cerebral autoregulatory capacity, i.e.

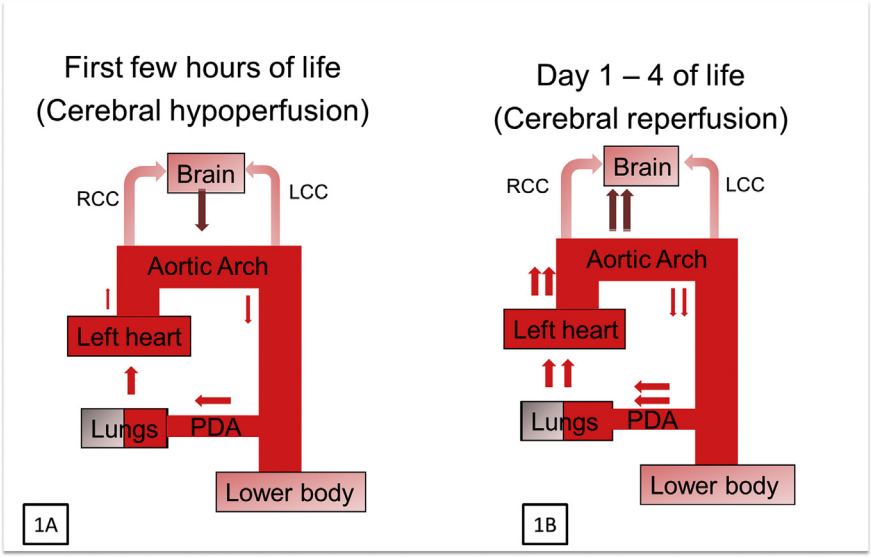


**Fig. 1.** Hypothetical mechanism of the contributory role of the transitional left-to-right ductal shunt in development of intraventricular hemorrhage in preterm neonates. Immediately following birth, left ventricular output is relatively low as the developmentally non-complaint preterm left ventricle takes longer to adapt to the sudden increase in afterload. As the pulmonary vascular resistance falls, post resuscitation, the ductal flow suddenly becomes exclusively left to right, lowering the systemic vascular resistance. In the absence of cerebral autoregulation, much of the left ventricular output may preferentially be "sucked" downstream towards the circulatory path of lower resistance, resulting in relative cerebral hypoperfusion (A). As the left ventricle adapts to the changes in loading conditions, it increases its output first to normal range and subsequently even higher, if left-to-right ductal shunt continues to persist and increase in volume, leading to cerebral reperfusion (B), thus creating an ischemia–reperfusion state, predisposing preterm neonates to intraventricular hemorrhage. RCC, right common carotid artery; LCC, left common carotid artery.

hyperperfusion. Further, sick preterm infants may exhibit periods of a lack of autoregulation of cerebral blood flow, making them even more prone to the occurrence of intraventricular hemorrhage [60,61]. It is therefore possible that the subgroup of infants with evidence of pre-existing cerebral hypoperfusion, if identifiable, may benefit most from prophylactic indomethacin or even early-targeted treatment to promote ductal closure. The association between earlier identification of these changes and improvement in clinical outcomes, however, has not been consistently proven and warrants further investigation [51,54].

Eliciting the definitive trajectory of ductal physiological changes during transition in human subjects-based research has been limited by the lack of equipment that allows for continuous measurement of hemodynamic changes. Echocardiography only permits periodic assessments to confirm the presence of DA and collect surrogate markers of its

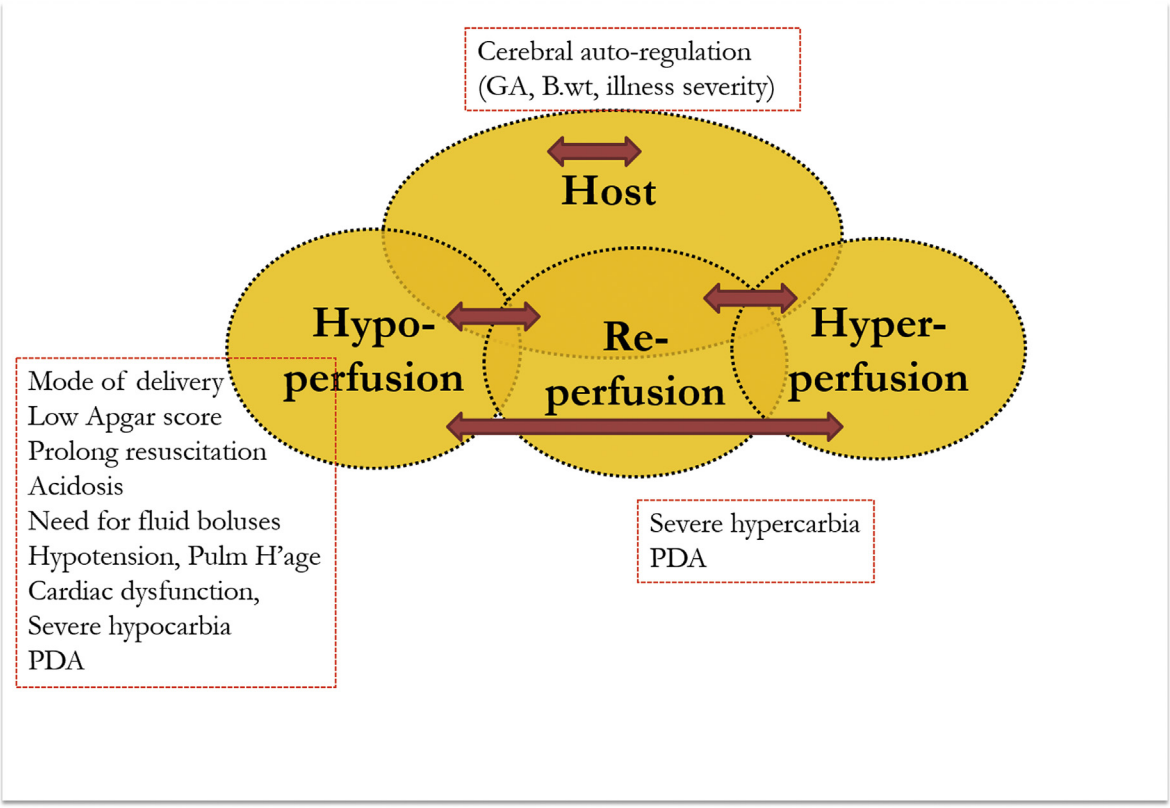


**Fig. 2.** The pathophysiology of intraventricular hemorrhage (IVH) is likely to be a variable interplay between susceptible host, pre-existing insults related to hypoperfusion, and subsequent exposure to rapid reperfusion or even hyperperfusion. In one group of patients the severity of pre-existing hypoperfusion may be such that a 'normal' reperfusion state is sufficient to cause IVH with no contribution from ductus arteriosus shunt, whereas in others it may be a combination of both. On the other hand, in some patients, the extent of ductus arteriosus shunt may itself be high enough to supersede cerebral autoregulatory capacity, i.e. state of hyperperfusion. Further, sick preterm infants may exhibit periods of lack of autoregulation of cerebral blood flow, making them even more prone to the occurrence of IVH. GA, gestational age; B.wt, body weight; Pulm H'age, pulmonary hemorrhage; PDA, pulmonary hemorrhage.

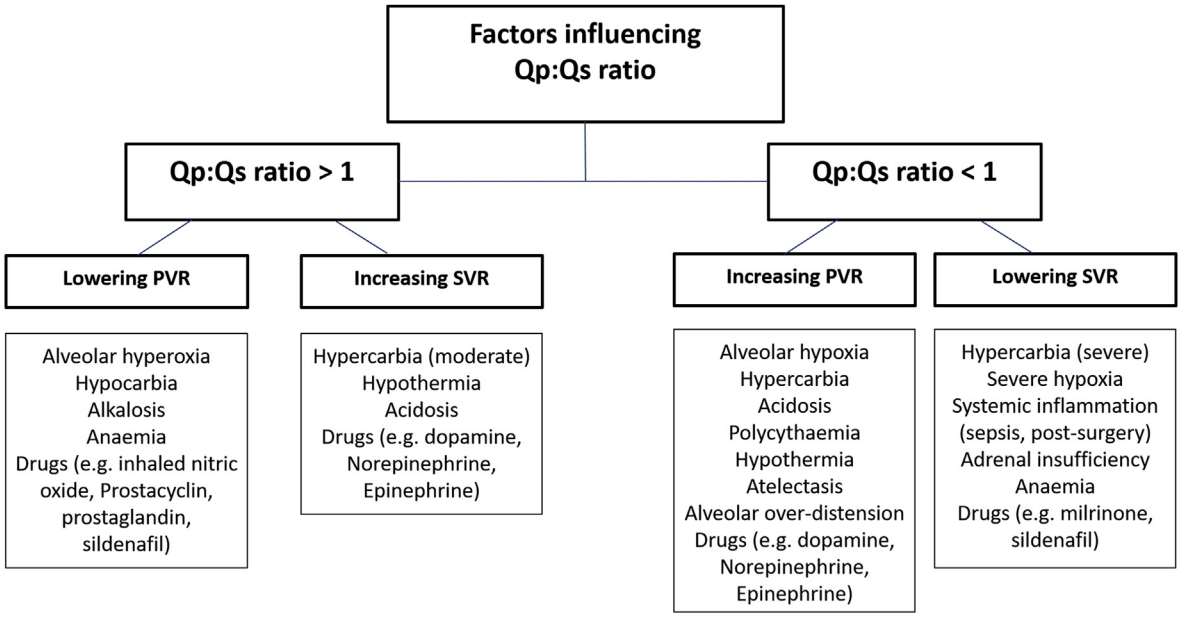


**Fig. 3.** In duct-dependent circulatory states, the therapeutic success and patient outcomes are dependent on maintaining a critical balance between pulmonary blood flow (Qp) and systemic blood flow (Qs). In the absence of real-time precise measurements of Qp:Qs ratio, vigilant surveillance for clinical symptoms, a high index of suspicion, and familiarity with factors governing pulmonary and systemic vascular resistances are of utmost importance. PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

shunt volume. It is important to recognize that these measurements have not been subject to rigorous testing or validation against a reference standard measure or relevant clinical outcomes. The availability of non-invasive cardiac output monitoring and/or cerebral near-infrared spectroscopy in combination with echocardiography may help enhance our knowledge of early transitional hemodynamics and the potential mechanistic role of a high-volume PDA shunt in the etiology of major complications, e.g. IVH, PH, during this period of vulnerability.

## 4. Ductus arteriosus in disorders of transition

Although the DA closes in the majority of term neonates as part of postnatal transition and persistent patency is associated with several complications in preterm neonates, in certain clinical situations, maintaining its patency is a desired therapeutic goal [62,63]. Typically, these conditions include duct-dependent structural heart defects, where maintaining ductal patency using prostaglandin infusion is an established life-saving intervention until a definitive surgical repair or palliation can be provided. These conditions include both duct-dependent systemic and pulmonary circulations. Duct-dependent systemic circulation includes conditions associated with the inability of the left ventricule to fill (e.g. hypoplastic left heart syndrome, total anomalous pulmonary venous return, hypertrophic cardiomyopathy) [64], its inability to pump against an obstruction (e.g. aortic stenosis, coarctation of the aorta or interrupted aortic arch) [65] or, rarely, inability of its output to be distributed throughout the body due to 'systemic steal' by a low-resistance arteriovenous malformation (e.g. vein of Galen malformation) [66]. Similarly, duct-dependent pulmonary circulation includes conditions with compromised right ventricular filling capacity (e.g. tricuspid valve atresia or severe Ebstein's anomaly) or inability of the right ventricle to pump against a fixed obstruction (e.g. pulmonary atresia, critical pulmonary artery stenosis, severe tetralogy of Fallot). Whereas the structural defects needing preservation of ductal patency are well recognized, functional conditions such as arteriovenous malformations, which may benefit from this approach, are less well understood. One of the most discussed of such conditions is severe pulmonary hypertension in the immediate newborn period, typically described in the context of congenital diaphragmatic hernia [67,68]. In this situation, a patent DA can serve two functions, first, in the absence of a response to pulmonary vasodilator therapies, it may preserve right ventricular function by "offloading" to systemic circulation. Second, it provides support to the adequacy of systemic circulation in patients with profound right ventricular dysfunction and low pulmonary inflow or patients with severe pulmonary hypertension and low pulmonary venous return, both of which lead to low left ventricular preload and output. Other rare functional conditions which may benefit from ductal patency include severe left ventricular systolic dysfunction (e.g. birth asphyxia, viral myocarditis).

In these duct-dependent conditions, the therapeutic success and hence the health and outcome of patients is largely dependent on being able to maintain the delicate balance between the distribution of ductal shunt between pulmonary blood flow (Qp) and systemic blood flow (Qs). In the absence of intra- and/or extracardiac shunts, equal volume of blood passes through the pulmonary and systemic vascular beds, resulting in a Qp:Qs ratio of 1. In patients with duct-dependent circulation, it is clinically not feasible to maintain an equilibrium of Qp: Qs at all times. The clinical goal is to maintain a Qp:Qs ratio within a "safe range", as determined by the clinical assessment of a patient's symptoms. Early symptoms of critically low pulmonary blood flow include unexplained worsening hypoxia, signs of respiratory distress and oligemic lung fields on chest X-ray; symptoms of low systemic blood flow include decreased capillary refill time, mottled skin, a reduction in urine output, low pulse volume, tachycardia, metabolic acidosis, lactic acidosis and other signs of end-organ dysfunction. Sequential measurement of serum lactate is a widely used strategy for monitoring the adequacy of systemic perfusion and, in our experience, can help in early identification of critical deviations. In the absence of real-time precise measurement of Qp:Qs ratio, vigilant surveillance for clinical symptoms, a high index of suspicion and familiarity with factors governing pulmonary and systemic vascular resistances is of utmost importance (Fig. 3).

The Qp:Qs ratio can be calculated in several ways: (i) Fick's principle from oximetry using flow and resistance measurements obtained from cardiac catheterization; (ii) functional cardiac magnetic resonance imaging; and (iii) calculation of left and right ventricular outputs using

blood flow measures on Doppler echocardiography. Cardiac catheterization and oximetry are invasive procedures, which are available only in specialized centers and not suitable for use in the vast majority of neonates due to a high risk of complications [69]. Cardiac magnetic resonance imaging has distinct advantages over these techniques, as it is non-invasive and correlates well with invasive oximetry measurements, however, access is limited to specialized centers [70–72]. Further, it usually requires out-of-unit transport of patients and it is not feasible to perform sequential studies in sick neonates. Though echocardiography is both non-invasive and readily available for sequential bedside monitoring, its accuracy in calculating right ventricular output against a reference standard method is unknown. Further, it cannot be used in cases of outflow tract obstruction, in the presence of shunting across both the DA and FO or if a bidirectional shunt is present at the level of the DA, which is a frequent occurrence in these neonates. The use of near-infrared spectroscopy for continuous non-invasive regional tissue oxygenation to estimate Qp:Qs is a novel approach, but there are limited data on its utility in ductal-dependent circulation [73].

## 5. Conclusion

The ductus arteriosus shunt plays a key contributory role in ensuring a normal postnatal adaptation during the first minutes to hours of age. Knowledge of the relationship of DA shunt behavior with time in healthy neonates may facilitate assessment of transitional circulation in symptomatic infants. Unlike term infants, transition circulation in preterm infants is defined by exposure to unrestrictive left-to-right DA shunt in the majority, including cases where it undergoes spontaneous closure a few days later. The DA shunt may play a significant contributory role in the pathophysiology of key hemodynamic complications known to occur during this time; however, biological studies to define the exact mechanism are still awaited. In situations where preservation of ductal shunt is necessary to maintain adequate pulmonary and/or systemic blood flow, it is prudent that clinicians are aware of the factors determining the delicate balance between flows in the two vascular beds. Close monitoring and a high index of suspicion are required to diagnose deviations early, before catastrophic clinical deterioration ensues.

### 5.1. Practice points

- Ductal arteriosus shunt plays a key contributory role in normal postnatal adaptation during the first minutes to hours of age.
- Contrary to infants born at full term, preterm transition circulation is defined by exposure to an unrestrictive left-to-right ductal shunt in the majority of infants, including cases where it undergoes spontaneous closure a few days later.
- In situations where preservation of ductal shunt is necessary to maintain adequate pulmonary and/or systemic blood flow, it is prudent that clinicians are aware of the factors determining the balance of flows between the two vascular beds.

### 5.2. Research directions

- Application of the knowledge of the relationship between quantitative and qualitative changes in ductal arteriosus shunt pattern with time in healthy neonates to facilitate early diagnosis of disruption of normal transition in symptomatic infants and assess response to therapies as well as prediction of their clinical trajectory.
- Targeted use of strategies limiting ductus arteriosus shunt, such as prophylactic indomethacin or early screening and treatment for PDA, in preterm neonates with significant underlying cerebral hypoperfusion and/or lack of cerebral autoregulation to improve major short- and long-term clinical outcomes.

## Conflicts of interest

None declared.

## Funding sources

None.

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