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Transitional Fetal Circulation: A Comprehensive Review of Physiological Adaptation, Failure, and Neonatal Outcomes

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Abstract

The change from fetal to neonatal circulation is one of the most rapid and consequential physiological reorganizations in human life, and it is more accurately described as an integrated cardiopulmonary and placental sequence than as simple closure of fetal shunts. Before birth, the placenta is the organ of gas exchange, pulmonary vascular resistance (PVR) is high, and the ductus venosus, foramen ovale, and ductus arteriosus sustain a parallel circulation that preferentially directs relatively oxygenated umbilical venous blood to the myocardium and brain. At birth, lung aeration, clearance of fetal lung liquid, a rise in alveolar and arterial oxygen tension, and mechanical recruitment of the pulmonary microvasculature produce a steep fall in PVR and a several-fold increase in pulmonary blood flow. Pulmonary venous return then replaces umbilical venous return as the dominant source of left ventricular preload, while interruption of the low-resistance placental circuit raises systemic vascular resistance (SVR) and left ventricular afterload. These pressure and flow changes, rather than any intrinsic anatomical event, drive functional closure of the foramen ovale and progressive constriction of the ductus arteriosus.

Failure or delay of this coordinated sequence produces a spectrum of hemodynamic disorders: persistent pulmonary hypertension of the newborn (PPHN), myocardial dysfunction, inadequate preload, hemodynamically significant patent ductus arteriosus (PDA) in the preterm infant, and decompensation of previously unrecognized duct-dependent congenital heart disease. The mechanisms include incomplete alveolar recruitment, hypoxemia, acidosis, inflammation, impaired nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling, excess endothelin-1 and Rho-kinase activity, oxidative stress, ventricular maladaptation, and adverse ventriculo-ventricular interaction. Because hypoxemia, hypotension, acidosis, and poor perfusion are shared surface features of mechanistically distinct states, assessment based on blood pressure or oxygen saturation alone is inadequate.

This review synthesizes fetal circulatory physiology, the molecular and mechanical basis of normal transition, the principal failed-transition phenotypes, and contemporary physiology-guided monitoring and management. It integrates recent evidence on deferred and physiology-based cord clamping, including the 2023 individual participant data meta-analysis of preterm cord management and the 2024 ABC3 randomized trial; the 2024 American Society of Echocardiography update on targeted neonatal echocardiography; the 2025 American Heart Association and American Academy of Pediatrics neonatal resuscitation guidelines; randomized and network meta-analytic evidence on PPHN pharmacotherapy; and the shift from routine early PDA closure to selective, phenotype-based management. A mechanistic understanding of transitional circulation allows earlier recognition of neonatal cardiovascular compromise and discourages the indiscriminate treatment of numerical hypoxemia or hypotension.

Categories: Cardiology, Pathology, Pediatrics
Keywords: cord clamping, ductus arteriosus, fetal circulation, inhaled nitric oxide, neonatal hemodynamics, neonatal transition, persistent pulmonary hypertension of the newborn, preterm infant, pulmonary vascular resistance, targeted neonatal echocardiography

Introduction And Background

The first minutes of extrauterine life require the newborn to establish pulmonary gas exchange, convert the pulmonary circulation from a high-resistance to a low-resistance vascular bed, discontinue the placental circulation, redistribute ventricular loading, and progressively eliminate dependence on three fetal shunts [1-5]. The fetus develops in a relatively hypoxemic environment supported by placental gas exchange and a circulation in which the ventricles work predominantly in parallel. Within minutes of birth, this arrangement must become a serial circulation in which the entire systemic venous return traverses the lungs [1,5,6].

This transition is commonly oversimplified as closure of the fetal shunts. In physiological terms, shunt closure is a consequence rather than a cause: it follows changes in pressure gradients, vascular tone, and blood flow distribution [2,3,7]. Lung aeration is the pivotal event because it simultaneously permits alveolar

How to cite this article oxygen uptake and recruits the pulmonary circulation. The resulting rise in pulmonary venous return is particularly important, since it replaces umbilical venous flow as the major source of left-sided filling, stabilizes left ventricular output, and raises left atrial pressure above right atrial pressure [2-4,8]. Conversely, umbilical cord clamping abruptly removes a large low-resistance vascular bed and thereby increases systemic vascular resistance (SVR) and left ventricular afterload [2-4,9].

When the transition is incomplete, delayed, or disrupted, respiratory and circulatory failure typically coexist. Persistent elevation of pulmonary vascular resistance (PVR) may sustain extrapulmonary right-to-left shunting and refractory hypoxemia; impaired ventricular performance may cause low cardiac output and systemic hypoperfusion; and ductal constriction may unmask duct-dependent congenital heart disease. Preterm infants are especially vulnerable because of surfactant deficiency, structurally and functionally immature lungs, limited myocardial reserve, an unstable ductus arteriosus, and immature cerebral autoregulation [4,10-14].

The clinical stakes are substantial. Persistent pulmonary hypertension of the newborn (PPHN) is the archetypal failed-transition phenotype, characterized by elevated PVR, reduced pulmonary blood flow, extrapulmonary right-to-left shunting, and hypoxemic respiratory failure, and it affects approximately two per 1,000 live births in late preterm and term cohorts [15-19]. However, not every hypoxemic neonate has PPHN, and not every hypotensive neonate has low systemic blood flow. A physiology-based framework is therefore required to distinguish pulmonary vascular maladaptation, parenchymal lung disease, ventricular dysfunction, ductal shunting, inadequate preload, sepsis-related cardiovascular dysfunction, and critical congenital heart disease [11,20-24]. This review aims to provide that framework.

Aims and objectives

The primary aim of this review is to explain the fetal-to-neonatal circulatory transition as an ordered physiological sequence and to use that sequence to interpret neonatal cardiovascular failure. The specific objectives are to: (1) describe how the fetal parallel circulation is organized and why it depends on the placenta; (2) set out the mechanical and molecular events, from lung aeration to shunt closure, that convert it into a serial circulation at birth; (3) classify failed transition into distinct hemodynamic phenotypes, each with characteristic clinical and echocardiographic features (Tables *1*-*2*); (4) show how these phenotypes should guide monitoring and treatment; and (5) identify the main unresolved questions for future research.

Physiological variable	Normal transition	Failed transition
Lung aeration and fetal lung liquid clearance	Rapid aeration; functional residual capacity established within the first breaths [3,7,25-27]	Delayed or non-uniform aeration from surfactant deficiency, retained lung liquid, meconium, pneumonia, or hypoplasia [3,15,18,25,26]
Pulmonary vascular resistance	Falls steeply within minutes after aeration and an increase in oxygen tension [1-4,7,15,16,28,29]	Remains elevated relative to systemic vascular resistance; may be maladaptive, maldeveloped, or underdeveloped [15-19,30,31]
Pulmonary blood flow	Rises approximately eight- to tenfold; lungs become the sole gas-exchange organ [1-4,7,25].	Reduced; a large fraction of right ventricular output continues to bypass the lungs [5,6,15,18,19,32].
Left ventricular preload	Pulmonary venous return replaces umbilical venous return [2-4,7,8,25].	Falls if the cord is clamped before adequate aeration, or if pulmonary blood flow remains low [2,4,8,9,33,34]
Systemic vascular resistance	Rises after removal of the low-resistance placental circuit [2-4,9,32]	May be inappropriately low in sepsis or vasodilatory shock, or excessively high with impaired output [11,13,20,24,35]
Foramen ovale	Functionally closes as left atrial pressure exceeds right atrial pressure [2-6,32,36]	Persistent bidirectional or right-to-left shunting with high pulmonary vascular resistance or right ventricular dysfunction [11,15,20-22,37]
Ductus arteriosus	Constricts with rising oxygen tension and falling prostaglandin; transient bidirectional or left-to-right flow is normal [5,6,32,36].	Sustained right-to-left shunting in pulmonary hypertension; large left-to-right shunting in preterm infants; ductal constriction precipitates collapse in duct-dependent lesions [15,18,38-48].
Oxygenation	Preductal saturation reaches 90%-95% by approximately 10 minutes of age [16,17,49,50].	Labile or refractory hypoxemia, often with a preductal-postductal saturation gradient [15-19,50,51]
Systemic perfusion	Stable output with adequate organ oxygen delivery [2-4,6,32]	Lactic acidosis, oliguria, prolonged capillary refill, and impaired cerebral, renal, and mesenteric perfusion [10,12-14,20,24,52]

TABLE 1: Normal versus failed cardiovascular transition.

Phenotype	Dominant physiology	Characteristic echocardiographic findings	Management emphasis
Pulmonary vascular maladaptation (PPHN)	High pulmonary vascular resistance with extrapulmonary right-to-left shunting [15-19,30,31,47]	Right-to-left or bidirectional ductal and atrial shunting; high tricuspid regurgitation velocity; short pulmonary artery acceleration time; flattened or leftward-bowing interventricular septum; dilated right ventricle [11,15,19-22,37,53,54]	Lung recruitment; avoidance of hypoxemia and hyperoxemia; maintenance of normocarbia; correction of acidosis; use of inhaled nitric oxide in selected infants; and escalation to an ECMO-capable center if the condition is refractory [15-19,50,55-57]
Myocardial dysfunction	Impaired right, left, or biventricular performance with low cardiac output [11,20-24,35,58]	Reduced tricuspid annular plane systolic excursion or fractional area change; reduced left ventricular output and ejection fraction; raised myocardial performance index; elevated left atrial pressure with pulmonary venous congestion [11,20-22,37,53,58]	Inotropic support; cautious use of pulmonary vasodilators when left ventricular filling or systolic function is poor; and treatment of the precipitating cause [13,20,22,24,31,55,58]
Inadequate preload	Low ventricular filling with preserved contractility [7,20-24,52]	Small ventricular end-diastolic dimensions; reduced ventricular outputs; low superior vena cava flow; underfilled inferior vena cava [10,11,20-23,53]	Targeted volume replacement for demonstrable hypovolemia or blood loss; reassessment of any ventilation strategy that impedes venous return; and avoidance of reflexive, repeated boluses [7,20,22,24,59]
Hemodynamically significant patent ductus arteriosus (preterm)	Large left-to-right shunt with pulmonary overcirculation and systemic diastolic runoff [4,38,41,43,44]	Wide, unrestrictive duct with continuous left-to-right flow; dilated left atrium and left ventricle; raised left ventricular output; and absent or reversed diastolic flow in postductal arteries [11,21,37,41,44,53]	Selective, phenotype-based management; conservative care for many infants; pharmacological or procedural closure only for persistent significant shunting with end-organ consequences [38-42,60]
Duct-dependent congenital heart disease	Systemic or pulmonary blood flow dependent on ductal patency [5,6,32,45-48]	Structural lesion identified; ductal flow supplying systemic or pulmonary circulation; arch or outflow obstruction; abnormal atrioventricular or ventriculoarterial connections [5,32,37,45-47,53]	Immediate administration of prostaglandin E1; urgent involvement of pediatric cardiology; anticipation of apnea and hypotension; and transfer to a surgical center [45-48,51]
Mixed or sepsis-associated cardiovascular dysfunction	Combined vasodilatation, myocardial depression, and raised pulmonary vascular resistance [11,13,20,24,35]	Variable and evolving; frequently biventricular dysfunction with bidirectional shunting and low systemic vascular resistance [11,20-22,24,37,53]	Source control and antimicrobial therapy; serial reassessment; and a combined inotrope-and-vasopressor strategy titrated according to repeated echocardiographic and perfusion assessments [13,20,22,24,35]

TABLE 2: Hemodynamic phenotypes of failed transition, characteristic echocardiographic findings, and management implications.

ECMO, extracorporeal membrane oxygenation; PPHN, persistent pulmonary hypertension of the newborn

This review goes beyond a compilation of established physiology in three ways. First, it links each step of normal transition to the specific way in which that step fails, allowing the reader to move directly from mechanism to bedside phenotype and from phenotype to treatment. Second, it interprets classical physiology in light of evidence published mainly between 2023 and 2026 that has changed or challenged practice, including the 2025 American Heart Association and American Academy of Pediatrics neonatal resuscitation guidelines [49], the individual participant data meta-analysis showing lower mortality with deferred cord clamping in preterm infants [61], the ABC3 trial of physiological-based cord clamping [62], the 2024 network meta-analysis of PPHN pharmacotherapy [55], the BeNeDuctus trial of expectant management of patent ductus arteriosus (PDA) [60], the SafeBoosC-III trial of cerebral oximetry-guided care [63], and the 2024 American Society of Echocardiography update on targeted neonatal echocardiography [53]. Third, it draws explicit inferences from this evidence for clinical practice and identifies where current practice has moved ahead of the evidence.

Review

Methods: Literature search and study selection

Review Design

This study is a narrative review based on a structured literature search. A narrative rather than a systematic design was chosen because the topic spans fetal physiology, molecular biology, delivery room practice, and neonatal intensive care, and the relevant evidence ranges from experimental animal studies to randomized trials and guidelines, which cannot be meaningfully pooled.

Information Sources and Timeline

PubMed/MEDLINE, Scopus, and Google Scholar were searched for publications from January 1990 to July 2026; the final search was performed on July 30, 2026. The start date was chosen to capture foundational physiological studies of the birth transition. The reference lists of included reviews and guidelines were also screened by hand, and the websites of the American Heart Association, the American Academy of Pediatrics, and the American Society of Echocardiography were checked for current guidance.

Search Strategy

Search terms combined Medical Subject Headings (MeSH) and free-text words. A representative PubMed search string was: (“fetal circulation” OR “transitional circulation” OR “neonatal transition” OR “cardiovascular transition”) AND (newborn OR neonat* OR preterm OR “Infant, Premature”[MeSH]) AND (“Persistent Fetal Circulation Syndrome”[MeSH] OR “persistent pulmonary hypertension of the newborn” OR “Ductus Arteriosus, Patent”[MeSH] OR “umbilical cord clamping” OR “deferred cord clamping” OR “targeted neonatal echocardiography” OR “neonatal resuscitation” OR hemodynamic*). The string was adapted to the syntax of each database.

Inclusion Criteria

Studies were included if they (1) involved term or preterm human newborns or experimental animal models, mainly lamb and rabbit models, that directly examined transitional physiology; (2) were randomized controlled trials, systematic reviews and meta-analyses, cohort studies, professional society guidelines and consensus statements, foundational physiological studies, or authoritative textbook chapters; and (3) had full text available in English.

Exclusion Criteria

Studies were excluded if they (1) were case reports or small case series; (2) were conference abstracts, letters, and editorials without original data; (3) were studies of pulmonary hypertension or ductal disease beyond the neonatal period, except where directly relevant to transitional physiology, such as bronchopulmonary dysplasia-associated pulmonary hypertension; (4) were studies limited to the surgical management of complex congenital heart disease; or (5) were duplicate reports of the same cohort.

Study Selection

Titles and abstracts were screened by the author against the objectives of the review, and potentially relevant articles were read in full. Where several publications addressed the same question, preference was given to the highest level of evidence and the most recent publication, while older primary studies were retained when they remain the definitive description of a physiological mechanism. The search identified 90 records; after removal of duplicates and screening, 80 full-text articles were assessed, and 79 were included in this review.

Synthesis and Limitations

Evidence was synthesized thematically and organized to follow the physiological sequence of transition: fetal circulation, birth, molecular regulation, shunt closure, prematurity, failed-transition phenotypes, assessment, management, and outcomes. Where trial results differed from physiological expectation, as for physiological-based cord clamping, both are presented. No formal risk-of-bias assessment or quantitative pooling was performed, so the review shares the selection limitations inherent to the narrative format.

Fetal circulation as an adaptive parallel system

Fetal circulation is not an immature version of the neonatal circulation; it is a circulation fully adapted to life in the uterus [5,6,32]. In the fetus, the placenta, not the lung, is the organ of gas exchange, and it is also a low-resistance vascular bed that receives a large share of the combined output of both ventricles. Blood is oxygenated in the placenta and is then carried to the fetus by the umbilical vein. The umbilical vein therefore carries the most highly oxygenated blood in the fetal circulation: it is oxygen-rich blood supplied from the placenta to the fetal venous system, not deoxygenated blood returning from the fetal tissues. In

this review, the term umbilical venous return refers to this flow of oxygenated placental blood into the fetal liver, inferior vena cava, and heart [5,6,64]. On reaching the liver, part of the umbilical venous blood perfuses the hepatic circulation, while the rest bypasses the liver through the ductus venosus and enters the inferior vena cava. Because this stream is fast and well oxygenated, it mixes only partly with the less oxygenated blood returning from the lower body. In the right atrium, it is preferentially directed across the foramen ovale into the left atrium, left ventricle, and ascending aorta. As a result, the heart, through the coronary arteries, and the brain receive the most oxygen-rich blood available, even though fetal arterial oxygen tension is only 20-30 mmHg [5,6,32,64].

The fetal pulmonary circulation receives only a small fraction of combined ventricular output, conventionally estimated at 8%-25%, depending on gestational age and the species studied. Fluid-filled alveoli, low alveolar oxygen tension, mechanical compression of intrapulmonary vessels, and active vasoconstrictor signaling maintain high PVR. Most right ventricular output entering the pulmonary trunk is diverted through the ductus arteriosus into the descending aorta. The right ventricle therefore contributes the larger share of combined output, and the two ventricles pump in parallel rather than in series [5,6,32].

Adequate fetal oxygen delivery despite low arterial oxygen tension depends on several compensations operating together: high placental blood flow, the leftward-shifted oxygen dissociation curve of fetal hemoglobin, a high combined cardiac output indexed to body weight, elevated hemoglobin concentration, and preferential streaming of oxygenated blood toward the brain and heart [5,6,32,64]. The three fetal shunts are flow-dependent regulatory structures rather than passive conduits, and each is sensitive to changes in placental vascular resistance, umbilical venous return, ventricular performance, and pulmonary vascular tone. This is clinically relevant because fetal growth restriction, placental insufficiency, and congenital cardiac malformations alter shunt flow patterns antenatally and thereby modify the infant's capacity to complete a normal transition [64,65].

Birth as an ordered cardiopulmonary sequence

Cardiovascular transition begins with lung aeration. Fetal lung liquid is cleared by a combination of late gestational reduction in secretion, epithelial sodium channel-mediated active sodium absorption, transpulmonary pressure generated by inspiration or applied inflation, and movement of liquid from the airways into the interstitial tissue and thence into the pulmonary circulation and lymphatics. Establishment of functional residual capacity permits alveolar gas exchange and relieves mechanical compression of the intra-acinar vessels [3,7,25-27].

Aeration lowers PVR through at least three simultaneous mechanisms: mechanical recruitment of previously compressed and unperfused vessels as the lung expands; oxygen-dependent active vasodilatation; and ventilation-associated release of vasodilator mediators. Pulmonary blood flow rises approximately eight- to tenfold within minutes. This increase is physiologically decisive because it generates the pulmonary venous return that fills the left atrium. In a well-aerated infant with an intact cord, pulmonary venous return can progressively substitute for umbilical venous return before the placental circulation is interrupted, moderating the swing in cardiac preload [2-4,7,25].

Cord clamping removes the placenta from the circulation and raises SVR. If clamping precedes effective aeration, left ventricular preload can fall transiently because umbilical venous return has ceased before adequate pulmonary venous return is established, while afterload rises simultaneously. In preterm lambs, this sequence produces a fall in cardiac output, a surge in arterial pressure, and cerebral hemodynamic instability, whereas establishing ventilation before clamping preserves output and cerebral oxygenation [8,9,33,34]. Human evidence supports deferred clamping for at least 60 seconds in infants not requiring immediate resuscitation, and the 2023 individual participant data meta-analysis of 48 preterm trials found that deferred clamping reduced mortality compared with immediate clamping [49,61,66]. The ABC3 randomized trial of physiological-based versus time-based clamping in very preterm infants did not demonstrate superiority for its composite primary outcome, indicating that the biological rationale for intact-cord stabilization has not yet translated into proven clinical benefit and that implementation should follow current resuscitation guidance and local capability [62,67].

The rise in pulmonary venous return elevates left atrial pressure while loss of placental return reduces right atrial filling. This reverses the fetal interatrial gradient and functionally closes the foramen ovale. Increased arterial oxygen tension, withdrawal of placentally derived prostaglandin E2, reduced prostaglandin receptor signaling, and oxygen-dependent inhibition of potassium channels, with subsequent calcium entry, promote constriction of ductal smooth muscle. Early after birth, ductal flow is frequently bidirectional or left-to-right as PVR falls below SVR; this is transitional rather than pathological. Anatomical closure occurs later and varies with gestational age, oxygenation, prostaglandin exposure, and illness severity [5,6,32,36].

Molecular regulation of pulmonary vascular transition

The fall in PVR reflects a coordinated shift from a vasoconstrictor-dominant fetal pulmonary circulation to a vasodilator-responsive neonatal circulation. Endothelium-derived nitric oxide (NO) is central. Increased oxygen tension and the shear stress accompanying increased pulmonary blood flow upregulate endothelial

NO synthase activity. NO diffuses into pulmonary vascular smooth muscle, activates sGC, raises cGMP, reduces intracellular calcium availability through protein kinase G-dependent mechanisms, and produces relaxation [15,16,28,68-70]. Phosphodiesterase type 5 degrades cGMP and is the molecular target of sildenafil, whereas phosphodiesterase type 3 inhibition by milrinone raises cyclic adenosine monophosphate (cAMP) and provides combined inodilator and pulmonary vasodilator effects [15,16,55].

The prostacyclin-cAMP axis provides complementary vasodilatation and inhibits platelet activation and smooth muscle proliferation. Opposing this are endothelin-1 acting on ET-A receptors, thromboxane A2, serotonin, Rho-kinase-mediated calcium sensitization, and hypoxic inhibition of oxygen-sensitive potassium channels [15-17,28,29]. The clinical phenotype of PPHN can arise from maladaptation of a structurally normal pulmonary vascular bed, maldevelopment with excessive medial muscularization and distal extension of smooth muscle, or underdevelopment with reduced vascular cross-sectional area, as in pulmonary hypoplasia and congenital diaphragmatic hernia [15-19,30,31].

Oxygen occupies a dual role. It is required for the normal fall in PVR, yet excessive exposure generates reactive oxygen species, uncouples endothelial NO synthase, increases phosphodiesterase type 5 activity, consumes NO through peroxynitrite formation, blunts responsiveness to inhaled NO (iNO), and contributes to lung injury. Experimental and clinical work therefore supports targeting preductal saturations of approximately 91-95% with a partial pressure of arterial oxygen of roughly 55-80 mmHg rather than maximizing inspired oxygen [16,17,50,56]. Oxygen should be regarded as a pulmonary vasodilator with a dose-dependent toxicity profile.

Acidosis raises PVR and depresses myocardial contractility, while inflammation, sepsis, and perinatal asphyxia amplify vasoconstrictor signaling and impair endothelial function. Historical strategies of hyperventilation and induced alkalosis are no longer favored because hypocapnia reduces cerebral blood flow and is associated with neurodevelopmental harm. Normocarbia, optimal lung recruitment, normothermia, correction of hypoglycemia and hypocalcemia, and treatment of infection are therefore substantive hemodynamic interventions rather than background supportive care [16-19,71]. Where disturbed pulmonary vascular signaling persists beyond the transitional period, as in bronchopulmonary dysplasia-associated pulmonary hypertension, the same physiology-based rather than label-based reasoning remains the most useful framework [72].

Functional closure and remodeling of the fetal shunts

The foramen ovale closes functionally when left atrial pressure exceeds right atrial pressure, which requires an adequate rise in pulmonary blood flow and pulmonary venous return. Where PVR remains high, pulmonary venous return is low, right ventricular function is impaired, or right atrial pressure is elevated, atrial shunting may remain bidirectional or right-to-left. Atrial shunt direction is therefore a dynamic bedside index of the relationship between pulmonary vascular load, right ventricular performance, and atrial filling [20-22,37].

The ductus arteriosus responds to rising oxygen tension and falling prostaglandin concentration. In term infants, functional constriction usually begins within hours, and anatomical closure follows within days. In preterm infants, the ductal wall is thinner, more prostaglandin-sensitive, less responsive to oxygen, and more vulnerable to persistent patency. A PDA is not inherently pathological: its significance depends on shunt magnitude and direction, the ratio of pulmonary to systemic vascular resistance, ventricular loading, evidence of pulmonary overcirculation, and evidence of systemic diastolic runoff with impaired organ perfusion [38-44].

The ductus venosus closes over days after cessation of umbilical venous flow. These divergent time courses reinforce a central principle: anatomical closure is neither immediate nor necessary for a successful early cardiovascular transition. What matters in the first hours is the direction, magnitude, and physiological consequence of flow.

Prematurity and impaired adaptation

Preterm birth interrupts late-gestation maturation of the lung, myocardium, vascular endothelium, autonomic nervous system, and cerebral circulation. Surfactant deficiency, low compliance, residual lung liquid, and susceptibility to atelectasis make aeration difficult, so PVR may fall slowly and limit both pulmonary blood flow and left ventricular preload. Conversely, excessive mean airway pressure can impede systemic venous return, increase right ventricular afterload, reduce cardiac output, and destabilize systemic and cerebral perfusion [4,11-14,59].

The preterm myocardium contains a lower proportion of contractile elements, has higher resting tension, and tolerates abrupt changes in preload and afterload poorly. Diastolic dysfunction and ventriculo-ventricular interaction are particularly consequential: right ventricular pressure overload shifts the interventricular septum leftward, reduces left ventricular end-diastolic volume, and lowers stroke volume. An infant with pulmonary hypertension may therefore have low systemic blood flow despite an apparently acceptable mean arterial pressure [11,20-24,58].

In very preterm infants, the ductus may evolve from a compensatory transitional communication into a left-to-right shunt that increases pulmonary blood flow, contributes to pulmonary edema and ventilatory dependence, volume-loads the left heart, and causes systemic diastolic runoff. Nonetheless, randomized evidence has not demonstrated benefit from routine early pharmacological closure. The BeNeDuctus trial found expectant management non-inferior to early ibuprofen for the composite of necrotizing enterocolitis, bronchopulmonary dysplasia, or death at 36 weeks postmenstrual age, and network meta-analysis of pharmacological agents shows that ductal closure is achievable without consistent improvement in patient-important outcomes [38-41,60]. Contemporary practice therefore favors conservative or selective treatment based on comprehensive assessment of hemodynamic significance rather than ductal diameter alone, with procedural closure reserved for carefully selected infants [42].

The immature cerebral circulation magnifies the consequences of hemodynamic instability. Fluctuations in carbon dioxide tension, systemic blood flow, ductal shunting, venous pressure, and arterial pressure contribute to germinal matrix and intraventricular hemorrhage and to white matter injury, and low superior vena cava flow in the first postnatal day predicts adverse outcome more reliably than blood pressure [12-14,52]. The therapeutic objective is stable oxygen delivery and avoidance of abrupt perturbation in cerebral blood flow, not normalization of a numerical blood pressure. The SafeBoosC-III trial showed that cerebral oximetry-guided treatment in extremely preterm infants did not reduce death or severe brain injury, illustrating that a monitoring technology is only as useful as the treatment algorithm attached to it [63,73].

Failed transition: A spectrum of hemodynamic phenotypes

Failed transition is best conceptualized as a syndrome with distinct and frequently overlapping physiological phenotypes rather than a single diagnosis. This framing prevents the common clinical error of treating hypoxemia, hypotension, or lactatemia as free-standing problems. Table *1* contrasts normal and failed transition, and Table *2* summarizes the phenotypes with their characteristic echocardiographic findings and management implications.

Pulmonary Vascular Maladaptation (PPHN)

PPHN is defined by PVR that remains elevated relative to SVR after birth, with reduced pulmonary blood flow and right-to-left shunting across the ductus arteriosus, the foramen ovale, or both. It complicates meconium aspiration syndrome, pneumonia, sepsis, respiratory distress syndrome, perinatal asphyxia, pulmonary hypoplasia, and congenital diaphragmatic hernia, and it also occurs idiopathically with structurally remodeled vessels. Severe hypoxemia further elevates PVR, establishing a self-perpetuating cycle of hypoxemia, pulmonary vasoconstriction, reduced pulmonary blood flow, and worsening right-to-left shunting. This explains why ventilatory support alone often fails and why lung recruitment, oxygenation, acid-base status, cardiac output, and pulmonary vascular tone must be addressed together [15-19,30,31].

Myocardial Dysfunction

Perinatal hypoxia-ischemia, sepsis, inflammation, metabolic acidosis, and acute pressure overload can impair right, left, or biventricular performance. Right ventricular dysfunction reduces forward pulmonary flow and lowers left-sided filling; left ventricular systolic or diastolic dysfunction raises left atrial pressure, produces pulmonary venous hypertension, worsens gas exchange, and can convert a pulmonary vasodilator from a beneficial to a harmful intervention by increasing pulmonary blood flow into a non-compliant left heart. Lowering PVR alone will not correct systemic hypoperfusion in these infants [20-24,35,58].

Inadequate Preload and Altered Loading Conditions

Hypovolemia is not synonymous with hypotension, and reflexive fluid boluses can worsen pulmonary edema and ventricular dysfunction. A low-preload phenotype may follow early cord clamping before adequate aeration, perinatal blood loss, capillary leak in sepsis, or positive-pressure ventilation that impedes venous return. Echocardiographic assessment of chamber filling together with clinical volume assessment should guide therapy rather than arterial pressure alone [7,20-24].

Ductal Shunt-Related Compromise

In preterm infants, a large left-to-right ductal shunt causes pulmonary overcirculation and systemic hypoperfusion. In certain critical cardiac lesions, the same channel is required for systemic or pulmonary blood flow. The ductus arteriosus can therefore be harmful, neutral, or lifesaving depending entirely on anatomy and the prevailing pressure relationships [38-46].

Duct-Dependent Congenital Heart Disease

Critical coarctation of the aorta, interrupted aortic arch, critical aortic stenosis, hypoplastic left heart syndrome, pulmonary atresia, critical pulmonary stenosis, and selected complex cyanotic lesions may

remain clinically subtle while the ductus is patent. Deterioration with weak pulses, a widening arteriovenous carbon dioxide gradient, metabolic acidosis, oliguria, shock, or cyanosis as the ductus constricts should prompt urgent evaluation. Prostaglandin E1 should be started when duct-dependent disease is plausible, while definitive echocardiography and pediatric cardiology support are arranged [45-48]. Pulse oximetry screening reduces but does not eliminate the risk of late presentation, and a negative screen never overrides clinical suspicion [51].

Clinical Recognition and Physiology-Guided Assessment

Structured clinical examination remains indispensable. Tachypnea, grunting, cyanosis, temperature instability, prolonged capillary refill, weak or discrepant pulses, hepatomegaly, oliguria, metabolic acidosis, and rising lactate may all indicate impaired transition, but none is independently specific. The time course carries diagnostic weight: immediate severe hypoxemia suggests major parenchymal disease, PPHN, or cyanotic congenital heart disease, whereas collapse after a period of apparent well-being suggests ductal constriction in a duct-dependent systemic circulation [45-48].

Preductal saturation should be measured at the right hand or wrist and postductal saturation at either foot. A sustained preductal-postductal difference of at least 5-10% supports ductal right-to-left shunting, but its absence excludes neither PPHN with predominantly atrial-level shunting nor congenital heart disease. The gradient must be interpreted alongside blood gases, the oxygenation index where applicable, chest radiography, examination, and echocardiography [16-19,51].

Blood pressure is a late and incomplete surrogate for circulatory adequacy. A normal mean arterial pressure may coexist with low systemic blood flow when vascular resistance is high, and a modestly low pressure may be tolerated when perfusion and oxygen delivery remain adequate; observational data indicate that low blood pressure alone in preterm infants does not independently predict adverse neurodevelopmental outcome [52]. Serial trends in lactate, urine output, capillary refill, core-peripheral temperature gradient, and acid-base status, as well as near-infrared spectroscopy and echocardiographic flow measurement where available, provide a more meaningful assessment [20-24,54,63,73].

Targeted neonatal echocardiography (TNE) is now central to physiology-guided neonatal care. It identifies shunt direction at the ductal and atrial levels; estimates pulmonary artery pressure from tricuspid regurgitation velocity and ductal Doppler; evaluates interventricular septal configuration; assesses right and left ventricular systolic and diastolic performance using tricuspid annular plane systolic excursion, tissue Doppler indices, myocardial performance index, and deformation imaging; quantifies ductal shunt burden; measures ventricular outputs and superior vena cava flow; and excludes structural cardiac disease. The 2024 American Society of Echocardiography update defines scenario-based indications, training and competency requirements, and quality assurance components, and its central caution is that TNE must be practiced within a governance framework that includes formal training and pediatric cardiology collaboration [20-22,37,53]. B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide are increasingly used as adjunctive markers of ductal shunt burden and pulmonary hypertension severity, though thresholds remain assay- and population-dependent [19,44].

Principles of Management

Management should correct the identified phenotype rather than pursue a single universal target. Initial stabilization includes normothermia, correction of hypoglycemia and significant electrolyte disturbance, treatment of sepsis and parenchymal lung disease, attention to hemoglobin concentration where clinically indicated, avoidance of acidosis, and establishment of effective but lung-protective ventilation. Both atelectasis and overdistension raise PVR: under-recruitment causes hypoxic pulmonary vasoconstriction, while excessive mean airway pressure compresses alveolar capillaries and impairs venous return [16-19,71].

For PPHN with significant hypoxemic respiratory failure, treatment begins with optimization of lung inflation. Surfactant is useful where inactivation or deficiency contributes to parenchymal disease, as in meconium aspiration syndrome, pneumonia, or respiratory distress syndrome. iNO remains the best-established selective pulmonary vasodilator in appropriately selected term and near-term infants with hypoxemic respiratory failure and echocardiographic or clinical evidence of pulmonary hypertension; it reduces the composite of death or need for extracorporeal membrane oxygenation (ECMO) in this population, although the same benefit has not been shown in preterm infants, and routine use in prematurity is not recommended [15-17,57,74,75].

iNO is not a substitute for hemodynamic assessment. A poor response should prompt reconsideration of alveolar recruitment, severe parenchymal disease, vascular remodeling, pulmonary venous hypertension from left ventricular dysfunction, congenital diaphragmatic hernia physiology, and unrecognized structural cardiac disease. Adjunctive agents, including sildenafil, milrinone, prostacyclin analogues, and bosentan, may be considered in specialized centers; a network meta-analysis of 23 randomized trials supports activity for several of these agents, but the evidence base is heterogeneous, largely from resource-variable settings, and does not establish equivalence with iNO [55]. Milrinone is physiologically attractive when myocardial

dysfunction coexists with elevated PVR, but systemic hypotension is a material risk, and loading doses require caution [24,55].

Cardiovascular support should be matched to ventricular function and vascular tone. A vasopressor may be appropriate when SVR is inadequate and right-to-left shunting is driven by low systemic pressure, whereas an inotrope is indicated for impaired contractility; indiscriminate elevation of SVR increases ventricular afterload and may reduce cardiac output. Volume expansion should be reserved for demonstrable reduced preload or blood loss. Hydrocortisone may be considered in refractory hypotension with suspected relative adrenal insufficiency [20-24,35,58].

Where duct-dependent congenital heart disease is suspected, prostaglandin E1 should be initiated promptly while urgent echocardiography and specialist referral are arranged; clinicians should anticipate apnea, hypotension, fever, and possible need for airway support. The risk of delaying treatment in an unstable infant with plausible duct-dependent circulation exceeds the risk of a short course of prostaglandin [45-48].

For preterm PDA, current evidence does not support prophylactic or routine early treatment of all infants. Management should be individualized using clinical evidence of pulmonary overcirculation and systemic hypoperfusion together with echocardiographic assessment of shunt magnitude and end-organ consequences. Pharmacological closure or transcatheter or surgical intervention may be appropriate for selected infants with persistent hemodynamically significant PDA after multidisciplinary evaluation [38-44,60]. ECMO remains the final escalation for term and near-term infants with reversible hypoxemic respiratory failure refractory to maximal therapy, and timely referral to an ECMO-capable center should be considered before irreversible injury occurs [17-19].

Outcomes and Emerging Research Directions

Severe failed transition is associated with prolonged mechanical ventilation and intensive care stay, exposure to vasoactive and pulmonary vasodilator therapy, ECMO in selected term infants, and multi-organ injury. The brain and kidneys are especially vulnerable to impaired oxygen delivery. Survivors of severe PPHN, extreme prematurity, congenital diaphragmatic hernia, or major neonatal cardiovascular instability require structured surveillance for neurodevelopmental impairment, sensorineural hearing loss, chronic lung disease, growth faltering, and late pulmonary vascular disease. Contemporary cohorts continue to report cognitive, motor, and language impairment in a substantial minority of children assessed between one and five years after PPHN, and comorbidity burden remains high across gestational age strata [30,31,76-79].

Research is moving toward precision hemodynamics. Rather than treating a blood pressure threshold, investigators are integrating echocardiographic phenotype, regional oxygenation, biomarkers, continuous cardiorespiratory waveform data, and clinical trajectory to identify which infants need pulmonary vasodilation, afterload support, inotropy, ductal intervention, or simply time and meticulous supportive care [20-22,37,53]. Artificial intelligence-assisted image analysis, automated quantification of ventricular function, and multimodal waveform analysis may augment interpretation, but these tools must be validated against patient-centered outcomes rather than diagnostic concordance alone.

Several questions remain open and are appropriate priorities for the coming decade: the optimal cord management strategy for non-vigorous and extremely preterm infants; whether physiological-based clamping confers benefit in subgroups not identified by ABC3; which infants with hemodynamically significant PDA benefit from closure and at what time; whether earlier or phenotype-selected pulmonary vasodilation improves outcomes in preterm pulmonary hypertension; the role of oral or intravenous adjunctive vasodilators where iNO is unavailable, a pressing issue in many low- and middle-income settings; and whether TNE-guided care, now widely adopted, demonstrably improves survival and neurodevelopment in randomized evaluation [42,53,55,60,62,67,72].

Conclusions

The fetal-to-neonatal transition is an ordered sequence rather than a set of independent events. Lung aeration is the rate-limiting step: it lowers PVR, increases pulmonary blood flow, and provides the pulmonary venous return that replaces umbilical venous return as the source of left ventricular preload. Functional closure of the foramen ovale and constriction of the ductus arteriosus follow these pressure and flow changes; they do not cause them.

Several definite inferences for practice follow from the evidence reviewed. First, the timing of cord clamping matters: deferring clamping for at least 60 seconds in infants who do not need immediate resuscitation reduces mortality in preterm infants and should be standard care, whereas physiological-based clamping, although biologically sound, has not yet been shown to be superior and is best used within protocols or research. Second, hypoxemia, hypotension, acidosis, and poor perfusion are shared by different failed-transition phenotypes, so blood pressure or oxygen saturation alone should not determine treatment; preductal and postductal oximetry, serial perfusion markers, and targeted neonatal echocardiography

should be used to identify the phenotype before therapy is chosen. Third, oxygen should be prescribed as a pulmonary vasodilator with a defined target, a preductal saturation of approximately 91%-95%, and hyperoxemia should be avoided. Fourth, iNO is effective in term and near-term infants with hypoxemic respiratory failure and pulmonary hypertension but is not recommended for routine use in preterm infants, and a poor response should prompt a search for left ventricular dysfunction, inadequate lung recruitment, or structural heart disease. Fifth, routine early pharmacological closure of the preterm ductus arteriosus does not improve patient-important outcomes and should be replaced by selective, phenotype-based treatment. Sixth, when duct-dependent congenital heart disease is plausible, prostaglandin E1 should be started without waiting for a definitive diagnosis.

Finally, the evidence shows that monitoring technology improves outcomes only when it is linked to an effective treatment pathway, as the SafeBoosC-III trial demonstrated for cerebral oximetry. The same standard should now be applied to targeted neonatal echocardiography, physiological-based cord clamping, and adjunctive pulmonary vasodilators: each is physiologically promising, but each requires randomized evaluation against survival and neurodevelopmental outcomes. A physiology-first, phenotype-based approach is therefore the most defensible basis for current practice and the most productive framework for future research.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Acquisition, analysis, or interpretation of data: Usha Rani Moravineni

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