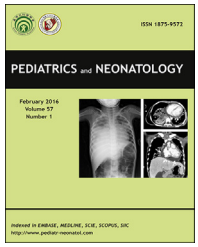
Pediatrics and Neonatology (2016) **57**, 7—18

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.pediatr-neonatol.com



INVITED REVIEW ARTICLE

Transitional Hemodynamics in Preterm Neonates: Clinical Relevance

Tai-Wei Wu [a], **Timur Azhibekov** [b,c], **Istvan Seri** [d,*]

[a] *Division of Neonatology, Department of Pediatrics, Chang Gung Children's Hospital and Chang Gung Memorial Hospital, Chang Gung College of Medicine, Taoyuan, Taiwan*
[b] *Division of Neonatology, Department of Pediatrics, Children's Hospital Los Angeles, CA, USA*
[c] *Center for Fetal and Neonatal Medicine LAC+USC Medical Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA*
[d] *Center of Excellence in Neonatology, Department of Pediatrics, Sidra Medical and Research Center and Weill Cornell Medical College, Doha, Qatar*

Received Jul 1, 2015; accepted Jul 3, 2015
Available online 29 August 2015

Key Words
Preterm neonate;
fetal circulation;
developmental hemodynamics;
neonatal hypotension;
persistent ductus arteriosus

Background: Each newborn enters this world facing tremendous respiratory, hemodynamic and neuroendocrine challenges while going through drastic physiological changes during the process of adaption from fetal to postnatal life. Even though the vast majority of term infants transition smoothly without apparent consequences, this task becomes increasingly arduous for the extremely preterm infant.
Methods & results: This article reviews the physiology and pathophysiology of cardiovascular adaptation of the very preterm neonate. In particular it describes the physiology of fetal circulation, summarizes the hemodynamic changes occurring during preterm births and discusses the impact of the most frequently seen clinical scenarios that place additional burden on the premature infant during immediate transition. Finally an emphasis is placed on discussing common clinical dilemmas and practical aspects of developmental hemodynamics such as neonatal hypotension and patent ductus arteriosus; clinical presentations the neonatologist encounters on a daily basis.
Conclusion: The review provides a physiology-based view on the hemodynamics of the immediate postnatal transitional period.

* Corresponding author. Weill Cornell Medical College, Neonatology Center of Excellence, Department of Pediatrics, Sidra Medical and Research Center, P.O. Box 26999, Doha, Qatar.
E-mail address: iseri@sidra.org (I. Seri).

http://dx.doi.org/10.1016/j.pedneo.2015.07.002

1. Introduction

"It is not the strongest or the most intelligent that survive, but who can best manage change." — Charles Darwin

Perhaps the most significant and drastic human adaptation to change occurs during the first few breaths of postnatal life, as the fetus transitions from intrauterine to extrauterine environment with major rerouting of fetal hemodynamics. At term, successful postnatal transition is accomplished by a decrease in pulmonary vascular resistance following lung expansion, an increase in systemic vascular resistance as a result of removal of the placenta, and the subsequent closure of fetal vascular channels. Vascular rerouting, exposure to higher oxygen tension, and neuroendocrine surge all contribute to the significant redistribution of systemic and organ blood flows to meet the metabolic and functional demands of extrauterine life.

In the preterm infant, normal physiologic transition is affected by several factors, including but not limited to immaturity of organ systems, maternal conditions and medications, timing of cord clamping, and resuscitation maneuvers. Understanding of this complex process is critical in the care of preterm newborns, especially in the neonatal intensive care setting. The purpose of this article is to review fetal cardiovascular physiology and the hemodynamic changes during transition following preterm birth and their clinical relevance.

2. Fetal to postnatal transition of the circulation

2.1. Fetal-placental unit

The placenta is the principal site of gas and metabolic exchange for the fetus. On the fetal side, blood enters and exits the placenta by way of the umbilical artery and umbilical vein, respectively. Within the placenta, chorionic villi are bathed in mixed arterio-venous maternal blood with a pO_2 around 55 mmHg[1] and gas exchange occurs as blood moves across the vessels within the fetal villus tree.

Overall, absolute placental-umbilical blood flow increases with gestational age, but it exhibits a moderate decrease when normalized for fetal weight. It remains in the range of 110—125 mL/kg/min in the third trimester of pregnancy to meet the metabolic demands of the growing fetus.[2] This constitutes about 30% of the overall fetal biventricular cardiac output.

The fetoplacental unit holds a blood volume of approximately 110 mL per fetal weight in kg. The mean blood volume of the term infant is estimated to be ~80 mL/kg following immediate cord clamping.[3] Based on studies that used either weight-based estimation or dilutional method, an additional 20—35 mL/kg of blood is transferred from placenta to the term infant as a result of placental transfusion when clamping of the umbilical cord is delayed for up to 5 minutes.[4] The volume of placental transfusion is time-dependent; up to 50% of the volume is transferred within 1 minute,[3] and most of the transfusion is complete by 3 minutes. In preterm infants, delay in clamping of the umbilical cord results in increased blood volume as well.[5]

2.2. Fetal circulation

The distinct feature of the fetal circulation is that it is routed for parallel flow under physiologic conditions. Both ventricles work together to provide systemic blood flow resulting in a systemic cardiac output that is nearly double of the left ventricular output in postnatal life. Indeed, in human fetuses during the second half of pregnancy, fetal biventricular output estimated with Doppler ultrasound remains fairly constant in the range of 470—503 mL/kg/min,[6] similar to a combined cardiac output of approximately 450 mL/kg/min as measured with the microsphere method in fetal lambs.[7] Existence and patency of the fetal channels are key for establishing the parallel circulatory pattern. After receiving relatively less saturated blood from the caval veins with a superior vena cava (SVC) dominance, up to 90% of the right ventricular output is shunted through the ductus arteriosus (DA) to the descending aorta in the animal model. Thus, the majority of the right ventricular output bypasses the unaerated lungs and provides blood flow to the lower body and placenta. In human fetuses, however, pulmonary blood flow was reported to be significantly higher as estimated with Doppler ultrasound.[6] Furthermore, an increase in pulmonary blood flow was observed after 20 weeks' gestation, approximating 22—25% of the combined cardiac output during the third trimester. The left ventricle receives relatively oxygen-rich blood, directed from the umbilical vein by the ductus venosus (DV) via the inferior vena cava and foramen ovale (FO). This configuration allows for preferential streaming of blood with the highest oxygen saturation reaching the left side of the heart, thus, prioritizing oxygen delivery to coronary arteries and cerebral circulation. After 20 weeks' gestation, the right ventricle becomes the predominant pump and is responsible for approximately 60% of the combined cardiac output.[6,8] A somewhat decreased blood flow to the left atrium secondary to decrease in DV shunt flow and a more restrictive FO in later gestation have been suggested as important contributing factors to the right ventricular predominance.[9] Figure 1 depicts the fetal circulation and the blood flow changes from 20 weeks, 30 weeks, to 40 weeks of gestation, respectively.

The patency of the DA is primarily maintained by nitric oxide and prostaglandins synthesized within ductal tissue in the low intrauterine oxygen environment. Premature closure of the DA, either spontaneous or drug-induced, has been documented in case reports and case series, and this can result in right heart congestion, persistent pulmonary hypertension postnatally, or fetal demise.[10] The role of the DV as a critical fetal channel is less obvious. Relatively oxygen-rich blood from the placenta returns to the heart by either passing through the liver, or being shunted directly to the IVC via the DV. During midgestation, ~30% of the umbilical venous blood is shunted through the DV, and it decreases to only 20% between 30 weeks and 40 weeks of gestation. *In utero* closure of DV in the human fetus has varying fetal impact, ranging from normal fetal growth to fetal demise, while experimental obstruction of DV in fetal

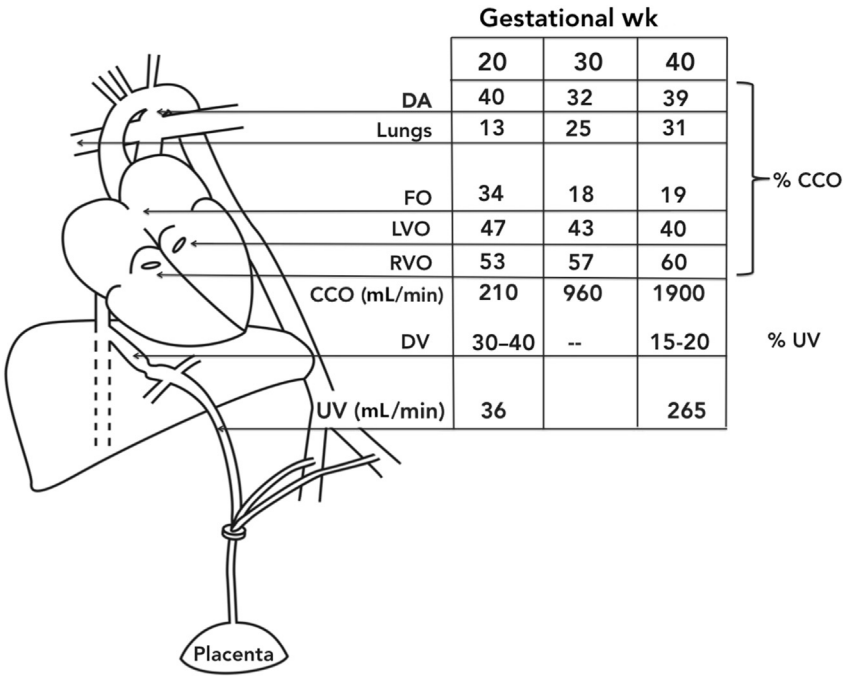


Figure 1 Changes in fetal blood flow distribution as a percentage of combined cardiac output and umbilical venous flow are organized according to increases in gestational age. Note the increase in pulmonary blood flow and decreased shunting through the foramen ovale as gestational age advances. These changes contribute to establishment of right ventricular dominance. CCO = combined cardiac output; DA = ductus arteriosus; DV = ductus venosus; FO = foramen ovale; LVO = left ventricular output; RVO = right ventricular output; UV = umbilical venous flow.

lambs has minimal impact on cardiac output or oxygen delivery.

3. Transitional circulation

3.1. Early transition

Immediately after birth, cardiovascular transitional physiological changes are highlighted by an initially significant and later more gradual decrease in pulmonary vascular resistance after lung aeration. In addition, following the standard obstetrical practice of immediate cord clamping, a sudden increase in systemic vascular resistance (SVR) occurs. However, when physiologic cord clamping is used, i.e., clamping of the umbilical cord after effective ventilation is established, an improved maintenance of cardiac preload takes place. This is ensured by the increasing pulmonary blood flow, which gradually replaces the decreasing placental blood flow as the umbilical vessels contract. As a consequence, SVR and afterload increase only gradually (also see later).[11] Avoiding the sudden increase in SVR is of great importance especially for the very preterm neonate whose immature myocardium is unable to overcome the associated increase in afterload. When immediate cord clamping is used, the sudden increase in the afterload combined with the decrease in preload results in decreased systemic blood flow in these patients. Therefore, the authors have postulated that very preterm neonates presenting without apparent systemic hypotension are, by definition, in the compensated phase of shock during the immediate transitional period.[12] In addition to the loss of the low-resistance placental circulation, neuroendocrine changes such as increased production and release of catecholamines, renin, angiotensin, and vasopressin also contribute to the postnatal increase in SVR. These changes are primarily initiated by the intermittent decrease in oxygen delivery associated with the uterine contractions during labor. Once systemic blood pressure exceeds pulmonary pressure, the increased pulmonary blood flow results in increased left atrial blood return and pressure, the FO closes, and redirection of the circulatory pattern ensues from a parallel into a serial pattern although the DA is still open. As a result of increasing effective pulmonary gas exchange and the circulatory changes, arterial oxygen saturation increases from 60—70% at 1 minute to above 90% within 10 minutes following delivery.[13] To complete the transition, at least in term neonates, DA constricts within hours after birth and undergoes functional closure by 48—72 hours of life in the majority of healthy neonates.[14] However, in preterm infants ductal closure is often significantly delayed. Tables 1 and 2 show the blood flow changes in the systemic circulation in term and preterm neonates.

3.2. Timing of umbilical cord clamping

One of the first standard obstetric maneuvers following delivery of the preterm infant is the clamping of the umbilical cord. As mentioned above, a significant volume of the fetal-placental blood remains in the placenta immediately after birth.[4,5] There is a growing body of evidence to support that delayed clamping of the cord in relation to

Table 1 The healthy term infant demonstrates minimal changes in right ventricular output after birth and the ductus arteriosus shunts left-to-right during the 1st day. Left ventricular output is lowered by Day 2 of postnatal life as the patent ductus arteriosus functionally closes. LVO = left ventricular output; PDA = patent ductus arteriosus; RVO = right ventricular output; SVC = superior vena cava.

Transitional central blood flow changes in healthy term newborns					
	Birth				Post-transitional
Flow (mL/kg/min)	3–7 min	9–14 min	15–19 min	4–6 h	24–48 h
SVC‡	—	—	—	68 (32–166)	89 (54–167)
RVO*,†	200 ± 32	204 ± 34	197 ± 47	216 (122–338)	207 ± 47
LVO*,†	169 ± 42	186 ± 26	180 ± 27	193 (148–278)	156 ± 24
PDA*,† (flow or pattern)	Net (L–>R) 1 ± 46	Net (L–>R) 35 ± 54	Net (L–>R) 57 ± 52	L–>R (76%) R–>L (14%) Closing (14%)	100% closed or restrictive

* Noori S, Jpeds 2012, Transitional changes in cardiac and cerebral hemodynamics in term neonates at birth.
† Kluckow M, Neonatology 2012, Non-invasive assessment of early transitional circulation in healthy term infants.
‡ Skinner JR, Arch Dis Child Fetal Neonatal Ed 2008, Echocardiographic assessment of blood flow volume in the superior vena cava and descending aorta in the newborn infant.

Table 2 After birth, the very preterm infant (<29 weeks cohort)[79] demonstrates a gradual increase in both ventricular output throughout the 1st 4 postnatal days, attributed to improvement in ventilation and preload and adaptation to the initial abrupt increase in afterload due to immediate cord clamping. Concomitantly, superior vena cava flow increases. By 3–4 days of postnatal life, about 20% of patients present with the ductus arteriosus patent and the majority of them shunt left-to-right. There is currently no data on blood flow distribution changes minutes after birth in premature infants. LVO = left ventricular output; PDA = patent ductus arteriosus; RVO = right ventricular output; SVC = superior vena cava.

Transitional central blood flow changes in preterm newborns*				
Flow (mL/kg/min)	Birth	4–6 hours	24 hours	3–4 d
SVC	—	81 ± 26	93 ± 26	106 ± 30
RVO	—	264 ± 90	312 ± 83	360 ± 112
LVO	—	243 ± 69	294 ± 77	311 ± 93
PDA	—	(37%)	(20%)	(22%)
(% >1.5 mm)		(38%)	(22%)	(18%)
(% L<–>R flow)				

* Waal K, Early Human Development 2014, Transitional hemodynamics in preterm infants with respiratory management strategy directed at avoidance of mechanical ventilation.

lung inflation, spontaneous or caregiver-initiated, is beneficial to the infant, especially those delivered preterm. As mentioned earlier, this practice allows better maintenance of preload and for extra blood volume to be directed to the preterm neonate.[11,15] Depending on the clinical practice, the volume of placental transfusion is measured to be around 20–35 mL/kg in term[4] and 12–15 mL/kg in preterm neonates.[5] However, when estimated neonatal blood volume following delayed cord clamping is extrapolated from the blood volume measured at ~30 minutes of postnatal life, the estimated volume of placental transfusion is significantly higher in both term and preterm infants.[3] Findings of meta-analyses suggest that delayed cord clamping in preterm infants improves short-term outcomes: lower incidence of late-onset sepsis, fewer transfusions, improved systemic blood pressure[16] and decreased use of vasopressor-inotropes[17] and, most importantly, significantly lower incidence of peri/intraventricular hemorrhage (P/IVH)[18] were found. In 2012, the practice of delaying cord clamping in preterm infants was first advocated by the American College of Obstetricians and Gynecologists and endorsed by the American Academy of Pediatrics.[19]

As briefly mentioned earlier, the potentially deleterious cardiovascular effects of immediate clamping of the umbilical cord include: (1) occlusion of the umbilical vein with an abrupt drop in right ventricular venous return and thus preload by 40–50%; and (2) occlusion of the umbilical artery resulting in elimination of blood flow to the low-resistance placental circulation, which in turn leads to an immediate increase in left ventricular afterload. Both the decrease in preload and the increase in afterload negatively affect cardiac contractility and output. In preterm infants with limited cardiac reserve, this drastic hemodynamic change following immediate cord clamping has a negative impact on postnatal circulatory adaptation. Indeed, premature infants following immediate cord clamping have lower right ventricular output and lower SVC flow compared with preterm infants with delayed cord clamping[20] or umbilical milking during the first 48 hours of postnatal life.[16] Furthermore, in preterm infants with

delayed cord clamping or umbilical cord milking, regional cerebral oxygen saturation is higher in the first 24–36 hours of life, compared with immediate cord clamping.[21] Finally, as also mentioned earlier, preterm infants who undergo delayed cord clamping or umbilical cord milking have higher initial mean blood pressure[16] and require less vasopressor use or volume administration.[17] While these findings are encouraging, their exact clinical implications as well as effects on short- and long-term outcomes remain to be further investigated in randomized controlled trials.[11]

Interestingly, in asphyxiated infants, placental transfusion appears to occur *in utero*, as their blood volume is higher than that of nonasphyxiated infants born after immediate cord clamping.[22] However, more research is needed to determine the role of physiologic cord clamping in depressed preterm infants who may appear asphyxiated and require immediate resuscitation.

4. "Hypotension" in preterm infants in the transitional period

In the preterm infant, circulatory maladaptation is most commonly recognized clinically as hypotension when compensatory mechanisms are overwhelmed or absent. Although studies have shown early hypotension to be associated with P/IVH and poor neurodevelopment outcome in extremely premature infants,[23] retrospective studies found that subsequent efforts to maintain blood pressure within a certain "normal range" with antihypotensive agents do not appear to have improved clinical outcomes.[24] However, no appropriately designed, prospective study has compared treatment of hypotension with placebo (no treatment). Interestingly, findings of a prospective trial suggest that neonates responding to dopamine or epinephrine administration with increased blood pressure and cerebral tissue oxygenation do as well from a neurodevelopmental standpoint as their nonhypotensive counterparts.[25]

Most importantly, using blood pressure alone without information on systemic and organ blood flow to establish the diagnosis of compensated or uncompensated shock and initiate treatment will not lead to resolution of this problem.[26]

One of the reasons for this clinical conundrum is that hypotension remains difficult to define in the preterm infant.[27] As alluded to earlier, in the clinical setting, we often describe an infant's hemodynamic status by measuring heart rate and blood pressure only. Because of its availability and ease of measurement, blood pressure is routinely assessed and erroneously in itself may be used as a surrogate measure of cardiovascular function. From population-based studies reporting normative blood pressure values in preterm and term infants, mean blood pressure increases as gestational and postnatal age increase.[28,29] Again, it is imperative to understand the limitations of such an approach, as blood pressure is the dependent variable in the simplified Ohm's law of fundamental fluid dynamics (pressure gradient = flow × resistance). When applied to the cardiovascular system, the equation becomes:

$$\text{Mean blood pressure} - \text{right atrial pressure} = \text{Cardiac output} \times \text{SVR}$$

Thus, mean blood pressure is dependent on the two other, mathematically independent variables, cardiac output and SVR. Accordingly, blood pressure may remain within the "normal range", even though cardiac output may be decreased but compensated for an increased SVR. Similarly, blood pressure may be "normal" when vasomotor tone is low but it is compensated for an increase in cardiac output[26] (Figure 2). In addition, it is important to note that normal blood pressure does not equate to normal organ blood flow. Despite a "normal blood pressure", end organ perfusion may still be compromised, as the compensated phase of shock is about to give way to the uncompensated phase. Two infants of similar gestational age may have similar "normal" blood pressure values, but the underlying state of their organ blood flow may be potentially different from each other, depending on their capacity to compensate by adjusting their cardiac output and/or local end-organ vascular resistance. Thus, the inability to assess organ blood flow accurately on a routine basis makes hemodynamic evaluations challenging in the clinical setting.

Indirect measures of organ perfusion are commonly incorporated into the bedside clinical assessment to guide further management of a particular patient. In most

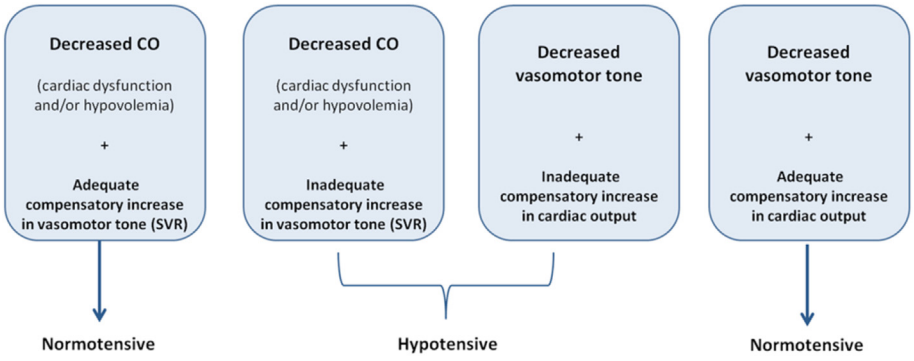


Figure 2 Infants who are normotensive may still have underlying abnormalities in cardiac output or vasomotor tone. For those who are hypotensive, the compensatory mechanisms become inadequate. CO = cardiac output; SVR = vasomotor tone. *Note*: From "*Workbook in practical neonatology*" by Wu T-W, Noori S, Seri I, 2014. Copyright 2014, Elsevier/Saunders Co; Philadelphia, PA. Reprinted with permission.

instances, these include capillary refill time (CRT), lactic acid level, and urine output. A CRT greater than 3 seconds is generally considered as abnormal. Of note is that CRT can be influenced by the site of evaluation, the ambient temperature (higher temperature leads to a shorter CRT), and medications. As for the site of assessment, the sternum and forehead are considered most appropriate sites to assess perfusion. In addition, CRT was reported to have 55% sensitivity and 81% specificity in detecting low SVC flow in preterm infants of less than 30 weeks' gestation during the immediate transitional period.[30] Lactic acidosis develops when tissue perfusion decreases to the point that increased oxygen extraction cannot further support tissue energy demand and anaerobic metabolism commences. This usually happens as compensatory mechanisms are exhausted and shock reaches its uncompensated phase. Furthermore, when organ perfusion is severely affected and perfusion virtually "shuts down" in a given organ, lactic acid accumulates locally and will not become evident until circulation improves and the "lactic acid wash out" phenomenon occurs. Thus, in cases where circulation appears to have improved, increasing lactic acid levels might be the sign of organ reperfusion and the return of hemodynamic stability. Contrary to lactic acidosis, the development of oliguria is an early finding in neonatal shock as it occurs in the beginning of the compensated phase. In the immediate transitional period after birth, stress hormone concentrations such as serum arginine vasopressin, epinephrine, norepinephrine, and serum renin-angiotensin are elevated and largely explain the diminished urine output seen in healthy term and relatively well preterm infants during the first 24 hours of postnatal life. In preterm infants, the immature renal tubules are unable to absorb solutes and water despite a decreased glomerular filtration rate, leading to a higher fractional excretion of solutes and thus a relatively higher urine output. Consequently, urine output may not accurately reflect renal perfusion and may falsely reassure the clinician, as long as the patient is only in the compensated phase of shock.

Functional echocardiography has been increasingly used for the bedside assessment of cardiac function such as myocardial contractility and cardiac output. Importantly, due to the presence of fetal channels, right and left ventricular output does not simply equate to pulmonary and systemic blood flow, respectively. Right ventricular output represents systemic blood return plus interatrial flow through a patent foramen ovale, while left ventricular output overestimates systemic blood flow if left-to-right ductal shunting is present. Indeed, the preterm infant is capable of increasing the left ventricular output well above 300 mL/kg/min to compensate for the flow through a hemodynamically significant patent ductus arteriosus in an attempt to maintain systemic and, importantly, cerebral blood flow.[31] Another caveat is that, even in preterm infants with a closed ductus arteriosus, correlation between blood pressure and left ventricular output during the first 24 hours following birth is poor ($r = 0.38$).[32] In the presence of fetal shunts, SVC blood flow, an assessment of the blood returning from the upper body and brain, has been used as a more accurate surrogate measure of systemic blood flow compared with ventricular output measurements alone.[33] Although a significant association between low SVC flow and abnormal developmental outcome at 3 years of age has been reported, no association was found between treatment of these patients with an inotrope or a vasopressor-inotrope and long-term outcome.[34]

Thus, the therapeutic goal to maintain blood pressure within a reference range oversimplifies neonatal circulatory dynamics and may be misleading for the clinician. However, the debate over whether to treat abnormal blood pressure versus blood flow is nugatory as it is the understanding of their relationships that would aid the clinician in formulating a physiologically relevant management plan. Design and execution of randomized control trials to answer such questions are extremely challenging and unlikely to be successful because of the need for timely parental consent and the refusal of most neonatologists to leave "hypotension" untreated.[35]

Specific pharmacological management of neonatal hypotension is beyond the scope of this article, and the reader is directed to other reviews on this subject.[28,36]

4.1. Preterm myocardium in the transitional period

Under normal conditions immediately after birth, left ventricular output increases significantly because of an increased heart rate, increased left ventricular end-diastolic volume due to increased pulmonary blood flow, increased inotropy secondary to circulating catecholamines, and improved left ventricular wall compliance due to decreased right ventricular systolic and diastolic load.[37] In the healthy term infant, the highly contractile state and high left ventricular output gradually decreases over the first 1—2 days after birth as the patent ductus arteriosus (PDA) constricts and venous return to the left atrium normalizes. The left ventricle assumes the role of the dominant ventricle with subsequent developmental increase in cardiomyocyte size and number. In the preterm newborn, although Frank-Starling relationships are preserved and the baseline contractile state immediately after birth is higher than in children and adults, the properties of the immature myocardium render this population more vulnerable to circulatory compromise during the immediate transitional period. These include fewer contractile elements, higher water content, greater surface-to-volume ratio, and a reliance on L-type calcium channels that utilize extracellular calcium, instead of the sarcoplasmic reticulum (intracellular calcium stores), as a source of the second messenger driving cardiomyocyte contraction.

Earlier studies found that, during the first 24 hours after delivery, more than one-third of preterm infants born at less than 30 weeks' gestation have low SVC flow. However, by 48 hours of postnatal life, SVC flow remained low only in about 5% of these infants.[38] Interestingly, more recent studies have found a lower proportion of very preterm neonates to present with low SVC flow. It is tempting to speculate that improvements in obstetric and neonatal cardiorespiratory care may be responsible for this finding. A recent study examining arterial blood pressure trends in extremely preterm infants (23—26 and 6/7-weeks' gestation) during the 1st 24 hours of postnatal life found arterial blood pressure to be the lowest during the 1st 5 hours, followed by a steady increase thereafter at a rate of

0.2 mmHg/hour.[39] It appears that in the early transitional period when the cord is clamped immediately, the sudden increase in SVR exceeds the immature myocardium's capacity to maintain adequate contractility and output. However, the myocardium adapts over the course of the 1st 24—48 hours as SVC flow, right ventricle output and arterial blood pressure normalize. There is emerging evidence that the extent of this initial period of vulnerability sets the stage for a hypoperfusion-reperfusion cycle and, in a portion of preterm infants, injury to the premature brain.[23,40] Details of this intriguing phenomenon are described in the section on cerebral autoregulation below.

4.2. Other factors affecting myocardial function in the transitional period

1. Perinatal asphyxia

In addition to the developmental immaturity of the myocardium, other factors contribute to myocardial dysfunction in the preterm and term neonate. Hypoxic insult in perinatal asphyxia can have a negative impact on the heart of the newborn. Cardiac function is depressed with decreased stroke volume and cardiac output,[41] leading to cardiogenic shock if the insult is severe. The severity of cardiac dysfunction after perinatal asphyxia correlates with elevated cardiac enzymes.[42] Of note, although acidosis has been shown to affect myocardial function negatively in adult humans and animal studies, the preterm myocardium appears to tolerate acidosis as low as pH 7.02 without evidence of altered myocardial contractility during the first 2 postnatal weeks.[43] This observation challenges the conventional approach to aggressively treat acidosis to prevent myocardial depression in the preterm infant. More studies are needed to determine if correcting acidosis with an alkalinizing agent improves myocardial function in this population.

2. Neonatal sepsis and fetal inflammatory response syndrome

Neonatal sepsis affects the vasomotor tone of the infant, which, if severe and uncompensated by the increase in cardiac output, will lead to systemic hypoperfusion and shock. Histological chorioamnionitis is a common finding in preterm deliveries, especially in those with preterm prolonged rupture of membrane (PPROM).[44] Fetal inflammatory response syndrome (FIRS) is an intrauterine condition characterized by elevated fetal proinflammatory cytokines and is associated with unfavorable neonatal outcome.[45] Data in literature on the effects of chorioamnionitis or FIRS on fetal myocardial function are scant. One retrospective study using indirect Doppler echocardiographic markers of function and flow found an alteration in ventricular diastolic function in fetuses with PPROM, marked by a higher left ventricular compliance compared to fetuses without PPROM.[46] This effect was more pronounced if amniotic fluid culture was positive for microorganisms. In another retrospective study, preterm infants less than 25 weeks' gestation with histopathological proof of placental or cord inflammation displayed higher heart rate, required more inotropic and vasopressor support and volume boluses in the first 24 hours of postnatal life, but had similar ejection fraction when compared with preterm controls without fetal inflammation.[47] Again, more studies are needed to elucidate the effects of chorioamnionitis or FIRS on transitional hemodynamic changes in preterm infants.

3. Fetal growth restriction

Fetal growth restriction is associated with myocardial remodeling and dysfunction. Cardiac remodeling may be an adaptive attempt in the face of increasing placental resistance and hypoxia to deliver more oxygenated blood to the brain and heart. Indeed, fetal echocardiographic studies in fetal growth restriction show decreased ventricular compliance, indicating a "stiffer" left ventricle and resultant diastolic dysfunction.[48] Postnatally, infants with intrauterine growth restriction (IUGR) display a relatively hypertrophied ventricular septum and left ventricular dilatation. Serum *brain natriuretic peptide* concentration is also elevated in IUGR infants during the first postnatal days.[49] While appropriate-for-gestational age infants increase left ventricular cardiac output and stroke volume, and decrease left myocardial performance index (a marker of ventricular dysfunction) and heart rate during the first 5 days of postnatal life, IUGR infants do not exhibit a similar pattern of postnatal adaptation. Instead, left myocardial performance index and left ventricular stroke volume remain unchanged and cardiac output is maintained primarily by a higher overall heart rate when compared with appropriate-for-gestational age controls.[50] Hence, preterm infants with IUGR are born with decreased myocardial reserve and display abnormal postnatal hemodynamic adaptation.

5. Early hemodynamic effects of patent ductus arteriosus

PDA results from the failure of the DA to close spontaneously in the early postnatal period leading to persistent shunting of blood between the systemic and pulmonary circulations. The direction and magnitude of shunting depend on the size of the DA and the difference between systemic and pulmonary pressures and the impedances in the two circulations. In extremely low birth weight infants, PDA closes spontaneously without treatment in up to 50% of cases.[51] The clinical challenges stem from our very limited ability to predict if PDA will close spontaneously in a given patient, and from the fact that the hemodynamic consequences of a PDA become clinically evident usually only days after birth. This gives the false perception that PDA is not hemodynamically significant during the early transitional period. Data indicate that a large ductal diameter is associated with decreased SVC flow at 5 hours of postnatal life; however, this effect is no longer observed at 24—48 hours after delivery.[38] To compensate for the decreased systemic blood flow resulting from the left-to-right shunting via the PDA, the preterm myocardium adapts with an increase in contractility and left ventricular output (LVO). However, despite the significant compensatory increase in LVO, decreased systemic perfusion in the lower body,

indicated by reversed diastolic flow in the descending aorta, has been demonstrated in preterm neonates with a large PDA.[52] This effect was observed starting at 4 hours after delivery, with nearly half of the neonates being affected by 24 hours of age. Similar findings were reported in preterm neonates with respiratory distress syndrome.[53] In these patients, the hemodynamically significant PDA (hsPDA), defined as a ductal diameter $\geq$1.5 mm with color Doppler and a left atrium-to-aortic-root ratio $\geq$1.4, was associated with increased LVO and decreased blood flow in abdominal aorta. Doppler measurements of blood flow in celiac, superior mesenteric, and renal arteries also showed decreased mean flow velocities and increased resistance indices. However, anterior cerebral artery flow parameters used as a surrogate of cerebral blood flow remained similar to that of the control group without a hsPDA. The differences in LVO and regional organ blood flow have disappeared following medical closure of PDA. In many cases of untreated hsPDA, as pulmonary vascular resistance continues to decrease, there is only a limited ability of the supra-normal LVO to maintain adequate systemic blood flow. In turn, signs of pulmonary overcirculation gradually become more evident and might result in the development of pulmonary hemorrhagic edema.[54]

A number of studies have reported association between PDA and various adverse outcomes in preterm neonates.[54–56] However, none of the clinical trials has demonstrated improvement in long-term outcomes following treatment of PDA.[57] In prophylactic trials, the investigators have used the most aggressive approach to treat all preterm neonates based on predefined gestational age or birth weight. The largest randomized clinical trial, the Trial of Indomethacin Prophylaxis in Preterm Infants,[51] was designed to use intravenous indomethacin as prophylaxis to treat the PDA in all infants with birth weight between 500 g and 999 g in the "treatment" group. This trial and the subsequent meta-analysis of prophylactic PDA treatment revealed similar results: there was a reduction in overall incidence of PDA and grade III and IV P/IVH, but no significant differences in the rate of bronchopulmonary dysplasia, overall mortality, and death or severe neurodevelopmental disability at 18–36 months corrected age were identified.[51,58] However, there remain several concerns over the generalizability of the findings of the Trial of Indomethacin Prophylaxis in Preterm Infants.[59]

Studies evaluating treatment of presymptomatic and symptomatic PDA have reported similar findings regarding long-term outcomes. In the RCT that evaluated efficacy and safety of ibuprofen compared with a placebo,[60] extremely preterm infants were randomized to one of the treatment groups prior to 72 hours of postnatal life if they had evidence of ductal shunting on echocardiogram but no clinical symptoms of a PDA. The investigators found that the proportion of neonates with symptomatic PDA requiring rescue treatment with indomethacin was significantly lower in the ibuprofen group. However, surgical ligation of PDA was similar in the ibuprofen and placebo groups. There was no difference in mortality, retinopathy of prematurity, necrotizing enterocolitis, P/IVH, and bronchopulmonary dysplasia between the two groups. Another RCT compared early (at 3 days of age) versus late (at 7 days of age) treatment of PDA that was evident on echocardiography using indomethacin, and it found overall improvement in the closure rate in the early group by postnatal Day 9. However, there was no difference in surgical ligation rates, mortality, and other morbidities (necrotizing enterocolitis, sepsis, progression of P/IVH), and no evidence of respiratory advantage was noted in the early treatment group.[61] While the authors reported higher incidence of renal complications in the early treatment group, less than half of the neonates randomized to the late treatment group were actually exposed to indomethacin. When predictors of PDA closure were analyzed separately, delayed treatment, lower gestational age, larger diameter of PDA, lower left-to-right shunt velocity on postnatal Day 3, and antenatal exposure to indomethacin within 48 hours of delivery were identified as independent predictors of the failure of ductal closure.

Thus, the major clinical challenge concerning the PDA is the dilemma of whether to treat a PDA in general, and if so, when and how to intervene. While the data in literature remain controversial, it is the opinion of these authors that early treatment of the subpopulations of preterm neonates that are more likely to develop complications of a hsPDA is likely to be justifiable and might lead to improvement in both short- and long-term outcomes. Supportive evidence for this approach comes from the limited observations in the DETECT trial.[62] Hemodynamic determinants of a hsPDA such as a ductal diameter $>$1.5 mm, left atrium-to-aortic-root ratio $>$1.4, the ductal shunt pattern and reversal of diastolic flow in the descending aorta, evaluated during the first 6–12 hours of postnatal life can potentially identify these high-risk patients. Continuous assessment of organ blood flow using comprehensive hemodynamic monitoring systems, complemented using point-of-care Doppler ultrasound measurements of systemic, cerebral, renal, and mesenteric blood flow, holds the promise to further enhance our diagnostic ability and also to allow monitoring of the response to intervention in these patients.

6. Cerebrovascular autoregulation

Adequate cerebral blood flow (CBF) is critical for brain oxygenation and nutrient supply, as well as the removal of pCO_2 and metabolic waste. CBF is normally maintained relatively constant over a range of blood pressures by varying arterial and arteriolar tone through complex autoregulatory mechanisms.[63] This is known as cerebral autoregulation illustrated as an autoregulatory plateau between the two ends of pressure passivity (Figure 3). Cerebral blood flow autoregulation appears to be intact in healthy term and well preterm infants, but the range of the autoregulatory plateau is narrow and the upper and lower blood pressure values are in debate. Some studies have shown premature infants receiving intensive care to maintain a constant blood flow at and above systemic blood pressure ranges of 25–30 mmHg.[64,65] Again, it is accepted that the autoregulatory plateau in the extremely premature infants is much narrower than in term infants and is attenuated or absent in the sick and distressed neonate.[66,67] It is also likely that the autoregulatory blood pressure range changes as the patient's condition changes and that CBF autoregulation is not an "on or off"

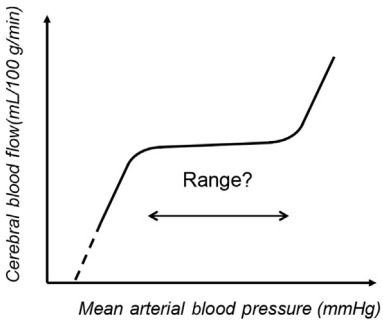


Figure 3 In the preterm infant, the blood pressure range at which cerebral blood flow remains relatively constant is unknown and can be present, attenuated, or absent. Please note though that cerebral blood flow autoregulation is not perfect and there is and approximately 10° slope in the autoregulatory range. Pathological conditions in the infant may alter the slope of the curve outside the autoregulatory plateau. *Note*. From "Autoregulation of cerebral blood flow in newborn babies" by Greisen G, 2005, *Early Human Development*, 81, p. 423–8. Copyright 2005, Elsevier/Saunders Co; Philadelphia, PA. Adapted with permission. Greisen G. Autoregulation of cerebral blood flow in newborn babies. *Early Hum Dev* 2005;**81**:423–8.

phenomenon. Thus, depending on the patient's level of immaturity and the underlying pathology, it might be present, attenuated, or absent in the given patient at any given time. Pressure passivity likely plays a role in the development of P/IVH and preterm brain injury in the critically ill preterm neonate with fluctuating blood pressure and CBF.[68] In clinical care, neonatologists will often set blood pressure goals in an attempt to maintain adequate CBF and prevent ischemia/hyperperfusion. However, without the knowledge of where the infant lies within the cerebrovascular autoregulatory curve in real time, blood pressure goal becomes a moving target. In addition, attenuated or absent CBF autoregulation is not restored rapidly. Therefore, unsuitable titration of medications used in blood pressure management will likely contribute to significant CBF fluctuations as blood pressure rapidly changes with inappropriate increases and/or weaning of the medications used.[36,41,42] Low SVC flow in the first 24 hours has also been associated with P/IVH (Grade 2 or more) and abnormal neurodevelopmental outcome at 3 years of age; yet only limited association was found between mean blood pressure in the first 24 hours and abnormal neurodevelopmental outcome.[69,70] Although SVC flow is an attractive hemodynamic parameter, more studies are needed to determine if maintaining adequate SVC flow reduces intraventricular hemorrhage.[34,71]

Other modifiers of CBF include the arterial tension of carbon dioxide ($PaCO_2$), pH, and oxygen. Carbon dioxide is the most potent regulator of CBF. Unlike bicarbonate, CO_2 readily penetrates the blood brain barrier and equilibrates between arterial blood and cerebrospinal fluid rapidly. Rapid diffusion of CO_2 alters the pH of the CBF and the perivascular tissue and acts on the vascular endothelium to cause cerebral vasodilatation or vasoconstriction in the setting of acute hypercapnea (acidosis) or hypocapnea (alkalosis), respectively.[72] Fluctuations in $PaCO_2$ frequently occur in the immediate postnatal period, when ventilator management for respiratory distress syndrome or other conditions may be challenging. Hypercapnea have also been found to disrupt and impair cerebral autoregulation in very low birth weight infants, diminishing innate protective mechanisms to maintain a relatively steady CBF.[73] Furthermore, extreme aberrations in $PaCO_2$ value in the first three postnatal days in preterm newborns have been associated with P/IVH and poor neurodevelopmental outcome.[74,75] Interestingly, a recent prospective study assessed CBF velocity using Doppler ultrasound at the time of blood gas analysis in preterm infants less than 30 weeks' gestation during the first 3 postnatal days, and it found $PaCO_2$ to have very little-to-no association with CBF velocity on postnatal Day 1.[76] The expected relationship between CBF velocity and $PaCO_2$ was only seen on postnatal Day 3. The cut-off point at which $PaCO_2$ was associated with a rapid change in cerebral blood flow velocity was around 51–53 mmHg for the entire dataset.[76] The authors explained their findings by the accumulating evidence that the forebrain vasculature of the very preterm neonate does not function as that of a "vital organ" immediately following delivery.[20] Since all of these patients are believed to be in the compensated phase of shock at birth, they have maximally constricted cerebral vessels overriding the vasoactive effects of perivascular pH changes.[12]

In summary, a number of factors contribute to compromised systemic and cerebral blood flow in the preterm or the sick term neonate during the transitional period. Indeed, the preterm myocardium faces an abrupt increase in afterload following removal of the placenta with immediate clamping of the cord. In addition, soon after delivery the myocardium is forced to generate significantly higher cardiac output in the presence of a hsPDA. Other factors, such as positive pressure ventilation compromising venous return, autonomic immaturity, relative adrenal insufficiency, and perinatal asphyxia are also likely to contribute to the difficulties of hemodynamic transition. It has been speculated that, with the improvement of low systemic blood flow over the next 24–72 hours, a hypoxia-reperfusion scenario takes place and P/IVH or brain injury may occur.[40,77,78]

7. Summary

While cardiovascular changes in premature infants during the transitional period are dynamic and complex, with the interplay between cardiac output, systemic blood flow, blood pressure, and CBF, premature infants are born with limited capacity to adjust to the hemodynamic challenges in the immediate postnatal period. A growing body of evidence suggests that compromised systemic blood flow is associated with the development of a number of short- and long-term complications such as P/IVH and persistent neurological deficits. It has also become obvious that only certain, albeit not well-defined, subgroups of patients are at significantly higher risk of complications. These subgroups of patients would benefit from targeted preventive and/or therapeutic interventions the most. Thus, early recognition of impeding cardiovascular compromise along with appropriate circulatory support during the transitional period is crucial, although limited evidence-based

information is available for the neonatologists. Continuous, real-time assessment of both systemic and regional organ perfusion along with continuously assessed changes in brain function is the next logical next step that will likely enable the clinician to develop and subsequently adjust an individualized management plan that would be pathophysiologically justified and most beneficial for a particular patient.

Conflicts of interest

None of the authors declare any conflict of interest.

References

1. Soothill PW, Nicolaides KH, Rodeck CH, Gamsu H. Blood gases and acid-base status of the human second—trimester fetus. *Obstet Gynecol* 1986;**68**:173—6.
2. Sutton MS, Theard MA, Bhatia SJ, Plappert T, Saltzman DH, Doubilet P. Changes in placental blood flow in the normal human fetus with gestational age. *Pediatr Res* 1990;**28**:383—7.
3. Usher R, Shephard M, Lind J. The blood volume of the newborn infant and placental transfusion. *Acta Paediatr* 1963;**52**: 497—512.
4. Farrar D, Airey R, Law GR, Tuffnell D, Cattle B, Duley L. Measuring placental transfusion for term births: weighing babies with cord intact. *BJOG* 2011;**118**:70—5.
5. Aladangady N, McHugh S, Aitchison TC, Wardrop CA, Holland BM. Infants' blood volume in a controlled trial of placental transfusion at preterm delivery. *Pediatrics* 2006;**117**: 93—8.
6. Rasanen J, Wood DC, Weiner S, Ludomirski A, Huhta JC. Role of the pulmonary circulation in the distribution of human fetal cardiac output during the second half of pregnancy. *Circulation* 1996;**94**:1068—73.
7. Rudolph AM, Heymann MA. The circulation of the fetus in utero. Methods for studying distribution of blood flow, cardiac output and organ blood flow. *Circ Res* 1967;**21**:163—84.
8. Mielke G, Benda N. Cardiac output and central distribution of blood flow in the human fetus. *Circulation* 2001;**103**:1662—8.
9. Kiserud T. Physiology of the fetal circulation. *Semin Fetal Neonatal Med* 2005;**10**:493—503.
10. Auer M, Brezinka C, Eller P, Luze K, Schweigmann U, Schwärzler P. Prenatal diagnosis of intrauterine premature closure of the ductus arteriosus following maternal diclofenac application. *Ultrasound Obstet Gynecol* 2004;**23**:513—6.
11. Hooper SB, Te Pas AB, Lang J, van Vonderen JJ, Roehr CC, Kluckow M, et al. Cardiovascular transition at birth: a physiological sequence. *Pediatr Res* 2015;**77**:608—14.
12. Noori S, Seri I. Hemodynamic antecedents of peri/intraventricular hemorrhage in very preterm neonates. *Semin Fetal Neonatal Med* 2015;**20**:232—7.
13. Saugstad OD. Oxygen saturations immediately after birth. *J Pediatr* 2006;**148**:569—70.
14. Walther FJ, Benders MJ, Leighton JO. Early changes in the neonatal circulatory transition. *J Pediatr* 1993;**123**:625—32.
15. Raju TN. Timing of umbilical cord clamping after birth for optimizing placental transfusion. *Curr Opin Pediatr* 2013;**25**: 180—7.
16. Katheria AC, Leone TA, Woelkers D, Garey DM, Rich W, Finer NN. The effects of umbilical cord milking on hemodynamics and neonatal outcomes in premature neonates. *J Pediatr* 2014;**164**. 1045—50.e1.
17. Patel S, Clark EA, Rodriguez CE, Metz TD, Abbaszadeh M, Yoder BA. Effect of umbilical cord milking on morbidity and survival in extremely low gestational age neonates. *Am J Obstet Gynecol* 2014;**211**:519.e1—7.
18. Backes CH, Rivera BK, Haque U, Bridge JA, Smith CV, Hutchon DJ, et al. Placental transfusion strategies in very preterm neonates: a systematic review and meta—analysis. *Obstet Gynecol* 2014;**124**:47—56.
19. Committee on Obstetric Practice, American College of Obstetricians and Gynecologists. Committee Opinion No.543: Timing of umbilical cord clamping after birth. *Obstet Gynecol* 2012; **120**:1522—6.
20. Sommers R, Stonestreet BS, Oh W, Laptook A, Yanowitz TD, Raker C, et al. Hemodynamic effects of delayed cord clamping in premature infants. *Pediatrics* 2012;**129**:e667—72.
21. Takami T, Suganami Y, Sunohara D, Kondo A, Mizukaki N, Fujioka T, et al. Umbilical cord milking stabilizes cerebral oxygenation and perfusion in infants born before 29 weeks of gestation. *J Pediatr* 2012;**161**:742—7.
22. Yao AC, Lind J. Placental transfusion. *Am J Dis Child* 1974;**127**: 128—41.
23. Fanaroff AA, Fanaroff JM. Short- and long-term consequences of hypotension in ELBW infants. *Semin Perinatol* 2006;**30**: 151—5.
24. Batton B, Li L, Newman NS, Das A, Watterberg KL, Yoder BA, et al. Use of antihypotensive therapies in extremely preterm infants. *Pediatrics* 2013;**131**:e1865—73.
25. Pellicer A, Bravo MC, Madero R, Salas S, Quero J, Cabañas F. Early systemic hypotension and vasopressor support in low birth weight infants: impact on neurodevelopment. *Pediatrics* 2009;**123**:1369—76.
26. Wu TW, Noori S, Seri I. Neonatal hypotension. In: Polin RA, Yoder MC, editors. *Workbook in practical neonatology*. 5th ed. Philadelphia: Elsevier/Saunders; 2014. p. 230—43.
27. Noori S, Seri I. Hypotension. In: Stevenson DK, Cohen RS, Sunshine P, editors. *Neonatology: clinical practice and procedural atlas*. 1st ed. New York: McGraw and Hill Company Inc.; 2015. p. 281—91.
28. Seri I, Evans J. Controversies in the diagnosis and management of hypotension in the newborn infant. *Curr Opin Pediatr* 2001; **13**:116—23.
29. Batton B, Batton D, Riggs T. Blood pressure during the first 7 days in premature infants born at postmenstrual age 23 to 25 weeks. *Am J Perinatol* 2007;**24**:107—15.
30. Osborn DA, Evans N, Kluckow M. Clinical detection of low upper body blood flow in very premature infants using blood pressure, capillary refill time, and central—peripheral temperature difference. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**: F168—73.
31. Shimada S, Kasai T, Konishi M, Fujiwara T. Effects of patent ductus arteriosus on left ventricular output and organ blood flows in preterm infants with respiratory distress syndrome treated with surfactant. *J Pediatr* 1994;**125**:270—7.
32. Kluckow M, Evans N. Relationship between blood pressure and cardiac output in preterm infants requiring mechanical ventilation. *J Pediatr* 1996;**129**:506—12.
33. Kluckow M, Evans N. Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. *Arch Dis Child Fetal Neonatal Ed* 2000;**82**:F182—7.
34. Osborn DA, Evans N, Kluckow M, Bowen JR, Rieger I. Low superior vena cava flow and effect of inotropes on neurodevelopment to 3 years in preterm infants. *Pediatrics* 2007; **120**:372—80.
35. Batton BJ, Li L, Newman NS, Das A, Watterberg KL, Yoder BA, et al. Feasibility study of early blood pressure management in extremely preterm infants. *J Pediatr* 2012;**161**:65—9. e1.

36. Noori S, Seri I. Neonatal blood pressure support: the use of inotropes, lusitropes, and other vasopressor agents. *Clin Perinatol* 2012;**39**:221—38.
37. Anderson PA. The heart and development. *Semin Perinatol* 1996;**20**:482—509.
38. Kluckow M, Evans N. Low superior vena cava flow and intraventricular haemorrhage in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2000;**82**:F188—94.
39. Batton B, Li L, Newman NS, Das A, Watterberg KL, Yoder BA, et al. Evolving blood pressure dynamics for extremely preterm infants. *J Perinatol* 2014;**34**:301—5.
40. Noori S, McCoy M, Anderson MP, Ramji F, Seri I. Changes in cardiac function and cerebral blood flow in relation to peri/-intraventricular hemorrhage in extremely preterm infants. *J Pediatr* 2014;**164**:264—70. e1—3.
41. Cavalli C, Dorizzi RM, Lanzoni L, Caputo M, Biban P. How much and for how long does the neonatal myocardium suffer from mild perinatal asphyxia? *J Matern Fetal Neonatal Med* 2005;**17**:85—6.
42. Trevisanuto D, Picco G, Golin R, Doglioni N, Altinier S, Zaninotto M, et al. Cardiac troponin I in asphyxiated neonates. *Biol Neonate* 2006;**89**:190—3.
43. Noori S, Wu TW, Seri I. pH effects on cardiac function and systemic vascular resistance in preterm infants. *J Pediatr* 2013;**162**. 958—63.e1.
44. Mueller-Heubach E, Rubinstein DN, Schwarz SS. Histologic chorioamnionitis and preterm delivery in different patient populations. *Obstet Gynecol* 1990;**75**:622—6.
45. Hofer N, Kothari R, Morris N, Müller W, Resch B. The fetal inflammatory response syndrome is a risk factor for morbidity in preterm neonates. *Am J Obstet Gynecol* 2013;**209**: 542.e1—542.e11.
46. Romero R, Espinoza J, Gonçalves LF, Gomez R, Medina L, Silva M, et al. Fetal cardiac dysfunction in preterm premature rupture of membranes. *J Matern Fetal Neonatal Med* 2004;**16**: 146—57.
47. Furukawa S, Sameshima H, Ikenoue T. Circulatory disturbances during the first postnatal 24 hours in extremely premature infants 25 weeks or less of gestation with histological fetal inflammation. *J Obstet Gynaecol Res* 2008;**34**:27—33.
48. Crispi F, Hernandez-Andrade E, Pelsers MM, Plasencia W, Benavides-Serralde JA, Eixarch E, et al. Cardiac dysfunction and cell damage across clinical stages of severity in growth-restricted fetuses. *Am J Obstet Gynecol* 2008;**199**. 254.e1—e8.
49. Leipälä JA, Boldt T, Turpeinen U, Vuolteenaho O, Fellman V. Cardiac hypertrophy and altered hemodynamic adaptation in growth-restricted preterm infants. *Pediatr Res* 2003;**53**: 989—93.
50. Fouzas S, Karatza AA, Davlouros PA, Chrysis D, Alexopoulos D, Mantagos S, et al. Neonatal cardiac dysfunction in intrauterine growth restriction. *Pediatr Res* 2014;**75**:651—7.
51. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med* 2001;**344**: 1966—72.
52. Groves AM, Kuschel CA, Knight DB, Skinner JR. Does retrograde diastolic flow in the descending aorta signify impaired systemic perfusion in preterm infants? *Pediatr Res* 2008;**63**:89—94.
53. Shimada S, Kasai T, Hoshi A, Murata A, Chida S. Cardiocirculatory effects of patent ductus arteriosus in extremely low-birth-weight infants with respiratory distress syndrome. *Pediatr Int* 2003;**45**:255—62.
54. Kluckow M, Evans N. Ductal shunting, high pulmonary blood flow, and pulmonary hemorrhage. *J Pediatr* 2000;**137**:68—72.
55. Clyman RI, Couto J, Murphy GM. Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? *Semin Perinatol* 2012;**36**:123—9.
56. Noori S, McCoy M, Friedlich P, Bright B, Gottipati V, Seri I, et al. Failure of ductus arteriosus closure is associated with increased mortality in preterm infants. *Pediatrics* 2009;**123**: e138—44.
57. Evans N. Preterm patent ductus arteriosus: a continuing conundrum for the neonatologist? *Semin Fetal Neonatal Med* 2015;**20**:272—7.
58. Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. *Cochrane Database Syst Rev* 2010;(7): CD000174.
59. Clyman RI, Saha S, Jobe A, Oh W. Indomethacin prophylaxis for preterm infants: the impact of 2 multicentered randomized controlled trials on clinical practice. *J Pediatr* 2007;**150**. 46—50.e2.
60. Aranda JV, Clyman R, Cox B, Van Overmeire B, Wozniak P, Sosenko I, et al. A randomized, double-blind, placebo-controlled trial on intravenous ibuprofen L-lysine for the early closure of nonsymptomatic patent ductus arteriosus within 72 hours of birth in extremely low-birth-weight infants. *Am J Perinatol* 2009;**26**:235—45.
61. Van Overmeire B, Van de Broek H, Van Laer P, Weyler J, Vanhaesebrouck P. Early versus late indomethacin treatment for patent ductus arteriosus in premature infants with respiratory distress syndrome. *J Pediatr* 2001;**138**:205—11.
62. Kluckow M, Jeffery M, Gill A, Evans N. A randomised placebo-controlled trial of early treatment of the patent ductus arteriosus. *Arch Dis Child Fetal Neonatal Ed* 2014;**99**:F99—104.
63. Greisen G. Autoregulation of cerebral blood flow in newborn babies. *Early Hum Dev* 2005;**81**:423—8.
64. Pryds O, Andersen GE, Friis-Hansen B. Cerebral blood flow reactivity in spontaneously breathing, preterm infants shortly after birth. *Acta Paediatr Scand* 1990;**79**:391—6.
65. Munro MJ, Walker AM, Barfield CP. Hypotensive extremely low birth weight infants have reduced cerebral blood flow. *Pediatrics* 2004;**114**:1591—6.
66. Soul JS, Hammer PE, Tsuji M, Saul JP, Bassan H, Limperopoulos C, et al. Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. *Pediatr Res* 2007;**61**:467—73.
67. Tsuji M, Saul JP, du Plessis A, Eichenwald E, Sobh J, Crocker R, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics* 2000;**106**:625—32.
68. Miall-Allen VM, de Vries LS, Dubowitz LM, Whitelaw AG. Blood pressure fluctuation and intraventricular hemorrhage in the preterm infant of less than 31 weeks' gestation. *Pediatrics* 1989;**83**:657—61.
69. Kluckow M. Low systemic blood flow and pathophysiology of the preterm transitional circulation. *Early Hum Dev* 2005;**81**: 429—37.
70. Alderliesten T, Lemmers PM, van Haastert IC, de Vries LS, Bonestroo HJ, Baerts W, et al. Hypotension in preterm neonates: low blood pressure alone does not affect neurodevelopmental outcome. *J Pediatr* 2014;**164**:986—91.
71. Paradisis M, Evans N, Kluckow M, Osborn D. Randomized trial of milrinone versus placebo for prevention of low systemic blood flow in very preterm infants. *J Pediatr* 2009;**154**: 189—95.
72. Wolf ME. Functional TCD: regulation of cerebral hemodynamics-cerebral autoregulation, vasomotor reactivity, and neurovascular coupling. *Front Neurol Neurosci* 2015;**36**:40—56.
73. Kaiser JR, Gauss CH, Williams DK. The effects of hypercapnia on cerebral autoregulation in ventilated very low birth weight infants. *Pediatr Res* 2005;**58**:931—5.
74. Kaiser JR, Gauss CH, Pont MM, Williams DK. Hypercapnia during the first 3 days of life is associated with severe intraventricular

hemorrhage in very low birth weight infants. *J Perinatol* 2006; **26**:279—85.
75. McKee LA, Fabres J, Howard G, Peralta-Carcelen M, Carlo WA, Ambalavanan N. PaCO2 and neurodevelopment in extremely low birth weight infants. *J Pediatr* 2009;**155**:217—21.e1.
76. Noori S, Anderson M, Soleymani S, Seri I. Effect of carbon dioxide on cerebral blood flow velocity in preterm infants during postnatal transition. *Acta Paediatr* 2014;**103**:e334—9.
77. Greisen G. Autoregulation of vital and nonvital organ blood flow in the preterm and term neonate. In: Kleinman C, Seri I, editors. *Neonatology questions and controversies: hemodynamics and cardiology*. 2nd ed. Philadelphia: Saunders/Elsevier; 2012. p. 29—47.
78. Noori S, Stavroudis TA, Seri I. Systemic and cerebral hemodynamics during the transitional period after premature birth. *Clin Perinatol* 2009;**36**:723—36.
79. Lakkundi A, Wright I, de Waal K. Transitional hemodynamics in preterm infants with a respiratory management strategy directed at avoidance of mechanical ventilation. *Early Hum Dev* 2014;**90**:409—12.