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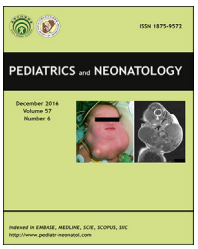

REVIEW ARTICLE

Circulatory Management Focusing on Preventing Intraventricular Hemorrhage and Pulmonary Hemorrhage in Preterm Infants

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The goal of modern neonatal care of extremely preterm infants is to reduce mortality and long-term neurological impairments. Preterm infants frequently experience cerebral intraventricular or pulmonary hemorrhage, which usually occurs within 72 hours after birth and can lead to long-term neurological sequelae and mortality. These serious hemorrhagic complications are closely related to perinatal hemodynamic changes, including an increase in the afterload on the left ventricle of the heart after the infant is separated from the placenta, and an increased preload from a left-to-right shunt caused by a hemodynamically significant patent ductus arteriosus (PDA). The left ventricle of a preterm myocardium has limited ability to respond to such an increase in afterload and preload, and this can result in cardiac dysfunction and hemodynamic deterioration. We suggest that delayed umbilical cord clamping or umbilical cord milking to maintain optimal blood pressure and systemic blood flow (SBF), careful assessment to keep the afterload at an acceptable level, and a strategy of early targeted treatment of significant PDA to improve perfusion during this critical time period may reduce or prevent these serious complications in preterm infants.

1. Introduction

Preterm infants undergo a perinatal transition from fetal to postnatal circulation that causes significant hemodynamic stress on the cardiovascular system, especially in preterm infants with premature myocardial function. The major cause of this hemodynamic stress is interruption of the placental circulation at birth. The placental circulation is a

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low resistance, highly compliant vascular bed that receives a large proportion (30—50%) of total cardiac output.[1] Sudden interruption of the placental circulation results in an abrupt increase in resistance in the systemic arteries, and thus in an increase in the afterload on the left ventricle of the heart.[2—5] In addition, the left ventricle may also face increased preload from a left-to-right shunt caused by a hemodynamically significant patent ductus arteriosus (PDA).[6,7]

The immature myocardium in premature infants has limited ability to respond to such an increase in afterload and change in preload. Some infants may experience serious hemorrhagic complications such as cerebral intraventricular hemorrhage (IVH) or pulmonary hemorrhage, which usually occurs within 72 hours after birth and can affect the long-term neurological development of premature infants and even cause mortality.

The goal of modern neonatal care of extremely preterm infants is to reduce mortality and neurological impairments. Without understanding the underlying cardiovascular mechanism of transition, appropriate interventional management strategies cannot be implemented. As the serious hemorrhagic complications are closely related to perinatal hemodynamic changes, we focused on the clinical perspective of circulatory management to prevent IVH or pulmonary hemorrhage in preterm infants in this review.

2. Delayed umbilical cord clamping versus umbilical cord milking in preterm infants

2.1. Delayed cord clamping

Delayed cord clamping (DCC) by 30—120 seconds rather than immediate clamping has been reported to be associated with less need for transfusion and lower rate of IVH.[8] In December 2012, the American College of Obstetricians and Gynecologists recommended a delay of 30—60 seconds in umbilical cord clamping for all preterm deliveries.[9] Although DCC has been shown to decrease the overall incidence of IVH, it has not been shown to have a beneficial effect on severe IVH, and thus its clinical application has been limited.[10]

2.2. Umbilical cord milking

The lack of a beneficial effect of DCC on severe IVH may reflect a lack of adequate placental transfusion during DCC for infants delivered by cesarean delivery.[11—13] An alternative to DCC is umbilical cord milking (UCM), a procedure that can be performed in 20 seconds.[14] UCM is performed by holding the infant at or 20 cm below the level of the placenta. The cord is pinched as close to the placenta as possible and milked toward the infant for 2 seconds. The cord is then released and allowed to refill with blood for 1—2 seconds between each milking motion. This is repeated a total of four times. After completion, the cord is clamped and the neonate handed to the resuscitation team. Milking the cord four times provides a similar amount of placental-fetal blood compared with DCC for 30 seconds.[15]

A recent meta-analysis of UCM including seven randomized clinical trials involving 501 infants delivered at $<$ 33 weeks, demonstrated that infants who underwent UCM had a higher hemoglobin level and lower risk of oxygen requirement at 36 weeks and IVH of all grades compared with those who underwent immediate cord clamping.[16]

2.3. Comparison between UCM and DCC

Most preterm infants are delivered by cesarean section, and a placental blood transfusion may be less effective in a cesarean delivery than in a vaginal delivery. A recent study which enrolled 197 infants (mean gestational age 28 $\pm$ 2 weeks) reported a higher hemoglobin level at birth, improved hemodynamics (higher blood flow and improved blood pressure), and improved urine output with UCM compared with DCC in preterm infants delivered by cesarean section.[17] The authors also noted superior venous cava (SVC) flow and higher right ventricular output in infants treated with UCM. SVC flow represents cardiac input, and is therefore a useful measure of systemic blood flow (SBF) in the newborn heart and an important marker of neonatal transition.[18,19] Previous reports have demonstrated that lower right ventricular output is closely associated with worsening respiratory disease, severe IVH, and death.[20] A higher overall SBF is probably related to an increased blood volume from a placental transfusion resulting in improved hemodynamics. Infants undergoing UCM have also been reported to have higher urine output and blood pressure, suggesting that these infants have some improvements in organ perfusion within the first 24 hours of life.[17] Improved perfusion during this critical time period may prevent IVH by stabilizing fluctuations in SBF.[18] There were fewer neonates with total and severe IVH in the UCM group, which is consistent with Rabe et al[15] who compared UCM and DCC.

An additional advantage of UCM is the short procedure time. This not only allows for a minimal delay in resuscitation, but also reduces the amount of time the newborn is exposed to a lower temperature.[17] A recent pilot study of 75 extremely premature neonates (born at a gestational age $<$ 29 weeks) randomly assigned to receive UCM or immediate cord clamping demonstrated a 50% reduction in total IVH.[21] In another recent retrospective study of UCM in 318 infants born at $<$ 30 weeks, UCM was associated with reductions in IVH, necrotizing enterocolitis, and death before hospital discharge.[22] The authors further suggested that UCM may be more beneficial for smaller, more immature neonates.[21,22]

Taken together, UCM provides a greater placental transfusion, as demonstrated by higher initial Hb level, higher blood pressure, and improved SBF and urine output in infants delivered by cesarean delivery. UCM may thus be preferable in preterm infants delivered by cesarean delivery, particularly when immediate resuscitation is needed.[17]

2.4. Concerns over UCM and DCC

Concerns have been raised over UCM as to whether it can provide a rapid bolus of blood. Rapid changes in venous pressure during UCM were addressed in an early trial that

demonstrated no greater increase in venous pressures with UCM compared with uterine contractions or a newborn cry during intact placental circulation.[23] With UCM, placental blood is directed towards the lungs during a time when there is a rapid fall in pulmonary resistance unlike any other period when volume is given.[17,23] A recent meta-analysis evaluating the safety and efficacy of UCM at birth concluded that there was a lower risk of oxygen requirement at 36 weeks and IVH of all grades.[16] Therefore, we suggest that UCM should no longer be considered as experimental, but rather as a proven intervention which can ensure that premature newborns receive an adequate placental transfusion at birth.

The potential for developing hyperbilirubinemia is another issue of concern. A Cochrane review found that none of the neonates with elevated bilirubin levels required phototherapy treatment or exchange transfusions.[8] However, in populations more susceptible to neonatal hyperbilirubinemia, and especially those of Asian ethnicity, careful monitoring of the serum bilirubin level is warranted.

2.5. The recommendations of the Umbilical Cord Management in the International Liaison Committee on Resuscitation for the Neonatal Resuscitation Program

According to the 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations[24] and subsequent review of DCC and cord milking in preterm newborns in the 2015 Umbilical Cord Management in the International Liaison Committee on Resuscitation (ILCOR) systematic review,[25,26] DCC for longer than 30 seconds is reasonable for both term and preterm infants who do not require resuscitation at birth. However, there is insufficient evidence to recommend cord clamping for infants who require resuscitation at birth, and more randomized trials involving such infants are needed.

In light of the limited information regarding the safety of rapid changes in blood volume for extremely preterm infants, the ILCOR suggest that cord milking should not be routinely used for infants born at $<$ 29 weeks of gestation outside of a research setting. Further studies are warranted to elucidate this issue, because cord milking may improve the initial mean blood pressure, hematologic indices, and reduce intracranial hemorrhage. However, there is currently no evidence with regards to improvements in long-term outcomes.

After the 2015 ILCOR systematic review, several studies[16,17,22] reported that UCM was associated with some benefits and no adverse effects in the immediate postnatal period in preterm infants (see Sections 2.2 and 2.3). It is possible that UCM may be more beneficial for smaller, more immature neonates who require resuscitation at birth;[21,22] however, further studies are warranted to assess the effect of UCM on neonatal and long-term outcomes.

Another recent randomized controlled trial reported the effects of placental transfusion on neonatal and 18-month outcomes in preterm infants.[27] For those receiving DCC, the obstetrician placed the infant in a sterile, warm towel or blanket and held them approximately 10–15 inches below the mother's introitus in a vaginal delivery, or below the level of the placenta in a cesarean delivery. Suctioning was performed at the discretion of the obstetrician. At 30–45 seconds, the obstetrician milked the infant's cord once, then clamped and cut the umbilical cord. If the DCC protocol could not be performed as planned, the cord was milked quickly two to three times before clamping when possible. The immediate cord clamping group received routine care of cord clamping in less than 10 seconds. Pregnant women in labor with singleton fetuses ($n = 208$) between 24 weeks of gestation and 31.6 weeks of gestation were enrolled. Infants in the DCC and immediate cord clamping groups weighed 1203 $\pm$ 352 g and 1136 $\pm$ 350 g, respectively, with a mean gestational age of 28.3 $\pm$ 2 weeks and 28.4 $\pm$ 2 weeks, respectively. There were no differences in the number of infants who received phototherapy, days of phototherapy, delivery room resuscitation, Neonatal Acute Physiology scores at 12 hours of age, and the rates of IVH or late onset sepsis between the groups. In addition, at 18–22 months, DCC was found to be protective against motor scores $<$ 85 on the Bayley Scales of Infant Development, Third Edition. The authors concluded that although DCC did not alter the incidence of IVH or late onset sepsis in preterm infants, it improved motor function at 18–22 months corrected age.

3. Optimal blood pressure in preterm infants

3.1. Definition of hypotension in preterm infants

Hypotension is a commonly diagnosed and treated complication in preterm infants. It is defined as any blood pressure value that falls below the fifth or 10th percentile for gestational and postnatal age, respectively.[28] Although the lower limits of normal blood pressure for gestational and postnatal age in extremely preterm infants are not known, many neonatologists routinely treat infants whose mean arterial blood pressure is less than their gestational age in weeks.[28–31] Treatment typically consists of volume infusions, followed by inotrope infusions, and predominantly dopamine.[29,32] If the initial inotrope therapy fails, dobutamine is the most popular second-line therapy.[33] There is also a growing trend in the use of hydrocortisone therapy in hypotensive very low birth weight infants.[34,35]

3.2. Blood pressure and SBF

In preterm infants during the first days of life, there is a poor association between blood pressure and SBF.[36,37] Low SVC flow, a useful measure of SBF, is a known risk factor for mortality and morbidity in preterm infants, however hypotension itself is not reliable in detecting low SBF.[18,19] The principal role of the circulation is to ensure adequate delivery of oxygen and nutrients to tissues, and this is achieved by maintaining appropriate perfusion pressure and cardiac output in the systemic and pulmonary circulations.[37] Preterm infants with a mean arterial blood pressure lower than their gestational age in weeks often have no clinical signs of shock and presumably have adequate tissue oxygen delivery, and may therefore not need treatment.[30]

There is no evidence that attempts to achieve a "normal" blood pressure based on arbitrary guideline values but with clinical evidence of good perfusion will improve outcomes, and the currently available therapies may be toxic or dangerous.[38] Dopamine may increase blood pressure at the expense of systemic perfusion in certain patients (see Section 4.2), and particularly at high doses.[39] Therefore, the drug should be carefully titrated to achieve an "optimal" blood pressure response to successfully increase blood pressure and SBF at low-to-moderate doses.[40]

We suggest that the best approach is to continuously monitor both blood pressure and SBF in these patients. Continuous arterial blood pressure monitoring using an indwelling catheter is considered to be the gold standard of measuring blood pressure in critically ill neonates.[41,42] Although blood pressure is also frequently measured noninvasively, it is less accurate (especially in severe hypotension, and with overestimation of hypotension and underestimation of hypertension). Most importantly, noninvasive measurements of blood pressure are not continuous and cannot provide reliable values of mean or diastolic blood pressure, although they can be used for trends in changes of blood pressure. In addition, various cuff sizes are needed, because if the cuff is too small the blood pressure will be overestimated.

The currently available tools to assess SBF in very low birth weight neonates at the bedside, such as near infrared spectroscopic topography, ultrasonic cardiac output monitor (USCOM), and electrical velocimetry have significant limitations and are primarily used for research purposes.[30,42–47] Based on the overall poor correlation between USCOM and invasive cardiac output measurement studies, the use of USCOM should be restricted to well-defined clinical trials before this noninvasive modality of monitoring cardiac output can be considered for routine use in preterm infants. In the future, USCOM may serve as a feasible and fast diagnostic tool to measure changes in cardiac output in response to treatment (such as vasopressor therapy and fluid challenge).

3.3. Global assessment of cardiovascular status

The global assessment of cardiovascular status (Table 1) includes assessments of easily evaluable physical observations such as capillary refill, skin color, heart rate, mean blood pressure, urine output, level of activity, and biochemical examinations, and in particular, the degree of acidosis.[28,30] Laboratory indices of perfusion such as serum lactate and acidosis (base excess) during anaerobic metabolism are frequently used in the diagnosis of poor tissue perfusion.[48] Correlations between lactate values with SBF have been shown to be improved by combining capillary filling time, lactate $>$ 4 mmol/L plus a prolonged capillary refill time $>$ 4 seconds, and have been shown to have a high positive predictive value (80%) and negative predictive value (88%) for identifying low SVC flow. This highlights the importance of combining clinical and biochemical data when assessing the adequacy of end-organ blood flow.[19,37]

3.4. Permissive hypotension

Dempsey et al[30] evaluated this approach (global assessment of cardiovascular status) in extremely low birth weight infants in the first 72 hours of life, and grouped the patients as either normotensive (blood pressure never less than gestational age), hypotensive untreated (blood pressure less than gestational age but with signs of good perfusion; termed as "permissive hypotension"), or hypotensive treated (blood pressure less than gestational age with signs of poor perfusion). Blood pressure was found to spontaneously improve in the extremely low birth weight infants during the first 24 hours, and the outcomes of the hypotensive infants using the gestational age criteria but with clinical evidence of good perfusion were as good as those of normotensive patients. Therefore, global assessments of cardiovascular status and interventions for hypotension restricted to infants with poor perfusion (skin color, capillary refill rate, urine output, blood lactate level, and acidosis) may result in good clinical outcomes.[30,49]

4. Hemodynamic evaluation of preterm infants by echocardiography

4.1. Hemodynamic changes in preterm infants

It is well known that the perinatal transition from the fetal to the postnatal circulation causes dramatic loading

Table 1 Global assessment of cardiovascular status including clinical signs, biochemical data and echocardiographic evaluation.*

Clinical signs	Refilling time, skin color, heart rate, mean blood pressure, urine output, activity
Biochemical examinations	Lactic acid, base excess, B-type natriuretic peptide
Echocardiography	Left ventricular (LV) systolic function Ejection fraction Fractional shortening Stress-velocity relationship (a relatively load-independent cardiac function index)[59] End-systolic wall stress (an index of LV afterload) LV rate-corrected mean velocity of circumferential fiber shortening (mVcfc, an index of LV pump function) Patent ductus arteriosus assessment Pulsed Doppler flow patterns[52,53] and color Doppler ductal diameter[78] left atrium/aorta Cardiac output : superior vena cava flow (a useful measure of systemic blood flow)[19]

* Summarized from Dempsey et al[30] and Toyoshima et al[39].

changes on the heart (Table 1). The immature myocardium of the left ventricle faces a high afterload after the neonate is separated from the placenta.[2–5] In addition, the left ventricle may also face increased preload from a left-to-right shunt caused by a hemodynamically significant PDA.[6,7,50] However, the preterm left ventricle has a limited ability to respond to such an increased afterload and change in preload. This results in depressed cardiac function and deterioration in hemodynamics.

4.2. Stress-velocity relationship: a sensitive echocardiographic index for evaluation of cardiac function

In addition to the global assessment of cardiovascular status described above, functional echocardiography performed by a neonatologist is also frequently used to evaluate and delineate the nature of hemodynamic instability, the significance of a PDA, and the presence or severity of pulmonary hypertension.[51–58] The LV ejection fraction and fractional shortening are commonly used to estimate LV systolic function, however both are largely influenced by preload, afterload, and heart rate.[59]

The stress-velocity relationship is a relatively load-independent index which has been used to effectively evaluate cardiac function in preterm infants.[3–5,50,59,60] This index is calculated from the end-systolic wall stress (ESWS, an index of left ventricle afterload), and the left ventricle rate-corrected mean velocity of circumferential fiber shortening (mVcfc, an index of left ventricle pump function). The stress-velocity relationship has been shown to have a steep slope in the low ESWS range, as illustrated in Figure 1.[39,59] The cardiac pumping function (represented as mVcfc) is easily impaired, and can be decreased by even a small increase in afterload (represented as ESWS) in smaller or younger infants with low ESWS.[5,50]

Preterm infants frequently have PDA, and concerns have been raised over its influence on the effectiveness of the stress-velocity relationship when used in preterm infants. However, it has been reported that mVcfc and ESWS do not change after PDA closure,[5] which indicates that a PDA does not affect the measurement of these parameters. Thus, we suggest that the stress-velocity relationship is a useful index to evaluate cardiac function in preterm infants in the early days of life.

5. Strategy to prevent IVH and/or pulmonary hemorrhage

Preterm infants frequently experience IVH or pulmonary hemorrhage that usually occurs within 72 hours after birth. The incidence rates of IVH and/or pulmonary hemorrhage have been reported to be higher in infants with cardiac dysfunction due to increased afterload.[39] According to the stress-velocity relationship (as described in Section 4.2), careful evaluation to keep the afterload at an acceptable level by vasodilator therapy may reduce or prevent these serious complications.

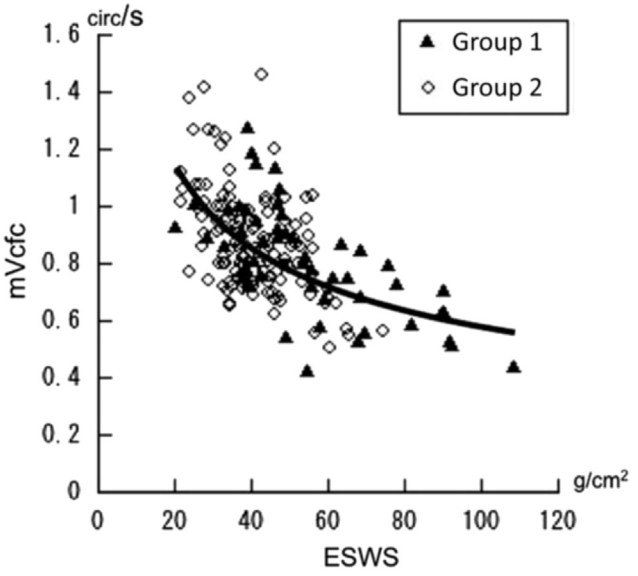

Figure 1 Stress-velocity relationship (mVcfc-ESWS relationship).[59] There were significant correlations between ESWS (an index of LV afterload) and mVcfc (an index of LV pump function) in both groups (mVcfc = 3.76 × ESWS-0.4; $p < 0.01$, R = 0.56). Group 1: infants with complications (pulmonary hemorrhage, intraventricular hemorrhage, and periventricular leukomalacia; $n = 9$). Group 2: infants without complications ($n = 24$). Systolic blood pressure (sBP) and mean blood pressure (mBP) changed over time, with no differences between the groups. ESWS, end-systolic wall stress; LV = left ventricle; mVcfc = mean velocity of circumferential fiber shortening. *Note*. From "Tailor-made circulatory management based on the stress-velocity relationship in preterm infants," by K. Toyoshima, M. Kawataki, M. Ohyama, J. Shibasaki, N. Yamaguchi, R. Hoshino, et al, 2013, *J Formos Med* Assoc, *112*, p. 510—7. Copyright 2013, Elsevier Taiwan LLC & Formosan Medical Association. Adapted with permission.

5.1. Germinal matrix: Venous origin of IVH

The subependymal germinal matrix is a fetus-specific component, and is the most common site of IVH. The germinal matrix increases in volume until about 26 gestational weeks and then begins to decrease, disappearing completely at around 34 weeks.[61,62]

The vein in the germinal matrix has poor supporting tissues and a thin vascular wall, and therefore is very susceptible to bleeding when the venous pressure increases. When bleeding occurs at the germinal matrix, periventricular veins will be occluded, and this congestion may extend to the periventricular parenchyma, causing periventricular hemorrhage (Grade 4 IVH).[62]

5.2. Relationship between increased left ventricular afterload and IVH

Cardiac dysfunction due to an increased afterload, as indicated by the stress-velocity relationship, has been reported to be associated with IVH in preterm infants.[39] To

cope with an increased afterload, preload to the heart is increased through preload reserve.[2,63] According to the ventricular interaction, the increase in left ventricular preload is very likely to be associated with an increase in right ventricular preload, that in turn is induced by an increase in central venous pressure, which then impedes systemic venous return and leads to an increase in cerebral venous pressure.[63] Finally, the fragile vein in the germinal matrix cannot tolerate the elevated intracardiac venous pressure, which induces germinal bleeding and IVH.

5.3. Increased LV afterload induces pulmonary hemorrhage

Cardiac dysfunction due to excessive afterload has also been associated with pulmonary hemorrhage in preterm infants.[39] Due to the preload reserve described in Section 5.2, an increased left ventricular afterload may induce an increase in left ventricular preload, which may in turn lead to an increase in pulmonary venous pressure, and finally cause hemorrhagic pulmonary edema.

5.4. Circulatory management based on the stress-velocity relationship in preterm infants to prevent IVH and pulmonary hemorrhage

Taken together, venous congestion is associated with IVH and pulmonary hemorrhage. Therefore, optimal circulatory management in preterm infants should be attempted to avoid increases in venous pressure caused by excessive afterload. Toyoshima et al[39] reported the outcomes of using circulatory management based on the stress-velocity relationship in preterm infants with a gestational age of 23 weeks or 24 weeks. This strategy emphasized the use of catecholamines restricted to infants with a blood pressure less than their gestational age and associated with poor perfusion as indicated by an inability to maintain urine volume, the development of metabolic acidosis, or continuous increases in lactic acid concentrations. The authors reported that cardiotonic therapy using catecholamines was indicated for cardiac pump dysfunction (ejection fraction $<$ 50% or mVcfc $<$ 0.8 circ/s) at an ESWS $<$ 40 g/cm^2 and that load reduction therapy was indicated for infants with cardiac pump dysfunction and an ESWS $>$ 45 g/cm^2, or in infants with an ESWS $<$ 45 g/cm^2 in whom there was a trend toward increased ESWS and decreased ejection fraction and mVcfc. In these infants, nitroglycerin at a dosage of 0.3 mg/kg/min was started, and the dosage was increased according to the efficacy. The authors reported that nitroglycerin treatment reduced afterload, even at a low dose (0.3—1.5 mg/kg/min), and did not affect the frequency or efficacy of indomethacin therapy. They also found that careful management to control excessive afterload improved morbidity and mortality in these extremely preterm infants. Furthermore, the incidence and severity of IVH and the survival rate improved, with a trend towards a decrease in mental retardation.

6. Management of significant PDA in preterm infants

6.1. Clinical implication of a significant PDA in preterm infants

PDA is a major morbidity in preterm infants, especially in extremely premature infants of $<$ 28 weeks. Persistent PDA shunting is associated with a range of adverse outcomes including necrotizing enterocolitis, IVH, pulmonary hemorrhage, chronic lung disease, and death.[64—68] However, neither individual trials nor meta-analyses have demonstrated better long-term neurodevelopmental outcomes with methods to close a PDA.[69,70] Therefore, the debate over whether or not to close a PDA is ongoing.

The most clinically important question seems to be how to change a hemodynamically significant PDA into a PDA that does not compromise the infant's circulation (either a decrease in size or fully closed). It is important that the decision to treat or not treat a PDA is made on a case by case basis, based on clinical findings and serial echocardiographic assessments of hemodynamic status rather than to depend only on a spot time measurement.[53,55—57]

The clinical signs and symptoms of PDA in preterm infants are nonspecific and insensitive to allow for an early diagnosis of significant ductal shunting. Functional echocardiography is emerging as a new valuable bedside tool for an early diagnosis of hemodynamically significant PDA, and it has also been used for early targeted treatment of ductus arteriosus.[55,58] Serial echocardiographic assessments can allow for significantly earlier identification and treatment of PDA compared to waiting for the evolution of clinical signs.[53,55,58] Severe IVH and the amount of time requiring ventilator support have been significantly decreased after the introduction of echocardiography.[58] In addition, the use of biomarkers such as B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide may be promising diagnostic tools when assessing the significance of PDA.[71,72]

The primary mode of treatment for PDA is pharmacological closure using cyclooxygenase inhibitors, with a closure rate of 70—80%. Randomized controlled trials of ibuprofen versus indomethacin in the early targeted treatment of PDA in preterm infants have shown that ibuprofen is as effective as indomethacin for the treatment of PDA without increasing the incidence rates of renal dysfunction or other complications.[55,56,58] Oral ibuprofen is emerging as a better alternative, especially in countries where intravenous indomethacin or ibuprofen are unavailable and because there are comparatively fewer side effects.[73] Although pharmacological closure of PDA is an established treatment modality, there is still a lack of evidence on the long-term benefits of such therapy, although there is evidence of possible adverse effects such as increased retinopathy of prematurity and chronic lung disease rates, especially if treated prophylactically.[69] Although prophylactic treatment is the best-studied regimen, improvements in short-term outcomes do not seem to improve the rate of survival without neurosensory impairment at 18 months.[74] Observations of very early postnatal hemodynamically significant PDA in extremely preterm infants suggest that targeting treatment on the

basis of the early postnatal constrictive response of the duct may be optimal.[52,53] Hence, it may be prudent to reserve treatment of PDA to infants with hemodynamically significant ductus on the basis of gestation, birth weight, serial echocardiography, and clinical status, and to make the decision to treat on a case by case basis.[55,58,69,70]

6.2. PDA and pulmonary hemorrhage and IVH

Around 24 hours after birth, pulmonary vascular resistance decreases and shunt flow through the ductus arteriosus increases rapidly to induce elevated preload. This condition has been reported to occur even more frequently in extremely preterm infants with RDS who receive supplementary surfactant treatment.[65–67] The left ventricle of preterm infants has low distensibility,[2,63] and pulmonary congestion may occur even when it is exposed to a relatively small increase in preload. An increase in left ventricular preload is manifested by an increase in pulmonary venous pressure and venous congestion, which in turn may lead to pulmonary hemorrhage. Preterm infants usually develop pulmonary hemorrhage at a mean age of around 36 hours, at which time they have significantly higher estimated pulmonary blood flow and significantly larger ducts, and therefore the clinical impact occurs early in life.[75]

It has been reported that ductal shunting is negatively associated with SBF, and that it occurs very early after birth during the vulnerable period of circulatory transition.[75] A significant association between early low SBF and the development of IVH and later necrotizing enterocolitis has also been noted, suggesting a possible mechanism by which PDA shunting partially causes these complications.

6.3. Early-targeted treatment of significant PDA

Taken together, for PDA treatment to be effective, it has to be given early after birth. Previous studies have reported that prophylactic treatment reduces the incidence of significant PDA, the need for rescue treatment and surgical ligation, but unnecessarily exposes a large number of infants to a drug that has important side effects (mainly affecting the kidneys) without conferring any significant short-term benefits.[74,76]

The protocol we use for significant PDA is early targeted treatment guided by echocardiographic PDA flow pattern rather than prophylactic prevention of PDA.[52,53,55] Preterm infants are treated as early as within the first 24 hours of life, and no increase has been found in the incidence of renal side effects or other severe complications. With this protocol, the PDA closure rate is around 88%, and the fewer number of doses (1.9 $\pm$ 1.5, mean $\pm$ standard deviation) of either ibuprofen or indomethacin may partially explain the lack of significant renal side effects.[55]

A recent study of the early treatment of PDA guided by echocardiographic ductal diameter reported that infants receiving early indomethacin treatment had a significantly lower rate of early pulmonary hemorrhage, a nonsignificant trend towards less IVH, and were less likely to receive later treatment for PDA.[77]

A strong correlation between early echocardiographic pulsed Doppler flow patterns and color Doppler ductal diameter has been noted. Both methods are significantly associated, and may be used as a cross-check to assist in the management of preterm infants with PDA. The addition of flow pattern classification to ductal diameter assessments may further enhance the clinical predictive ability of echocardiography.[56,78] We would like to highlight the importance of sequential echocardiographic assessments of the hemodynamic status of PDA rather than to depend only on spot time measurements.[57]

6.4. Surgical ligation of PDA

An increased trend of a less aggressive approach to ductal ligation has been reported, reflecting concerns that ligation of PDA may do more harm than good.[79] A retrospective comparative study reported the use of a conservative approach to treat asymptomatic PDA that failed to close after indomethacin treatment. In this strategy, the presence of a PDA was tolerable as long as signs of cardiopulmonary compromise did not develop, and was associated with a 28% decrease in the rate of ductus ligation with lower rates of necrotizing enterocolitis compared with early PDA ligation.[79] Several studies have shown acute, potentially detrimental hemodynamic effects after PDA ligation,[80,81] and in subanalysis of the Trial of Indomethacin Prophylaxis in Preterms (TIPP), babies who underwent surgical ligation had worse neurodevelopmental outcomes.[82]

Taken together, we suggest that PDA ligation should only be considered for infants who have echocardiographic evidence of a significant PDA, who have contraindications or have failed at least two courses of medical treatment, and who have cardiopulmonary compromise with progressive oxygen and ventilator demands.

7. Conclusions

Preterm infants frequently experience IVH or pulmonary hemorrhage, which usually occur within 72 hours after birth and can lead to long-term neurological impairments and mortality. As these serious hemorrhagic complications are closely related to perinatal hemodynamic changes, delayed umbilical cord clamping or umbilical cord milking to maintain optimal blood pressure and SBF, careful assessments to maintain the afterload at an acceptable level, and a strategy of early targeted treatment of significant PDA to improve perfusion during this critical time period may reduce or prevent these serious complications.

Conflicts of interest

All authors declare no potential conflicts of interest in relation to this work.

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