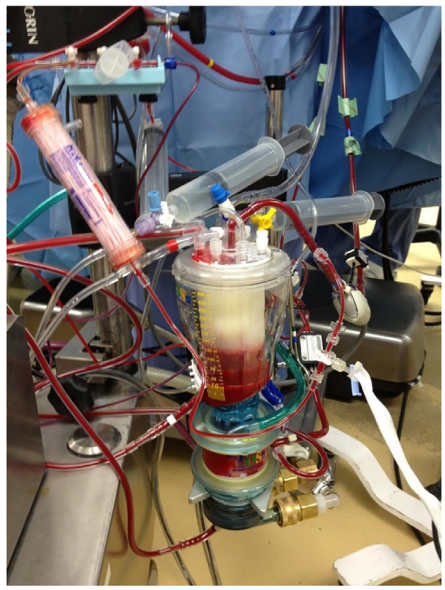
Cardiopulmonary Bypass in Premature and Low Birth Weight Neonates — Implications for Postoperative Care From a Neonatologist/ Intensivist Perspective

Ganga Krishnamurthy, MBBS

Prematurity and low weight remain significant risk factors for mortality after neonatal cardiac surgery despite steady gains in survival. Newer and lower weight thresholds for operability are constantly generated as surgeons gather proficiency, technical mastery, and experience in performing complex procedures on extremely small infants. Relationship between birth weight and survival after cardiac surgery is nonlinear with 2 kg being an inflection point below which marked decline in survival occurs. If strides toward improved survival in this weight category are to be made, understanding the inherent vulnerabilities of the premature and low birth weight infant is important in addition to acknowledging the vulnerabilities of the system in which care is delivered.

Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann 22:2—9 © 2019 Published by Elsevier Inc.

Keywords: Cardiopulmonary bypass, Low birth weight, Prematurity



Miniaturized circuit used for cardiopulmonary bypass.

Central Message

The inherent vulnerabilities of developing organ systems in premature infants are exposed after cardiac surgery. Understanding these functional limitations is critical in the pre- and postoperative management.

INTRODUCTION

Approximately 40,000 infants are born with congenital heart disease annually in the United States, and over 1 million babies are born every year worldwide [1—3]. Many of these infants will require surgery to correct or palliate their heart defect during their lifetime and some will require surgery in the newborn period. Continual advances in surgical and cardiopulmonary bypass techniques, as well as improved preoperative and postoperative management have resulted in a general decline in operative mortality across all age groups [4]. However, mortality rates after cardiac surgery remain highest among neonates, and higher still in those born prematurely, of low birth weight and with significant associated medical conditions or genetic syndromes [5—9].

Neonates born before 37 completed weeks of gestation are at greater risk of mortality after cardiac surgery than those born after 37 weeks [6,9,10]. However, the risk of death after 37 weeks is not uniformly equivalent. Population and single-center studies have revealed this phenomenon both in babies born with congenital heart disease and in those without [6,10,11]. There is an incremental decline in death rate from 37 to 40 weeks, with the nadir at 39—40 weeks [6]. Death rates increase again if delivery is delayed beyond 41 weeks. Prior to recent recommendations by the American College of Obstetricians and Gynecologists, fetuses with congenital heart disease were electively delivered at 37 weeks, this is often to allow better coordination of delivery, catheter intervention if necessary, and to avoid in utero demise [6]. Extending pregnancy from 37 to 38 weeks to 39—40 weeks provides a significant survival benefit and reduces the risk of complications [6]. Therefore, elective delivery of babies before 39 completed weeks of gestation, absent any obstetric or fetal risk, should be discouraged.

Division of Neonatology, Columbia University Medical Center, New York, New York

Address correspondence to: Ganga Krishnamurthy, MBBS, Columbia University Medical Center, West 168th Street, PH 17201-B, New York, NY 10032. E-mail: gk2008@cumc.columbia.edu

1092-9126/$—see front matter © 2019 Published by Elsevier Inc.
https://doi.org/10.1053/j.pcsu.2019.02.009

Term gestation is actually delineated by statistical probability and ranges from 37 to 42 weeks. Thirty-seven weeks is an entirely arbitrary beginning for term gestation and the period between the 2 limits represents a continuum where organ maturity continues. Therefore, babies born in the "early term" period are physiologically less mature than babies born at "late term." The exact physiological immaturity that places early term neonates at greater risk of mortality likely represents incomplete development of several organ systems. Even at "full term" (39, 40 weeks) and "late term" (41 weeks) birth, organ maturation is unlikely to be complete, but is a gradual process that continues for several months and years after birth.

Premature birth (prior to 37 weeks) and low birth weight (<2.5 kg) add substantial mortality risk before and after cardiac surgery [6–10]. Collectively, there is a 1.5–6-fold increase in cardiac surgical mortality in this population compared to infants born after 37 weeks with risk increasing at progressively lower gestational ages and lower birth weights [6,9]. Very premature (28–32 weeks) and extremely premature (<28 weeks gestational age) infants with severe congenital heart defects have a 5-fold increased risk of in-hospital mortality compared to very/extremely premature born infants born without congenital heart disease and nearly 2.5-fold increase in risk of mortality compared to infants born at term with congenital heart disease [8]. Presence of a cardiovascular malformation increases risk of mortality across all gestational ages but the additional or excess death risk due to cardiovascular lesion is most pronounced in term infants where mortality rates are low [12].

Multiple factors contribute to the increased mortality risk in premature and low birth weight infants. Lesions requiring surgery in the neonatal period are often quite complex. Technical challenges include tissue fragility, cannulation, and maintenance of adequate cardiopulmonary bypass. The performance of intricate procedures in tiny hearts requires superior technical skill and years of experience for mastery. Abnormal, preoperative circulation for several weeks to secure growth and weight gain and the effects of cardiopulmonary bypass on immature organ systems are additional factors that place premature and low birth weight neonates at greater risk for mortality and complications after surgery.

RECOGNIZING THE VULNERABILITIES OF THE PREMATURE/LOW BIRTH WEIGHT NEONATE

A summary of limitations of the various organ systems in premature and low birth weight (LBW) infants is provided below.

Cardiovascular

Postnatal Increase in Left Ventricular Output

At birth, the metabolic rate/oxygen consumption increases several-fold because of the additional demands imposed by heat conservation mechanisms and respiratory activity [13–15]. Oxygen delivery increases in a similar proportion to maintain normal oxygen reserve capacity. Much of the increase in oxygen delivery is attributed to a substantial increase in left ventricular output after birth. Enhanced left ventricular output is caused by an increase in heart rate, an increase in left ventricular preload, and greater inotropic state [16–18]. The exact mechanisms causing this postnatal increase in cardiac output are not completely known, but thyroid hormone is believed to play a role [19]. Fetal lambs in which the thyroid gland was removed 2 weeks before delivery demonstrated low plasma levels of T3 and failed to show the expected postnatal increase in T3 levels and cardiac output [19]. These same lambs had fewer β-adrenergic receptors on the myocardial surface and exhibited a blunted response to β-adrenergic stimulation [19]. Elevation in cortisol levels, a catecholamine surge, and relief from ventricular constrainment at delivery also contribute to the postnatal elevation in cardiac output [20–22].

Developmental Differences in Myocardial Structure and Excitation-Contraction Coupling

Generation of myocardial contractile force increases with maturation [23–25]. Developmental differences in contractility are mostly caused by age-related differences in myocardial structure. The immature myocyte is smaller and has greater intracellular spatial disorganization than its mature counterpart [25]. Also, a large proportion of the immature myocyte is inhabited by noncontractile organelles that do not contribute to force generation. The small, spherical structure of the immature myocyte and the central location of noncontractile elements imposes a biophysical disadvantage to shortening [25]. Immature myofibrils assume a random arrangement rather than the parallel arrangement seen in adult myocytes [24–26]. There are also far fewer myofilaments – the fundamental units of cross-bridge formation [24,25]. An increased number of myofilaments correlates with an increase in myocardial force generation [27]. Isoform switching of myofibrillar proteins with development also contributes to improved contractile efficiency with age [28,29].

The calcium handling mechanism in the neonate is both underdeveloped and inefficient [30–33]. The cytosolic calcium concentration is primarily dependent on trans-sarcolemmal flux of calcium as T-tubules and sarcoplasmic reticulum are scarce and intracellular calcium regulatory proteins are functionally immature [30–33].

Adult myocardium is densely innervated by a plexus of sympathetic nerves [34]. However, sympathetic innervation in neonatal myocardium is incomplete at birth and continues postnatally [34].

Cardiac stores of norepinephrine, a reflection of sympathetic innervation, is lowest in late-term fetuses but approaches adult levels by 4 weeks of age [35]. This is despite no significant quantitative difference between neonatal and adult β-adrenergic receptors on the myocardial cell surface [36,37]. Functional uncoupling of β receptor-G protein-adenylate cyclase complex in the newborn limits the effectiveness of catecholamine-modulated contractility in this age group [37].

Maturational changes in myocyte ultrastructure, calcium handling, and sympathetic innervation contribute to improved myocardial performance with age.

Neonatal Ventricular Performance

Ventricular performance improves with age. Circulatory adaptation at birth is vital to meet the increased metabolic demands of extrauterine life. An acute increase in heart rate, pulmonary venous return, and contractile state contributes to the postnatal enhancement in cardiac output. High-resting inotropes limit contractile reserve in newborns and immature hearts exhibit a blunted response to exogenous catecholamines compared with mature hearts [38,39]. Rate-dependent mechanisms to improve cardiac output are thus favored in neonates.

The immature heart has less recruitable preload reserve and only demonstrates a modest Frank-Starling relationship compared to the adult mature heart [40–42]. This limited response to volume loading is partly due to the decreased compliance of immature hearts. With age, maturational changes in cytoskeleton and extracellular matrix improve myocardial compliance [43,44].

Volume or pressure loading of 1 ventricle can impact filling of the contralateral ventricle to a greater extent in immature hearts than in more mature ones [45]. This restrictive effect is particularly evident in neonates who have endured an unfavorable postnatal transition and exhibit persistent fetal circulation. The pressure-loaded right ventricle alters septal dynamics and limits left ventricular filling and left ventricular stroke volume.

Increases in afterload profoundly diminish ventricular performance in the fetus and neonate [27]. When exposed to similar afterloads, the immature myocyte shortens to a lesser extent and more slowly than a mature myocyte. Developmental changes in myocyte architecture permits the adult heart to counteract afterload stressors more effectively [27].

Inherent limitations in cardiac mechanics of the premature heart as described previously are exposed with congenital heart defects. Neonates, particularly preterm neonates with severe outflow tract obstructions are limited in their ability to increase myocardial performance in the face of increased afterload. Lesions with left-to-right shunts require an increase in left ventricular output to maintain adequate systemic flow. Recruiting the Frank-Starling mechanism and increasing inotropic state accomplish much of the increased stroke work. Large shunts may overwhelm the limited preload and contractile reserves of the preterm heart.

Respiratory

Human lungs develop along 5 stages [46]. The terminal units — alveolar ducts and alveolar sacs necessary for gas exchange develop during the last 2 stages — saccular (24–36 weeks) and alveolar (36 weeks to early childhood) [46]. A term infant has approximately 50 million alveoli. Secondary septation of alveoli continues for several years beyond birth, to acquire the approximately 300 million alveolar units seen in adult lungs [46]. Lungs of premature babies are thus limited in their gas exchange functions and frequently require invasive or noninvasive respiratory support.

Respiratory distress syndrome (RDS) is unique to preterm infants. Underdeveloped lungs and deficient surfactant synthesis, secretion and function contribute to the disease. Surfactant, a unique mixture of phospholipids, neutral lipids, and proteins, lowers alveolar surface tension [47,48]. Incidence of RDS increases with decreasing gestational age with over 90% of infants born less than 28 weeks of gestation manifesting the disease [49,50]. Infants with RDS manifest symptoms of respiratory distress soon after birth. Unless modified by therapy, symptoms worsen over the first day or 2 before gradual improvement occurs, reflecting an increase in endogenous surfactant production and secretion. Our approach is to institute bubble nasal continuous positive airway pressure (nCPAP) with 5 cm of water pressure using nasal prongs soon after birth across all weight groups and gestational ages if signs of respiratory distress are present. Infants are allowed to breathe spontaneously, and threshold criteria for intubation and rescue surfactant replacement therapy are followed. Surfactant is reserved for infants who require mechanical ventilation, require fraction of inspired oxygen greater than 0.6 to maintain oxygen saturation above 90%, pCO_2 of >60 mm Hg or arterial pH less than 7.25. Threshold criteria for surfactant replacement differ among institutions with many favoring conservative set points and early rescue surfactant therapy.

Chest wall structure and limited diaphragmatic apposition introduces mechanical inefficiencies in ventilation in premature infants. The neonatal lung and chest wall possess variable compliances — the lungs are less compliant while the chest wall is extremely compliant [51]. This uncoupling predisposes the chest wall to deformational forces and much of the respiratory energy is expended in counteracting these forces [51]. Compensatory efforts with a higher resting respiratory rate are frequently overwhelmed and respiratory support is often required for several weeks after birth especially in extremely premature infants.

Renal

Nephrogenesis is completed at 35 weeks of gestation; however, structural and functional growth of the kidney continues for several months after birth [52]. The biggest limitation in renal function in the neonate is the rate of glomerular filtration, which, in the first few days of life, is one-third that seen in adults [53]. Tubular and medullary renal function limit the maximal urine concentrating ability of the newborn infant to half that of an adult [54]. The above functions are even more limited in premature babies who are thus more vulnerable to fluid overload or depletion than term born infants.

Temperature Regulation

Newborn infants, particularly those born prematurely are susceptible to hypothermia [55]. Their large surface area in relation to body weight permits greater heat loss than in older children. Neonates have only a modest ability to conserve heat in the presence of cold stressors [55,56]. Shivering thermogenesis is limited

in the first few weeks to months of life. Nonshivering mechanisms such as brown fat metabolism are recruited for heat production in neonates, but this increases oxygen consumption [55,56]. Therefore, neonates benefit from care in a thermoneutral environment – the temperature at which normal core temperature is maintained with minimal energy expenditure.

Immune System

Neonatal skin and mucosa are ineffective barriers and thus they are susceptible to infections. Immature cellular and humoral systems limit their ability to mount an effective immune response [57]. Particularly at risk are premature infants with long-standing indwelling venous catheters.

Gastrointestinal

Premature infants are limited in their ability to digest and absorb major and minor nutrients. Parenteral nutrition with high dextrose and protein contents are required for several weeks postnatally to mimic intrauterine growth rates. Necrotizing enterocolitis (NEC) is primarily a disease of premature infants, complicating the clinical course of 7–11% of very low birth weight infants (<1500 g) [49,58]. NEC occurs with increasing frequency with decreasing gestational age [58,59]. Although ischemic necrosis of the gut is the ultimate result, multiple factors influence the development of NEC in preterm infants. Interaction of milk (formula) substrate in the intestinal lumen, abnormal gut microbial colonization, and impaired innate host immunity leads to excessive inflammatory response and breach of a vulnerable intestinal epithelial barrier [58].

Presence of congenital heart disease substantially increases the risk of NEC. The incidence of NEC in these patients is approximately 3%; several-fold higher than the baseline risk of 0.3–3/1000 in live born infants [60]. Although all infants with congenital heart disease are at risk for NEC, the risk is considerably higher in patients with hypoplastic left heart syndrome, truncus arteriosus or aortopulmonary window and in those who are born prematurely or very low birth weight [60,61].

The benefits of early enteral feedings in preterm and term infants have been well established and are well recognized. Despite this, there is a lack of consensus on providing enteral nutrition to infants with ductal-dependent circulations and a wide variation in preoperative enteral feeding practices exists [62]. Almost 50% of caregivers in the United States do not provide enteral feedings to infants receiving PGE-1 infusion despite lack of convincing evidence that PGE-1 use increases risk of NEC [60,62,63]. The incidence of preoperative NEC was 0.3% in a large cohort of CHD infants who received PGE-1 and was not influenced by enteral feeding [63].

Central Nervous System

Intraventricular Hemorrhage

Twenty to twenty-five percent of very low birth weight infants develop intraventricular hemorrhage (IVH) [64]. Severe grades of IVH are seen in 10–15% of very low birth weight infants [49]. Survivors of severe IVH are at high risk of neurodevelopment impairment including cerebral palsy and mental retardation [64]. IVH is graded from I to IV depending upon the severity of ventricular bleeding and parenchymal extension [65]. Grade 1 IVH is restricted to the germinal matrix and grade IV is associated with parenchymal hemorrhagic infarction [65]. Grades III and IV are considered severe IVH and portend worse neurologic outcomes than grades I and II [64]. Pathogenesis of IVH is multifactorial and includes fragility of the germinal matrix and fluctuations in cerebral blood flow, which causes rupture of the germinal matrix [64]. As severe IVH has devastating consequences, prevention is key. Interventions that have proven efficacy in reducing IVH include maternal corticosteroids, delivery at a regional neonatal center, delayed cord clamping and indomethacin [64]. Although untested in trials, avoidance of events that result in perturbation in cerebral blood flow could potentially decrease risk of IVH [64].

Neurologic Injury and Impaired Brain Development in Premature Infants

Twenty-five to fifty percent of very low birth weight infants are at risk for subsequent development of cognitive, behavioral, attention, and socialization deficits. The neurodevelopmental sequelae are a consequence of brain injury causing a perturbation in the active brain developmental processes that occur between 24 and 40 weeks of gestation. Factors inherent in premature infants including limited cerebral autoregulatory function, susceptibility to infections and inflammatory processes, in addition to sensitivity to oxidative cellular injury make them more vulnerable to brain injury.

PREMATURE INFANTS AND CARDIOPULMONARY BYPASS

The functional limitations of the premature baby must be recognized in the operating room. The damaging effects of cardiopulmonary bypass including hemodilution, systemic inflammation, and bleeding are more pronounced in premature neonates than in term neonates, older children, and adults [66].

The total blood volume in term preterm neonates is approximately 80–90 ml/kg [67]. The priming volume of the extracorporeal circuit may be as high as 2 or 3 times the circulating blood volume of the neonate. This disparity between the circulating blood volume and bypass circuit size results in marked hemodilution causing anemia, hypoproteinemia, and a reduction in coagulation factors unless priming solution and circuitry is optimized for the preterm infant. Significant hypoproteinemia can lead to greater transflux of fluid into the extracellular space from the intravascular compartment.

Surgical trauma and extracorporeal circulation triggers an exuberant systemic inflammatory response, the adverse effects of which are more pronounced on the immature organ systems of premature neonates [66,68]. Others and we employ several strategies to counteract the damaging effects of cardiopulmonary bypass on premature neonates [69]. Reducing the extracorporeal circuitry by deploying tubes of smaller length and

diameter and decreasing distance of circuit from surgical table miniaturizes circuits. Such small circuits decrease the artificial surface area of exposure and offer the additional advantage of requiring a smaller priming volume. Other strategies include maintenance of a higher oncotic pressure in the bypass circuit, use of anti-inflammatory agents like corticosteroids, and removal of inflammatory mediators by continuous or modified ultrafiltration [69].

Exposure to cardiopulmonary bypass may result in surfactant dysfunction although there is no evidence that surfactant replacement offers any benefit [70–73]. Effects of hemodilution and inflammation are more pronounced in the preterm neonate. Postoperative "capillary leak syndrome" is more likely in this patient population.

IMPLICATIONS FOR POSTOPERATIVE CARE

The immature organ systems and the deleterious effects of cardiopulmonary bypass have been described in previous paragraphs. Cardiac surgery exposes the limited reserves of the premature neonate. Myocardial edema and ischemia-reperfusion injury after cardiac surgery decreases ventricular performance. Despite mounting a robust sympathoadrenal response during surgery, the immature neonatal heart is limited in its ability to augment ventricular performance [74,75]. Therefore, exogenous infusions of inotropes are required to enhance contractile state after separation from cardiopulmonary bypass. The inotropic response with exogenous agents is lesser in preterm and term neonates than in older children due to the high baseline adrenergic state [39].

There are no clear advantages of 1 inotrope combination over another and institutional choices determine practice. Dopamine exerts its cardiovascular, renal, and hormonal effects in a dose-dependent manner [76–78]. In older children and adults, renal effects predominate at low doses. Moderate doses (5–10 mcg/kg/min) stimulate cardiac adrenergic receptors and increase cardiac output while doses higher than10 mcg/kg/min stimulate vascular α-adrenergic receptors and increase systemic vascular resistance. Maturational differences in the expression and sensitivity of α- and β-adrenergic receptors in the neonate make the response to dopamine less predictable, particularly in the preterm neonate [76,79,80]. Therefore, α-adrenergic stimulation and increase in systemic vascular resistance may become apparent at low doses [76,79,80]. Metabolism and elimination of dopamine is a complex process and wide interindividual variations in clearance are noted [76,79–81]. Reduced dopamine clearances in premature neonates and patients with hepatic and/or renal failure may make the cardiovascular response to conventional dosing more difficult to predict [76,79,80]. Finally, dopamine exerts its effects on the heart in part by releasing norepinephrine from nerve terminals. Hence, it may be less effective when myocardial norepinephrine stores are depleted or low as seen in immature hearts [34,35].

Effects of epinephrine on β- and α-adrenergic receptors make it a good choice for postcardiac surgery patients with diminished cardiac function and vascular tone. However, there are limited data on cardiovascular effects of epinephrine in neonates. Metabolic effects of epinephrine like hyperlactatemia and hyperglycemia warrant cautious use [82]. Neonates are more susceptible to myocardial damage and necrosis after prolonged high-dose infusions of epinephrine [83]. Milrinone has several positive modulating effects on ventricular performance [79,84,85]. Decreased milrinone clearance in the setting of renal insufficiency may cause systemic hypotension. Premature neonates are particularly vulnerable as they have a low baseline glomerular filtration rate.

It is not uncommon for preterm neonates to develop catecholamine-resistant hypotension after cardiac surgery [86]. Downregulation of adrenergic receptors and relative insufficiency or resistance to corticosteroid action are speculated mechanisms for catecholamine resistance [86,87]. Hydrocortisone administration in these cases induces a dramatic improvement in hemodynamics through its genomic and nongenomic effects [86,88–90]. Finally, exploiting the Frank-Starling relationship to improve stroke volume may be less effective in preterm neonates due to decreased myocardial compliance and mismatch of afterload to contractile state [42].

Transcapillary fluid shifts, bleeding, and osmotic diuresis can deplete circulating volume and decrease venous return. Dynamic and static assessments of volume status and fluid responsiveness are often employed in older children and adults [91,92]. There are no perfect measures to assess intravascular volume status in neonates. Single point measurements of right atrial pressure are uninformative of volume status [93]. Despite this, most intensivists use right atrial pressure or central venous pressure to guide fluid therapy [94,95].

In the absence of bleeding, choice of replacement fluid for correction of hypovolemia is not clear [96]. There are no convincing data that 4–5% albumin secures sustained improvement in hemodynamics compared to 0.9% saline either in adults or in preterm neonates [96–99]. The postoperative course is more often than not accompanied by transcapillary fluid shifts [100]. Fluid shifts can be quite pronounced in preterm neonates if there is a concurrent leakage of albumin into the interstitial space. Attempts to maintain intravascular volume by increasing circulating albumin levels in such a "leaky" circulation may precipitate pulmonary edema particularly in premature infants with lung disease [101]. Spontaneous fluid mobilization from the extracellular space is accomplished by encouraging lymph flow. Lymph flow increases with muscle contraction and spontaneous breathing. It is our practice to allow early resumption of spontaneous respiratory and physical activity and avoidance of muscle relaxation when possible to improve mobilization of fluid.

Neonatal ventilator modes, that is pressure limited, time cycled, are employed at our center in the postoperative period. Transition to nCPAP maintains functional residual capacity, decreases the work of breathing, and has the advantage of permitting earlier extubation. In our institution, extubation to "bubble" CPAP is favored compared to constant pressure

ventilator-derived CPAP. Bubble-CPAP enhances gas exchange, lung mechanics, gas mixing efficiency, and lung volume compared with constant pressure CPAP [102,103]. Ventilator strategies favorable to premature lungs and chest wall should be employed. High peak inspiratory or high tidal volumes as described previously are particularly injurious to immature lungs and should be avoided. Positive end expiratory pressure stabilizes the highly compliant chest wall and maintains functional residual capacity. Oxygen should be used cautiously as it can worsen retinopathy of prematurity and bronchopulmonary dysplasia. Finally, maintenance of core temperature is crucial, premature infants are prone to hypothermia due to their thin skin and a relatively greater body surface area.

OPTIMAL TIMING OF SURGERY IN LBW AND PREMATURE INFANTS

The optimal timing to perform surgery on this inherently vulnerable population is unclear. Waiting for weight gain adds risk associated with waiting including the effects of unrepaired cardiovascular physiology on developing organs, infection, and other complications. The most prudent strategy appears to be to weigh the risk of pursuing an early vs delayed surgical approach on each patient on a case by case basis.

RECOGNIZING THE INHERENT VULNERABILITIES OF THE SYSTEM

Most newborn infants and children with congenital heart disease receive care in dedicated cardiac intensive care units or in pediatric cardiac intensive care units. In general, practitioners in these units are unfamiliar with the physiology and challenges of the premature or low birth weight infants. Neonatologists who have the most expertise with this patient population are unfortunately excluded or are not engaged. A collaborative model where the expertise of neonatologists is valued would be profoundly beneficial to these patients and should be encouraged.

CONCLUSION

Developing organ systems in premature and low birth weight infants exposes unique and inherent vulnerabilities. Extrinsic stressors including cardiac surgery and cardiopulmonary bypass can easily overwhelm the immature body. Understanding these intrinsic deficiencies of premature infants is critical in the pre- and postoperative management of these patients.

REFERENCES

[1] Hoffman JI, Kaplan S: The incidence of congenital heart disease. J Am Coll Cardiol 2002;39:1890–1900

[2] Botto LD, Correa A, Erickson JD: Racial and temporal variations in the prevalence of heart defects. Pediatrics 2002;107:E32

[3] van der Linde D, Konings EE, Slager MA, et al: Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol 2011;58:2241–2427

[4] Kaltman JR, Andropoulos DB, Checchia PA, et al: Report of the pediatric heart network and national heart, lung, and blood institute working group on the perioperative management of congenital heart disease. Circulation 2010;121:2766–2772

[5] Curzon CL, Milford-Beland S, Li JS, et al: Cardiac surgery in infants with low birth weight is associated with increased mortality: analysis of the Society of Thoracic Surgeons Congenital Heart Database. J Thorac Cardiovasc Surg 2008;135:546–551

[6] Costello JM, Polito A, Brown DW, et al: Birth before 39 weeks' gestation is associated with worse outcomes in neonates with heart disease. Pediatrics 2010;126:277–284

[7] Kalfa D, Krishnamurthy G, Duchon J, Najjar M, Levasseur S, Chai P, et al: Outcomes of cardiac surgery in patients weighing <2.5 kg: affect of patient-dependent and -independent variables. J Thorac Cardiovasc Surg 2014;148:2499–2506, e1

[8] Chu PY, Li JS, Kosinski AJ, et al: Congenital heart disease in premature infants 25-32 weeks gestational age. J Pediatr 2017;181:37–41

[9] Manchego PA, Cheung M, Zannino D, et al: Audit of cardiac surgery outcomes for low birth weight and premature infants. Semin Thorac Surg 2018;30:71–78

[10] Cnota JF, Gupta R, Michelfelder EC, Ittenbach RF: Congenital heart disease infant death rates decrease as gestational age advances from 34 to 40 weeks. J Pediatr 2011;159:761–765

[11] Tita AT, Landon MB, Spong CY, et al: Timing of elective repeat cesarean delivery at term and neonatal outcomes. N Engl J Med 2009;360:111–120

[12] Tanner K, Sabrine N, Wren C: Cardiovascular malformations among preterm infants. Pediatrics 2005;116:e833–e838

[13] Singer D, Muhlfeld C: Perinatal adaptation in mammals: the impact of metabolic rate. Comp Biochem Physiol A Mol Integr Physiol 2007;148:780–784

[14] Dawes GS, Mott JC: The increase in oxygen consumption of the lamb after birth. J Physiol 1959;146:295–315

[15] Hill JR, Rahimtulla KA: Heat balance and the metabolic rate of new-born babies in relation to environmental temperature; and the effect of age and of weight on basal metabolic rate. J Physiol 1965;180:239–265

[16] Anderson PA, Glick KL, Manring A, et al: Developmental changes in cardiac contractility in fetal and postnatal sheep: in vitro and in vivo. Am J Physiol 1984;247(3 Pt 2):H371–H379

[17] Anderson PA, Manring A, Glick KL, et al: Biophysics of the developing heart. III. A comparison of the left ventricular dynamics of the fetal and neonatal lamb heart. Am J Obstet Gynecol 1982;143:195–203

[18] Riemenschneider TA, Brenner RA, Mason DT: Maturational changes in myocardial contractile state of newborn lambs. Pediatr Res 1981;15(4 Pt 1):349–356

[19] Breall JA, Rudolph AM, Heymann MA: Role of thyroid hormone in postnatal circulatory and metabolic adjustments. J Clin Invest 1984;73:1418–1424

[20] Grant DA, Kondo CS, Maloney JE, et al: Changes in pericardial pressure during the perinatal period. Circulation 1992;86:1615–1621

[21] Grant DA: Ventricular constraint in the fetus and newborn. Can J Cardiol 1999;15:95–104

[22] Murphy BE: Human fetal serum cortisol levels related to gestational age: evidence of a midgestational fall and a steep late gestational rise, independent of sex or mode of delivery. Am J Obstet Gynecol 1982;144:276–282

[23] Davies P, Dewar J, Tynan M, et al: Post-natal developmental changes in the length-tension relationship of cat papillary muscles. J Physiol 1975;253:95–102

[24] Sheridan DJ, Cullen MJ, Tynan MJ: Qualitative and quantitative observations on ultrastructural changes during postnatal development in the cat myocardium. J Mol Cell Cardiol 1979;11:1173–1181

[25] Nassar R, Reedy MC, Anderson PA: Developmental changes in the ultrastructure and sarcomere shortening of the isolated rabbit ventricular myocyte. Circ Res 1987;61:465–483

[26] Anderson PA: The heart and development. Semin Perinatol 1996;20:482–509

[27] Friedman WF: The intrinsic physiologic properties of the developing heart. Prog Cardiovasc Dis 1972;15:87–111

[28] Lompre AM, Mercadier JJ, Wisnewsky C, et al: Species- and age-dependent changes in the relative amounts of cardiac myosin isoenzymes in mammals. Dev Biol 1981;84:286–290
[29] Cummins P, Lambert SJ: Myosin transitions in the bovine and human heart. A developmental and anatomical study of heavy and light chain subunits in the atrium and ventricle. Circ Res 1986;58:846–858
[30] Balaguru D, Haddock PS, Puglisi JL, et al: Role of the sarcoplasmic reticulum in contraction and relaxation of immature rabbit ventricular myocytes. J Mol Cell Cardiol 1997;29:2747–2757
[31] Mahony L: Maturation of calcium transport in cardiac sarcoplasmic reticulum. Pediatr Res 1988;24:639–643
[32] Mahony L, Jones LR: Developmental changes in cardiac sarcoplasmic reticulum in sheep. J Biol Chem 1986;261:15257–15265
[33] Pegg W, Michalak M: Differentiation of sarcoplasmic reticulum during cardiac myogenesis. Am J Physiol 1987;252(1 Pt 2):H22–H31
[34] Friedman WF, Pool PE, Jacobowitz D, et al: Sympathetic innervation of the developing rabbit heart. Biochemical and histochemical comparisons of fetal, neonatal, and adult myocardium. Circ Res 1968;23:25–32
[35] Braunwald E, Chidsey CA, Harrison DC, et al: Studies on the function of the adrenergic nerve endings in the heart. Circulation 1963;28:958–969
[36] Kojima M, Sperelakis N, Sada H: Ontogenesis of transmembrane signaling systems for control of cardiac Ca^{2+} channels. J Dev Physiol 1990;14:181–219
[37] Robinson RB: Autonomic receptor—effector coupling during post-natal development. Cardiovasc Res 1996;31(Spec No):E68–E76
[38] Artman M, Kithas PA, Wike JS: Inotropic responses change during postnatal maturation in rabbit. Am J Physiol 1988;255(2 Pt 2):H335–H342
[39] Teitel DF, Sidi D, Chin T, et al: Developmental changes in myocardial contractile reserve in the lamb. Pediatr Res 1985;19:948–955
[40] Downing SE, Talner NS, Gardner TH: Ventricular function in the newborn lamb. Am J Physiol 1965;208:931–937
[41] Kirkpatrick SE, Pitlick PT, Naliboff J, et al: Frank-Starling relationship as an important determinant of fetal cardiac output. Am J Physiol 1976;231:495–500
[42] Riemenschneider TA, Allen HD, Mason DT: Maturational changes in myocardial pump performance in newborn lambs. Am Heart J 1986;111:731–736
[43] Brady AJ: Mechanical properties of isolated cardiac myocytes. Physiol Rev 1991;71:413–428
[44] Granzier HL, Irving TC: Passive tension in cardiac muscle: contribution of collagen, titin, microtubules, and intermediate filaments. Biophys J 1995;68:1027–1044
[45] Romero T, Covell J, Friedman WF: A comparison of pressure-volume relations of the fetal, newborn, and adult heart. Am J Physiol 1972;222:1285–1290
[46] Wu S: Molecular bases for lung development, injury, and repair. In: Bancalari E, ed. The Newborn Lung. ed 2, Philadelphia: Elsevier Saunders; 2012:3–27
[47] Jobe AH: Why surfactant works for respiratory distress syndrome. Neoreviews 2006;7:e95–e106
[48] Jobe A: Surfactant for respiratory distress syndrome. Neoreviews 2014;15:e236–e245
[49] Stoll BJ, Hansen NI, Bell EF, et al: Neonatal outcomes of extremely premature infants from the NICHD neonatal research network. Pediatrics 2010;126:443–456
[50] Warren JB, Anderson JM: Core concepts: respiratory distress syndrome. Neoreviews 2009;10:e351–e361
[51] Papastamelos C, Panitch HB, England SE, Allen JL: Developmental changes in chest wall compliance in infancy and early childhood. J Appl Physiol 1995;78:179–184
[52] Vogt BA, Mac Rae Dell K, Davis ID: The kidney and urinary tract. In: Fanaroff AA, Martin RJ, eds. Neonatal Perinatal Medicine Diseases of the Fetus and Infant. ed 8. Philadelphia, PA: Mosby Elsevier; 2006:1659–1683
[53] Chevalier RL, Norwood VF: Functional development of the kidney in utero. In: Polin RA, Fox WW, Abman SH, eds. Fetal and Neonatal Physiology. ed 4. Philadelphia, PA: Elsevier Saunders; 2011:1316–1322
[54] Polacek E, Vocel J, Neugebauerova L, et al: The osmotic concentrating ability in healthy infants and children. Arch Dis Child 1965;40:291–295
[55] Power GG, Blood AB: Perinatal thermal physiology. In: Polin RA, Fox WW, Abman SH, eds. Fetal and Neonatal Physiology. ed 4. Philadelphia, PA: Elsevier Saunders; 2011:615–624
[56] Sahni R SK: Temperature control in newborn infants. In: Polin RA, Fox WW, Abman SH, eds. Fetal and Neonatal Physiology. ed 4. Philadelphia, PA: Elsevier Saunders; 2011:624–648
[57] Kapur R, Yoder MC, Polin RA: Developmental immunology. In: Fanaroff AA, Martin RJ, eds. Neonatal Perinatal Medicine Diseases of the Fetus and Infant. ed 8. Philadelphia, PA: Mosby Elsevier; 2006:761–882
[58] Sharma R, Hudak ML: A clinical perspective of necrotizing enterocolitis. Clin Perinatol 2013;40:27–51
[59] Sharma R, Hudak ML, Tepas 3rd JJ, et al: Impact of gestational age on the clinical presentation and surgical outcome of necrotizing enterocolitis. J Perinatol 2006;26:342–347
[60] McElhinney D, Hedrick HL, Bush DM, et al: Necrotizing enterocolitis in neonates with congenital heart disease: risk factors and outcomes. Pediatrics 2000;106:1080–1087
[61] Fisher JG, Bairdain S, Sparks EA, et al: Serious Congenital heart disease and necrotizing enterocolitis in very low birth weight neonates. J Am Coll Surg 2015;220:1018–1026
[62] Howley LW, Kaufman J, Wymore E, et al: Enteral feeding in neonates with prostaglandin-dependent congenital heart disease: international survey on current trends and variation in practice. Cardiol Young 2012;22:121–127
[63] Becker KC, Hornik CP, Cotton CM, et al: Necrotizing enterocolitis in infants with ductal-dependent congenital heart disease. Am J Perinatol 2015;32:633–638
[64] Ballabh P: Pathogenesis and prevention of intraventricular hemorrhage. Clin Perinatol 2014;41:47–67
[65] Volpe JJ: Intracranial hemorrhage: germinal matrix-intraventricular hemorrhage. Neurology of the Newborn. 5th ed. Philadelphia, PA: Elsevier; 2008
[66] Levy JH, Tanaka KA: Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 2003;75:715–720
[67] Usher R, Shephardz M, Lind J: The blood volume of the newborn infant and placental transfusion. Acta Pediatrica 1963;52:497–512
[68] Paparella D, Yau TM, Young E: Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002;21:232–244
[69] Shen I, Giacomuzzi C, Ungerleider RM: Current strategies for optimizing the use of cardiopulmonary bypass in neonates and infants. Ann Thorac Surg 2003;75:729–734
[70] McGowan Jr FX, Ikegami M, del Nido PJ, et al: Cardiopulmonary bypass significantly reduces surfactant activity in children. J Thorac Cardiovasc Surg 1993;106:968–977
[71] Paul DA, Greenspan JS, David DA, et al: The role of cardiopulmonary bypass and surfactant decompensation after surgery for congenital heart disease. J Thorac Cardiovasc Surg 1999;117:1025–1026
[72] Griese M, Wilnammer C, Jansen S, et al: Cardiopulmonary bypass reduces pulmonary surfactant activity in infants. J Thorac Cardiovasc Surg 1999;118:237–244
[73] Friedrich B, Schmidt R, Reiss I, et al: Changes in biochemical and biophysical surfactant properties with cardiopulmonary bypass in children. Crit Care Med 2003;31:284–290
[74] Anand AJS, Hansen DD, Hickey PR: Hormonal-metabolic stress responses in neonates undergoing cardiac surgery. Anesthesiology 1991;73:661–670

[75] Sun LS, Du F, Schechter WS, et al: Plasma neuropeptide Y and catecholamines in pediatric patients undergoing cardiac operations. J Thorac Cardiovasc Surg 1997;113:278–284
[76] Seri I: Cardiovascular, renal and endocrine actions of dopamine in neonates and children. J Pediatr 1995;126:333–344
[77] Driscoll DJ, Gillette PC, McNamara DG: The use of dopamine in children. J Pediatr 1978;92:309–314
[78] Lang P, Williams RG, Norwood WI, et al: The hemodynamic effects of dopamine in infants after corrective cardiac surgery. J Pediatr 1980;96:630–633
[79] Noori S, Seri I: Neonatal blood pressure support: the use of inotropes, lusiotropes and other vasopressor agents. Clin Perinatol 2012;39:221–238
[80] Seri I, Rudas G, Bors Z, et al: Effects of low-dose dopamine infusion on cardiovascular and renal functions, cerebral blood flow, and plasma catecholamine levels in sick preterm neonates. Pediatr Res 1993;34:742–749
[81] Bhatt-Mehta V, Nahata MC, McClead RE, et al: Dopamine pharmacokinetics in critically ill newborn infants. Eur J Clin Pharmacol 1991;40:593–597
[82] Valverde E, Pellicer A, Madero R, et al: Dopamine versus epinephrine for cardiovascular support in low birth weight infants: analysis of systemic effects and neonatal clinical outcomes. Pediatrics 2006;117:e1213–e1222
[83] Caspi J, Coles JG, Benson LN, et al: Age-related response to epinephrine-induced myocardial stress. A functional and ultrastructural study. Circulation 1991;84:III394–III399
[84] Chang AC, Atz AM, Wernovsky G, et al: Milrinone: systemic and pulmonary hemodynamic effects in neonates after cardiac surgery. Crit Care Med 1995;23:1907–1914
[85] Hoffman TM, Wernovsky G, Atz AM, et al: Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation 2003;107:996–1002
[86] Souminen PK, Dickerson HA, Moffett BS, et al: Hemodynamic effects of rescue protocol hydrocortisone in neonates with low cardiac output syndrome after cardiac surgery. Pediatr Crit Care Med 2005;6:655–659
[87] Landry DW, Oliver JA: The pathogenesis of vasodilatory shock. N Engl J Med 2001;345:588–595
[88] Sassidharan P: Role of corticosteroids in neonatal blood pressure homeostasis. Clin Perinatol 1998;25:723–740
[89] Seri I, Tan R, Evans J: Cardiovascular effects of hydrocortisone in preterm infants with pressor-resistant hypotension. Pediatrics 2001;107:1070–1074
[90] Shore S, Nelson DP, Pearl JM, et al: Usefulness of corticosteroid therapy in decreasing epinephrine requirements in critically ill infants with congenital heart disease. Am J Cardiol 2001;88:591–594
[91] Singh S, Ware G, Kuschner WG, et al: Perioperative intravascular fluid assessment and monitoring: a narrative review of established and emerging techniques. Anesthesiol Res Pract 2011;2011:231493
[92] Marik PE, Monnet X, Teboul JL: Hemodynamic parameters to guide fluid therapy. Ann Intensive Care 2011;1:1
[93] Marik PE, Baram M, Vahid B: Does the central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest 2008;134:172–178
[94] Boldt J, Lenz M, Kumle B, et al: Volume replacement strategies on intensive care units: results from a postal survey. Intensive Care Med 1998;24:147–151
[95] Kastrup M, Markewitz A, Spies C, et al: Current practice of hemodynamic monitoring and vasopressor and inotropic therapy in post-operative cardiac surgery patients in Germany: results from a postal survey. Acta Anaesthesiol Scand 2007;51:347–358
[96] The SAFE Study Investigators. Comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;350:2247–2256
[97] So KW, Fok TF, Ng PC, et al: Randomized controlled trial of colloid or crystalloid in hypotensive preterm infants. Arch Dis Child Fetal Neonatal Ed 1997;76:F43–F46
[98] Oca MJ, Nelson M, Donn SM: Randomized trial of normal saline versus 5% albumin for the treatment of neonatal hypotension. J Perinatol 2003;23:473–476
[99] Lynch SK, Mullett MD, Graeber JE, et al: A comparison of albumin-bolus therapy versus normal saline-bolus therapy for hypotension in neonates. J Perinatol 2008;28:29–33
[100] Brans YW, Dweck HS, Harris HB, et al: Effect of open heart surgery on the body composition of infants and young children. Pediatr Res 1981;15:1024–1028
[101] Watts CL, Bruce MC: Comparison of secretory component for immunoglobulin A with albumin as reference proteins in tracheal aspirate from preterm infants. J Pediatr 1995;127:113–122
[102] Lee KS, Dunn MS, Fenwick M, et al: A comparison of underwater bubble continuous positive airway pressure with ventilator-derived continuous positive airway pressure in premature neonates ready for extubation. Biol Neonate 1998;73:69–75
[103] Pillow JJ, Hillman N, Moss TJM: Bubble continuous positive airway pressure enhances lung volume and gas exchange in preterm lambs. Am J Respir Crit Care Med 2007;176:63–69