Adult Cardiovascular Health Risk and Cardiovascular Phenotypes of Prematurity

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Survival of extremely low birth weight (ELBW) infants has improved dramatically over the past 20 years.[1] The nature of these advances is multifactorial and relates to increased appreciation of organ vulnerability, improved understanding of disease mechanisms, enhanced diagnostic precision, and improved therapeutic options. Unfortunately, the advances that underlie enhanced survival do not guarantee avoidance of neonatal morbidity or adverse long-term outcomes. In addition, life-saving treatments may have unintended negative effects on organ development and performance. Recent evidence highlights the relationship between prematurity and increased risk of adverse cardiovascular health during infancy, childhood, and early adulthood, even in healthy and later-term premature infants.[2] These consequences are likely to be attributable, at least in part, to early postnatal cardiac remodeling, insults to the developing vasculature, and alterations in cardiovascular control. We suspect that lung diseases of prematurity and their therapeutic interventions play an important modulator role. Epidemiologic evidence supports adverse cardiovascular health, including heart failure, ischemic heart disease, cardiometabolic impairment, systemic hypertension, and pulmonary vascular disease (PVD) in adult survivors of prematurity.[3] As a result, some investigators have begun to explore the importance of lifestyle modifications through different developmental stages to reduce overall cardiovascular risk.[4]

A clinically meaningful correlation likely exists between the degree of prematurity and adult cardiac performance that has major implications for life-long cardiovascular health. Major knowledge gaps exist regarding the relative influence of exposures encountered during the perinatal period vs the postnatal period and the physiological nature of putative contributors to cardiac health and development. The immature cardiovascular system is impacted by early life events, which modulate the risk of poor cardiovascular outcomes. In addition, long-term cardiovascular consequences are likely linked to phenotypes that develop during the neonatal period (**Figure 1**). We propose that understanding how early life events impact cardiovascular development and physiology is valuable for reducing overall risk. In this review, we highlight the developmental vulnerability of the preterm cardiovascular system; appraise relevant neonatal comorbidities and their impacts on heart function, vascular performance, and cardiovascular control; and explore evidence for interventions that may lead to dysregulation of normal development. Based on the putative link between abnormal development and the long-term risk of adverse cardiovascular development, we propose the need for routine standardized frameworks for assessing and monitoring cardiovascular phenotypes in premature infants. Postdischarge care and scientific adjudication of the efficacy of treatments in the neonatal period have traditionally focused on neurodevelopmental health, with little consideration of childhood or adult cardiopulmonary outcomes. It is now incumbent on clinicians and researchers with expertise in this domain to educate providers on the health risks beyond the neonatal intensive care unit (NICU), set research priorities, and explore opportunities for innovation.

BP	Blood pressure
BPD	Bronchopulmonary dysplasia
DA	Ductus arteriosus
ELBW	Extremely low birth weight
FGR	Fetal growth restriction
iNO	Inhaled nitric oxide
LV	Left ventricular
LVH	Left ventricular hypertrophy
NICU	Neonatal intensive care unit
PA	Pulmonary artery
PH	Pulmonary hypertension
PVD	Pulmonary vascular disease
PVR	Pulmonary vascular resistance
RV	Right ventricular
TnECHO	Targeted neonatal echocardiography

Developmental Vulnerability of the ELBW Infant

Many mechanistic studies of fetal/neonatal development and the impact of perinatal stressors on growth have been conducted in animal models that require premature delivery of the fetus, including rat,[5] lamb,[6] pig,[7] and primates.[8] Animal

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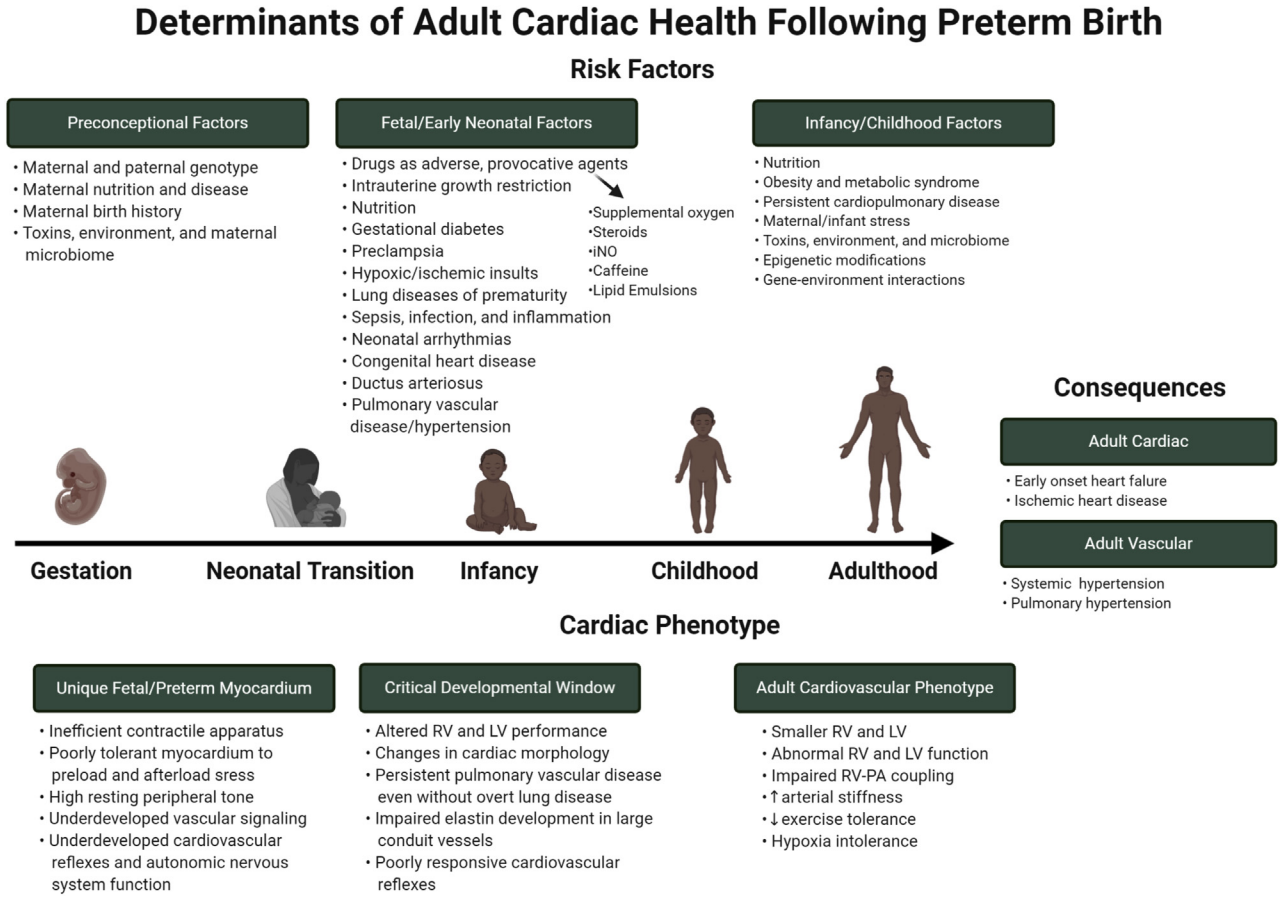

Figure 1. Determinants of adult cardiac health following preterm birth. Interruption of normal cardiac development confers a unique phenotype to the preterm infant's myocardium. The development of the myocardium is further interrupted by extrinsic and intrinsic factors that occur throughout gestation, the neonatal transition, infancy, and childhood to confer a unique cardiovascular phenotype in adulthood that may lead to poor cardiovascular outcomes.

models are valuable because they are often better suited—or the sole option—for invasive endpoints, histological examination of tissue, and genetic manipulation to determine the roles of various pathways in cardiovascular endpoints.

Determinants of Preterm Myocardial Mechanics

Intrinsic characteristics of the developing preterm myocardium put the infant at risk of hemodynamic compromise in the neonatal period and predispose to long-term cardiovascular complications.[9] Specific determinants include immaturity of the myocardium, the persistence of fetal shunts (ductus arteriosus [DA] or foramen ovale), adverse effects of ventilation strategies, and pharmaceutical intervention (eg, perinatal steroids, oxygen, caffeine, inhaled nitric oxide). The immature myocardium contains underdeveloped contractile machinery with disorganized myofibrils, an immature calcium handling system, and inadequately compliant collagen, predisposing it to diastolic dysfunction, poor tolerance to increased afterload, and lack of reserve to cope with states of reduced preload.[10] The effects of prematurity on long-term cardiovascular health[11,12] are likely related to alterations in cardiac function and morphometry associated with developmental programming of the heart.[13-15] The terminal differentiation of myocytes occurs in late fetal life, during the third trimester.[16] This dictates cardiomyocyte endowment for life, because the heart loses its proliferative capacity[17] as cardiomyocytes switch from cell proliferation (hyperplasia) to rapidly increasing cell size (hypertrophy) in the neonatal period.[17] In healthy term infants, myocardial cell volume increases approximately 30-fold over the first few months of postnatal life. Preterm birth may interrupt cardiomyocyte proliferation, thereby reducing cardiomyocyte endowment compared with infants born at term. This results in maladaptive structural remodeling in the neonatal period.

Cardiomyocyte endowment is a key factor influencing susceptibility to cardiac disease, particularly in heart failure, where cardiomyocyte loss contributes to disease progression.[18] Similarly, perturbations during the critical window of postnatal development in which organs accrue mass alter

normal maturation and contribute to the unique cardiac phenotype of prematurity.[15,19] The reduced heart mass following preterm birth is normalized by disproportionate cardiac hypertrophy and increased left ventricular (LV) mass in subsequent "catch-up" growth in the early postnatal period,[13] with differences in cardiac structure and function persisting in adulthood compared with individuals born at term.[20] Preclinical studies have demonstrated that myocyte hypertrophy may compensate for fewer cardiomyocytes to maintain mass, but in ELBW infants, the reduction in cardiomyocyte number may supersede this compensatory mechanism.[17] In a premature ovine model, both LV and right ventricular (RV) cardiomyocytes were hypertrophied compared with controls.[17] Sheep born prematurely have an ~7-fold increase in interstitial collagen deposition by age 9 weeks and by 14.5 months (adulthood equivalency) have thinner RV walls, a higher reserve of immature undifferentiated cardiomyocytes, lower cardiomyocyte numbers, and smaller cardiomyocyte areas, with reductions in RV functional and adaptive capacity.[6] There are also irreversible myocardial stress-related changes in DNA in these preterm-born animal models, reflected by alterations in nucleation and ploidy of the cardiomyocytes.[17]

Adverse Impact of Neonatal Disease and Therapeutic Interventions on Cardiovascular Development and Health

Altered cardiac programming may start in early life, but common perinatal morbidities, including a hemodynamically significant patent DA, PVD, fetal growth restriction (FGR), and neonatal intensive care practices (eg, steroids, parental nutrition, caffeine, oxygen) may modulate cardiovascular outcomes.

Patent Ductus Arteriosus. The biological role of the DA varies from an innocent bystander during the normal postnatal transition, supportive when there is a compromise to either systemic or pulmonary blood flow, or pathological, characterized by hemodynamically significant systemic-to-pulmonary shunts. In some preterm infants, closure of the DA is not spontaneous but rather is maladaptive, delayed, or even arrested,[21] and even after spontaneous or therapy-induced closure, the DA may reopen with changes in the hemodynamic milieu.[22] Persistent exposure to a high-volume shunt may have serious hemodynamic consequences, causing pulmonary overcirculation and compromising effective systemic blood flow. The long-term cardiovascular ramifications are poorly understood, although recent evidence suggests an increased risk of pulmonary hypertension (PH) and right heart disease.[23]

PVD in the Setting of Chronic Lung Disease. As the rate of survival of extremely preterm infants into childhood and early adulthood increases, the negative impact of chronic lung diseases of prematurity and PVD on RV mechanics and pulmonary hemodynamics has become more apparent.[24] PVD in preterm infants has 3 unique phenotypes: (1) early presentation in the neonatal period following delayed adaption of the lung circulation at birth; (2) late presentation in the neonatal period (often associated with bronchopulmonary dysplasia [BPD]); and (3) chronic or sustained presentation beyond the neonatal period extending into childhood and young adulthood. Echocardiography evidence of early PVD after preterm birth, in combination with other perinatal factors, is a strong risk factor for late PVD at 36 weeks[25] and chronic respiratory disease into early childhood,[26] but early PVD and PH may be difficult to detect clinically in the extremely preterm infant soon after birth,[27,28] and their incidence is inversely related to gestational age.[29] Although early PH tends to resolve by age 1 month, little is known about its impact on long-term cardiovascular adaptation.[26] Furthermore, the impact of early PH treatment options, most notably inhaled nitric oxide (iNO), on long-term cardiovascular health in preterm infants remains unclear. Although it is generally agreed that the use of iNO without comprehensive echocardiography assessment could be detrimental,[27] it appears that iNO therapy has a critical role for subgroups of preterm infants.[27,28]

Late PVD, characterized by progressive elevation of pulmonary artery (PA) pressure and maladaptive changes in ventricular morphology and function, contributes to both morbidity and mortality during and beyond the neonatal period.[30] Compared with infants born at term, infants born prematurely exhibit abnormal RV performance with remodeling as early as 32 weeks postmenstrual age that persists through 1 year corrected age, suggesting a less-developed intrinsic myocardial function response following preterm birth.[24] The challenge for the right ventricle is to remain hemodynamically coupled to a compliant pulmonary circulation; an increased vascular load in the setting of poor myocardial tolerance of afterload may cause the right ventricle to uncouple from the pulmonary circulation, leading to decreased RV performance and overt failure in late PVD. Given the clinical importance of earlier detection of PH,[25] advances in risk assessment and monitoring for PVD and right heart performance have led to more reliable quantitative modalities to detect and longitudinally follow PVD and to inform decision making processes.[31]

FGR. The influence of preterm birth on cardiovascular development is further complicated by FGR.[32] Cardiovascular changes (eg, cardiac morphology, subclinical myocardial dysfunction, arterial remodeling, impaired endothelial function) are evident in utero.[33] Preterm-born infants with FGR also display early alterations in cardiac function with changes in globular cardiac morphology, including a hypertrophied intraventricular septum, LV dilatation, and decreased myocardial reserve that may persist into young adulthood.[34] There is increased recognition of the association between FGR and an increased rate of cardiovascular mortality in adulthood.[33] Delayed cardiomyocyte maturation with altered contractile machinery is one likely mechanistic link between FGR and the associated cardiac dysfunction, but

more research is needed to understand the immediate and long-term cardiovascular consequences.[35]

Perinatal Corticosteroid Administration. The use of antenatal glucocorticoids for lung maturation and postnatal steroids for hemodynamic support or lung rehabilitation can improve the survival of preterm-born infants, but their impact on fetal, neonatal, and long-term cardiovascular development is unclear. Both antenatal and postnatal steroid administration might contribute to the risk of cardiovascular disease beyond the neonatal period. In utero, endogenous glucocorticoids promote functional, metabolic, and morphological remodeling in fetal cardiomyocytes, with cardiomyocyte proliferation dictating the morphological development of the heart. Interestingly, in glucocorticoid receptor knockout mice, the hearts are small, lack cardiomyocyte alignment, and develop impaired systolic and diastolic performance.[36] Treatment of fetal mouse cardiomyocytes with steroids for 24 hours was found to promote myocardial maturation.[36] Exogenous glucocorticoids may alter the natural biochemical endogenous production pathways (eg, hypothalamic-pituitary-adrenal axis), increasing the risk of adult cardiovascular disease. In lambs[37] and preterm infants,[13] exposure to antenatal steroids is associated with increased aortic arch stiffness and altered glucose metabolism in early adulthood.[38] Although both prematurity and antenatal steroids reduce cardiomyocyte endowment and lead to cardiomyocyte hypertrophy, antenatal steroids appear to be a minor contributor to changes in cardiac mass compared with preterm birth itself.[39]

The timing of steroid administration relative to subsequent delivery of the infant also may impact postnatal cardiac maturation and short- and long-term outcomes. When preterm birth occurs within 1 week of antenatal steroid administration, cardiomyocyte function is enhanced directly through rapid effects on metabolic and structural maturation and also possibly indirectly by improving hemodynamic stability; however, when delivery occurs more than 1 week after a single course, there is an increased risk of perinatal and neonatal death.[40] Taken altogether, the results of studies in sheep and rodents suggest that the beneficial effects of glucocorticoid treatment in utero[41] on heart function may come at the expense of cardiovascular reserve.[36]

Postnatal steroid use is associated with altered LV geometry, hypertrophic cardiomyopathy, outflow obstruction, and systemic hypertension in neonates.[42] LV hypertrophy (LVH) predicts cardiovascular events in term-born adults, and data are emerging on the prognostic impact of this endpoint in the preterm population. Skelton et al[42] found an increased risk of transient LVH following a short-term course of postnatal steroids. Choudhry et al[43] observed that both postnatal steroid use and small for gestational age status are important risk factors for altered LV geometry. The mechanisms of cardiac hypertrophy resulting from postnatal corticosteroid use remain unclear; because LVH is also seen in conditions with abnormal glucose or insulin metabolism, it is possible that the natural history of LVH associated with steroids reflects a direct effect on the heart through similar pathways. Long-term effects of postnatal steroid use on the developing cardiovascular system are less clear. There is evidence of a blunted cardiovascular stress response in children after dexamethasone treatment, but not after hydrocortisone treatment, in the early neonatal period.[44] Other studies have found no changes in blood pressure (BP), pulmonary hemodynamics, vascular intima-media thickness, or cardiac morphology/function among infants who received dexamethasone, those who received hydrocortisone, and those who received no postnatal steroids.[38,45]

Parenteral Nutrition. Intravenous lipid exposure in premature infants is associated with changes in aortic and cardiac function in adult life in a graded manner related to the rise in cholesterol levels.[46] These observations are independent of the native cholesterol beyond the neonatal period, suggesting that circulating cholesterol during these critical periods of developmental in preterm-born infants may have long-term impacts on the cardiovascular system.[46] The beneficial impact of fat emulsions on growth and neurodevelopment likely outweigh any negative impact on the heart. Although the direct effects of a high-lipid diet on heart function have been reported in several animal models,[47] whether certain lipids are more cardiotoxic than others is unclear. Future studies should focus on the type of intravenous lipid, timing of delivery, influence in early stages of cardiac development, and specific long-term effects in animal and human studies.

Caffeine. The short and intermediary effects of caffeine on brain and lung health in preterm infants have been well documented; however, there are no long-term studies evaluating the impact of neonatal caffeine administration on cardiac health into childhood and young adulthood.[48] Our understanding of the cardiovascular effects of this universal therapy, outside of clinically insignificant tachycardia, is limited to reported associations between caffeine citrate and a decreased need for treatment of a patent DA that is likely multifactorial in origin.[49] Potential mechanisms include direct diuretic and vasoconstrictor effects or indirect effects on cardiac output and BP, but the association with cardiac health beyond the neonatal period and in young adulthood is unclear and requires further research.

Supplemental Oxygen. Oxygen use in the NICU has evolved over the last 30 years from copious use at high FiO_2 to more judicious use in most centers today. At birth, the infant transitions from a low-PaO_2 to a high-PaO_2 environment, resulting in reactive oxygen stress that impacts the developing heart.[16] Hyperoxic rodent models have been used for decades to study the sequelae of premature birth and supplemental oxygen exposure, specifically around the development of BPD.[50] The rat model has been uniquely valuable in that, like the preterm infant heart, the rodent heart is largely mononucleated and transitions from hyperplasia to hypertrophy for cellular growth in the perinatal period.[51] Applying

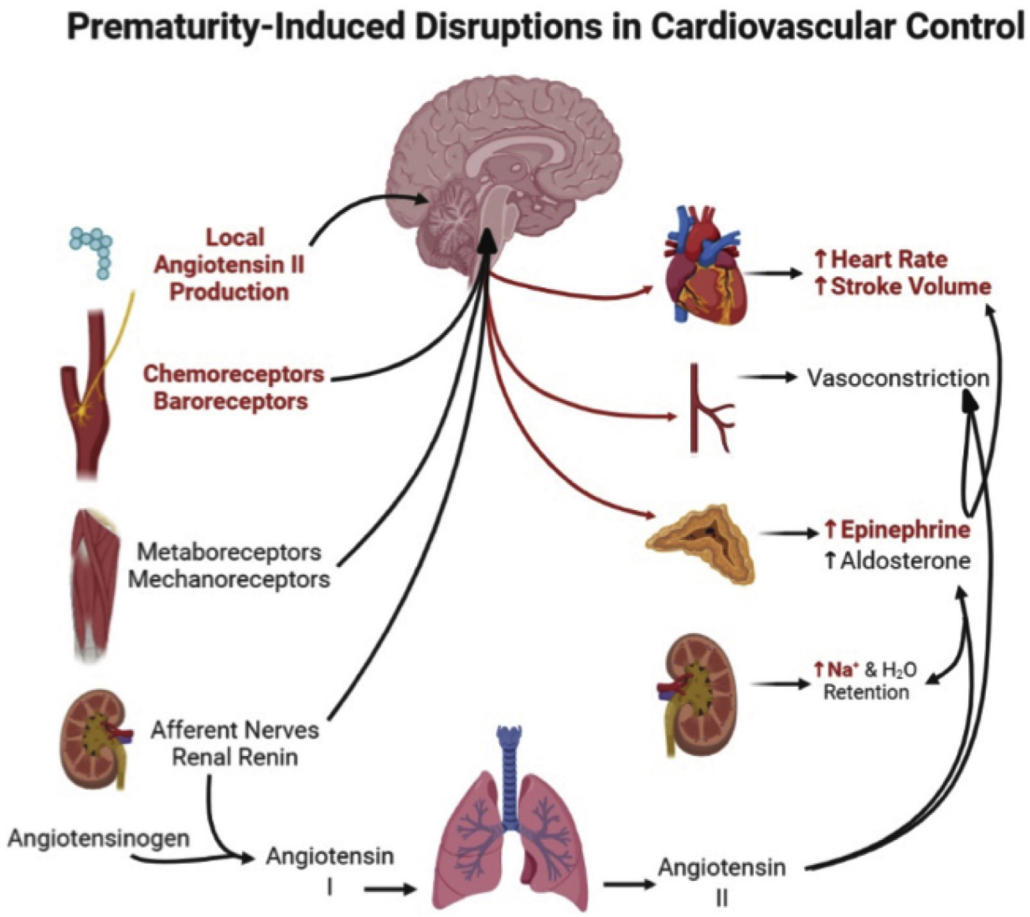

Figure 2. Prematurity-induced disruptions in cardiovascular control. Prematurity may disrupt the development of the renin-angiotensin system and autonomic nervous system. The schematic indicates the predicted response to hypotensive stress, and red, bolded items indicate a component of the response disrupted by prematurity as discussed in this review.

hyperoxia to the rodent model quickens cell cycle arrest by triggering DNA damage.[52] Postnatal supplemental oxygen exposure can expose the RV-pulmonary vascular and LV-systemic vascular complications of premature birth, including PH, right ventricle–PA uncoupling, and aortic stiffening. Although the clinical symptoms of moderate to severe PH often resolve, the pulmonary vasculature remains vulnerable to subsequent hypoxic insult and aging.[53] Postnatal supplemental oxygen also remodels the left ventricle, increasing cardiomyocyte hypertrophy, fibrosis, and senescence markers, collectively impairing systolic function and resulting in heart failure,[54] and may impact systemic vascular development. Although it is plausible that several adverse mechanisms for cardiac development are initiated by neonatal oxidative injury, there is now a critical need to prospectively understand how these findings in animals translate to the preterm infant.

Impact of Preterm Birth on Development of the Vasculature and Cardiovascular Control Centers

The normal term systemic vasculature requires the development of large conduit vessels that can withstand a large volume of high-pressure, pulsatile flow, and cardiovascular control centers that respond to changing metabolic demand. Many of the stimuli that disrupt myocardial development also disrupt these components (**Figure 2**), potentially contributing to an increased risk of hypertension and poor cardiovascular outcomes in this population.

Development of the Large Conduit Vessels and Their Extracellular Matrix. The unique mechanical properties of the large conduit vessels (eg, aorta) allow them to maintain structural integrity despite sustained hydrostatic stress.[55] Stiffening of the large conduit vessels leads to increased cardiovascular risk in the general population[56] and also may lead to a comparable risk profile in preterm infants.[57] Prematurity may disrupt the normal deposition of elastin in the large conduit arteries that typically occurs around term. This may be further compounded by perinatal interventions like oxygen and steroids. Perinatal supplemental oxygen exposure leads to increased aortic stiffness and disrupted elastin deposition in rats.[58] Increased aortic stiffness was observed in adult survivors of prematurity born between 1989 and 1991, when generous oxygen use was the standard of

care,[59] and translated to higher systolic BP during exercise. Aortic stiffness has been observed in young adults exposed to antenatal steroids[38] and is associated with decreased elastin and smooth muscle deposition in a lamb model.[60]

Consequences of elevated arterial stiffness in the perinatal period may include LV diastolic dysfunction and pulmonary venous hypertension that might not be immediately recognized in preterm infants with severe BPD. The degree to which conduit artery stiffness drives remodeling and dysfunction in the developing heart[61] is unknown. In the long term, vascular stiffening may contribute to LVH by both increasing afterload and impairing coronary artery blood flow during diastole. The impact of the higher afterload imposed by a stiffer aorta is potentially observable in apparently healthy, young preterm-born adults who have a higher heart rate but diminished stroke volume during exercise.[59] The timing and outcomes of these changes require prospective investigation. Although it is clear that some survivors of prematurity have stiffer arteries, the factors contributing to this phenotype are unclear. Studies in larger cohorts have yielded conflicting results,[62] likely because the index populations were exposed to different risk factors, including gestational age, maternal hypertension, ventilation strategy, exogenous agent administration, and birth weight. Additional studies are needed to define the factors contributing to premature arterial stiffening.

Development of the Cardiovascular Control System. The development of the baroreflex and chemoreflex is critical for the maintenance of systemic oxygen delivery when perfusion or arterial oxygen content is challenged. Abnormalities in either may contribute to long-term cardiac risk. Activation of the baroreceptors by a drop in BP and activation of the chemoreceptors by a drop in arterial oxygen tension activates the sympathetic nervous system to increase perfusion pressure and improve oxygen delivery to systemic tissue, respectively. There is considerable crosstalk between these systems, and both are vulnerable to injury because the majority of their development occurs near term.[63]

Incomplete baroreflex development may contribute to critical hypotension in the first days after birth and later risk of hypertension. Preterm lambs (90% of term gestation) experience life-threatening cardiorespiratory events at 7 days after birth but not at 14 days, coinciding with the development of baroreflex sensitivity.[64] There is little renal sympathetic nerve response to hypotensive challenges.[65] This suggests the preterm neonate relies purely on the heart rate component of the baroreflex to maintain BP when it drops, and that the 2 arms of the autonomic response mature at different rates. Baroreflex sensitivity at birth is further depressed by low birth weight,[66] and maturation is improved by antenatal steroids.[67] Although baroreflex sensitivity improves in the conscious preterm infant in the weeks and months after birth,[66] this maturation is impaired in extremely preterm infants[68] and does not translate to normal baroreflex sensitivity during sleep. In sleeping infants (24-42 weeks postmenstrual age), baroreflex sensitivity matures with advancing postmenstrual age,[69] consistent with maturation of vagal tone and a reduction in cardiac sympathetic tone[70]; however, postnatal baroreflex maturation is impaired in preterm infants (<32 weeks gestational age) during quiet sleep in both prone and supine positions, as well as in more mature infants (32-36 weeks gestational age) sleeping quietly only in the prone position.[71] Impairments in autonomic control persist into childhood and adulthood. Young adult survivors (aged 19-26 years) experience delayed heart rate recovery after exercise that is more severe in extremely and very preterm-born individuals (<34 weeks) compared with those born late preterm (34-36 weeks).[72,73] Reduced heart rate recovery in the general population is associated with a 4-fold increased risk of mortality.[74] Animal data suggest that impaired autonomic development is sex-dependent. In sheep, preterm birth (90% term gestation) depresses baroreflex sensitivity, and male sheep in particular develop increased BP and reduced heart rate baroreflex responses[75] that could translate to increased hypertension risk.[65]

The chemoreflex influences both the ventilatory and hemodynamic responses to changes in arterial oxygen tension and is disrupted by prematurity and perinatal intervention. In the rodent, perinatal supplemental oxygen, hypoxia, and intermittent hypoxia each disrupt normal chemoreflex development and diminish sensitivity to hypoxic stress later in life.[76] Preterm infants who receive supplemental oxygen have a depressed ventilatory chemoreflex to hypoxia[77] during infancy that persists into childhood and adulthood,[78] possibly caused by incomplete development of the carotid chemoreceptors.[79] Ventilatory components of the hypoxic chemoreflex response have been well characterized,[78] but the hemodynamic component remains to be clearly elucidated. Chemoreflex disruptions are important in the pathogenesis of heart failure and multiorgan dysfunction in the term population,[80] but it is not known whether chemoreflex modulates heart rate and cardiac output in response to hypoxic stress in the preterm, or how altered chemoreflex function in survivors of prematurity may contribute to the pathogenesis of cardiovascular disease.[81]

Development of the Renin-Angiotensin System. The renin-angiotensin system maintains BP by stimulating thirst, increasing sodium absorption in the kidney, activating sympathetic nerve activity, and causing systemic vasoconstriction.[82] Low birth weight, placental insufficiency, gestational undernutrition, glucocorticoid exposure, and intrauterine hypoxia are implicated in disruptions of renin-angiotensin signaling.[83] Animal models suggest that these factors, which are commonly associated with preterm birth, may increase expression of angiotensin II in the brain,[84] thereby increasing sympathetic nerve activity and the concentration of circulating plasma catecholamines.[85] This may then increase renal sodium transporter expression and sodium reuptake[86] in the kidney, collaborating with the vasoconstrictor effects of catecholamines to cause hypertension.

Cardiopulmonary Phenotyping in the First Year of Life

Early Phase, Late Phase, up to 1 Year

The transition from fetal to neonatal circulation is characterized by a period of intricate cardiovascular adaptation, during which neonates experience rapid and pivotal changes in cardiopulmonary physiology.[21] Preterm birth abruptly curtails cardiopulmonary development,[19,87] with ELBW infants exhibiting the highest rates of abnormal cardiac performance, disproportionate cardiac hypertrophy, and PVD irrespective of the degree of lung disease. Acquired cardiovascular disease following preterm birth is best characterized through a physiological hemodynamic spectrum accounting for variance in early, late, and chronic phenotypic signatures.

The impact of preterm birth on cardiovascular development is closely tied to ventricular–vascular coupling with each endotype.[88] Each disease process can be characterized by maladaptive changes in ventricular morphology and functional contributions that significantly alter morbidity and mortality during and beyond the neonatal period. Cardiac phenotyping can be traced to the central adaptive physiological principles that characterize the transition from the fetus to the newborn and include increased pulmonary blood flow, alteration in flow through fetal channels with successful closure of the pulmonary-to-systemic shunts, and increased LV and RV output. With increased recognition that infants born prematurely are more likely to develop myocardial dysfunction, recent evidence has linked ventricular independence and outcomes. For example, preterm infants with reduced LV diastolic function in the early transitional neonatal period not only are at an increased risk of invasive ventilation and pulmonary hemorrhage,[10] but also have a significant load exerted onto the right ventricle that has a lasting impact on cardiopulmonary performance.[89]

Preterm infants exhibit abnormal RV performance with remodeling, as early as 32 weeks post-menstrual age, that persists through 1 year corrected age, suggesting a less-developed intrinsic myocardial function response.[90] Inability of the immature right ventricle to tolerate elevated pulmonary vascular resistance (PVR) and afterload may cause the right ventricle to uncouple from the pulmonary vascular bed, leading to decreased RV performance and overt failure in PVD.[91] Similarly, the impact of elevated systemic afterload on LV performance has revealed that ex-preterm survivors are at increased risk of cardiovascular-related diseases, such as hypertension, heart failure, and ischemic heart disease, as they reach adulthood.[11,12] Given the extent of functional and structural cardiac changes during the neonatal period, it is likely that additional perturbations over time, such as chronically elevated systemic vascular resistance, will accelerate disease progression.

Emerging Diagnostic Tools to Assess Neonatal Hemodynamics

Coupled with clinical and biochemical evaluation, neonatal echocardiography can be used for diagnostic and monitoring purposes in neonates at risk for dysregulation of transitional physiology. Appraisal of all the clinical and laboratory measures of cardiovascular homeostasis combined with a compatible history and the use of imaging modalities (such as echocardiography) will offer a complete and accurate picture of the etiologies of hemodynamic instability, provide the potential to overcome some of the disadvantages of each monitoring technique, and more accurately identify appropriate interventions to guide possible therapeutic approaches. Targeted neonatal echocardiography (TnECHO) involves the use of comprehensive and standardized echocardiography by neonatologists who have completed formal hemodynamics training to evaluate heart function, shunt physiology, and hemodynamics; formulate a diagnostic impression; and make clinical recommendations. TnECHO has become the standard of care in many NICUs worldwide with the growing recognition that it can provide hemodynamic information that either complements what is clinically suspected or provides novel physiological insights.[92,93] The integration of hemodynamic information obtained by echocardiography relevant to an individual situation and directed by a specific clinical question offers a blueprint for formulating a scientifically based diagnostic impression, determining a pathophysiological choice for cardiovascular support, and evaluating the response to therapeutic intervention.[92] A number of prospective studies have highlighted the potential merits of TnECHO in identifying cardiovascular compromise and guiding neonatal cardiovascular care during the transitional period.[94] Improved mechanistic understanding of neonatal cardiovascular disease or the impact of specific treatments may enable the identification of signals that herald a modified risk of adult cardiovascular health. One limitation of studies of adult cardiovascular outcomes is the lack of reliable neonatal echocardiography data, which precludes thoughtful characterization of risk profiles. Cardiac magnetic resonance imaging offers the potential for comprehensive appraisal of ventricular geometry, performance, and interdependence.[95] These data may further enhance the identification of disease states or neonatal interventions that negatively modulate adult cardiovascular outcomes.

Long-Term Cardiovascular Consequences of Prematurity

Heart Failure

Population-based studies have identified preterm birth as a newly recognized risk factor for early-onset heart failure. Incidence rates are inversely related to gestational age at birth.[11] Observational studies demonstrating impaired LV systolic reserve with pump failure under physiological stress,[73,87,96] RV dysfunction,[19] and gestational age–dependent right ventricle–pulmonary arterial coupling mechanisms,[97,98] as well as distinct ventricular morphology,[15] may help explain these increased risks. A recent meta-analysis demonstrated that preterm-born individuals have persistently smaller ventricular dimensions,

lower LV diastolic function that worsens with age, RV systolic impairment across all developmental stages, and an accelerated rate of LV hypertrophy from childhood to adulthood.[2]

Ischemic Heart Disease

Register-based cohort studies have demonstrated an increased risk of ischemic heart disease in adults born preterm.[12] Similar to heart failure risk, there is an inverse relationship between ischemic heart disease and gestational age at birth that also extends to individuals born moderate to late preterm. The strength of these relationships is stronger in adults aged >30 years compared with younger adults born preterm. The data also suggest similar adverse risk profiles for the early term-born population with short- and long-term pulmonary morbidities, highlighting the potential cardiopulmonary vulnerabilities of this population.[99]

Cardiometabolic Disease

There is a growing recognition of the prevalence of cardiometabolic risk factors in children and young adults who were born prematurely.[3] Clinically, these factors manifest as higher insulin resistance,[100] lower glucose tolerance,[101] and possible altered lipid metabolism profiles,[102] all of which likely contribute to the increased risk of heart disease in childhood and adulthood.[103] In addition, preterm-born individuals are more likely to be obese[100] and to have poor exercise tolerance,[104] which can indirectly add to the risk for systemic hypertension.

Systemic Hypertension

Elevated systolic and diastolic BP are well documented in children, young adults, and adults born preterm,[105] with women appearing to be affected more frequently than men.[106] Because preterm birth can disrupt development of the vasculature,[107] individual cohort studies and systematic reviews have also found distinct structural changes in the cardiovascular system that persist into adulthood, including lower arterial distensibility and increased arterial wall thickness.[3] In addition to changes in arterial compliance discussed in this review, the impact of kidney performance,[108] oxygen-binding capacity,[109] sympathetic nervous autonomic system activation,[110] and hypothalamus-pituitary-adrenal axis dysregulation[111] merit further study as possible contributing factors to the etiology of systemic hypertension.

PVD

Children and adults born preterm are at an increased risk for developing PVD, even after correction for common PH risk factors, such as congenital heart disease, lung disease of prematurity, and chromosomal abnormalities.[112] Several clinical studies using echocardiography have shown evidence of increased PVR and PA pressure in children[113,114] and young adults[97] born preterm compared with individuals born at term. Data from a right heart catheterization study demonstrated that former preterm-born individuals have a stiffer and less recruitable pulmonary vascular bed with a dampened RV stroke volume response to exercise.[87,98] As a result, rising PVR and RV afterload without compensatory increases in contractility lead to alterations in right ventricle–PA coupling that appears more pronounced based on gestational age at birth.[97,98] Another study comparing term-born and preterm-born infants at age 1 year found a similar blunted gestational age-dependent response of the right ventricle to increased afterload.[24] Preclinical investigations in rats using postnatal hyperoxia exposure showed a bimodal RV dysfunction,[53] and we speculate that there may be a similar pattern with uncoupling hemodynamics that could be gestational age–dependent. Although the magnitude of the PVD was relatively mild in those follow-up studies, a recent meta-analysis demonstrating that preterm-born individuals have RV systolic impairment across the lifespan suggests that cumulative insults on the cardiovascular system could lead to a more severe presentation of chronic or sustained PVD in a subset of preterm-born individuals.[2] Given that even slight elevations in PA pressure have been associated with increased mortality in adults,[115] further preclinical and clinical studies are needed to evaluate the physiological response of the right ventricle to increased afterload in preterm born infants.

Adaptation to Environmental Stressors

The degree to which prematurity conveys additional cardiovascular risk in the context of common environmental stressors, including hyperbaria and hypobaria (eg, diving and altitude, respectively), air pollution, and hyperthermia and hypothermia, is not known. Given the increased participation of children and young adults in sporting events and travel that exposes them to environmental stressors, it is important to quantify how early-life experiences modify the risk of short-term exposures to such stressors. For example, at least one-third of the 34 million annual sojourners to altitude are children.[116] Case reports exist of children with congenital heart disease (CHD), BPD, and prematurity presenting with high-altitude pulmonary edema after ascent to altitude[117] and of worsened gas exchange in hypoxia among survivors of prematurity.[118,119] Several of the cardiorespiratory sequelae of prematurity outlined here are known risk factors for high altitude pulmonary edema including a hyperreactive pulmonary vasculature and arterial stiffening,[120] immature ventilatory drive,[121] increased risk of lung disease, and structural heart and vascular defects.[116,122] Infants born at altitude are more likely to be small for gestational age,[123] driven largely by impaired uterine artery blood flow.[124] High altitude birth may give rise to pulmonary vascular hyper-reactivity and erythrocytosis that compound pulmonary vascular dysfunction associated with prematurity.[125,126] Gestation and birth at altitude are also associated with impaired autonomic control,[127] myocardial architecture development,[128] and an increased risk of congenital heart disease.[129]

Therapeutic Strategies to Mitigate Cardiovascular Risk

Currently, there is a paucity of proven prophylactic and therapeutic interventions that mitigate the long-term effects of

Table. Research questions to guide cardiovascular investigations in preterm-born individuals

Focus area	Research questions and priorities
Developmental vulnerability of the ELBW infant	1. Determinants of preterm myocardial mechanics • Determine how the heart remodels following the development of common risk factors associated with preterm birth. • Explore the impact of gestational age on LV and RV mass throughout the lifespan. • Investigate determinants of abnormal myocardial development in prospective epidemiologic datasets inclusive of birth, childhood, and adulthood. • Delineate the natural history of PV-RV development in high-risk individuals. 2. Adverse impact of neonatal disease and potential therapeutic interventions on cardiovascular development and health • Understand the impact of FGR on long-term cardiovascular consequences. • Decipher the mechanisms of cardiac hypertrophy resulting from postnatal corticosteroid therapy. • Focus on the type of intravenous lipid, timing of delivery, and whether each has unique early and long-term effects on cardiac development. • Determine how the adverse mechanisms for cardiac development initiated by preclinical neonatal oxidative injury translate to the preterm infant. • Characterize the impact of chronic exposure to a high-volume patent ductus arteriosus shunt on pulmonary vascular and myocardial development. • Develop long-term studies to evaluate the impact of caffeine administration in the neonatal period on cardiac health in childhood and young adulthood. 3. Impact of preterm birth on the development of the vasculature and cardiovascular control centers • Understand common perinatal and neonatal interventions and complications in preterm infants and their role in abnormal cardiovascular control development. • Explore the degree to which conduit artery stiffness drives remodeling and dysfunction of the developing preterm heart. • Define additional factors that contribute to premature arterial stiffening. • Clarify the mechanisms of defective vascular tree development and/or repair (eg, epigenetic changes and accelerated senescence of progenitor cells).
Cardiopulmonary phenotyping during the first year of life	1. Phases of development • Investigate the roles of ventricular–vascular coupling mechanisms and interventricular dependence in the early, late, and chronic phases on long-term cardiovascular sequelae. • Develop long-term maternal–infant dyad cohorts to investigate the critical influence of perinatal risk factors on cardiovascular health, development, and disease. • Understand how additional perturbations over time (eg, chronic elevation in systemic vascular resistance and PVR) accelerate disease progression throughout development. 2. Emerging diagnostics • Use advanced hemodynamic evaluations with novel imaging modalities (echocardiography, cardiac magnetic resonance imaging) to follow the functional and structural cardiac changes in the neonatal period. • Refine echocardiography diagnostic criteria to allow early identification of neonates with significant progressive cardiovascular disease at-risk of subsequently developing long-term sequelae.
Long-term cardiovascular sequelae of prematurity and its burden	1. Heart failure • Examine whether current treatment strategies for heart failure adequately address myocardial dysfunction in preterm individuals. • Understand links between early myocardial development and future risk of heart failure. • Investigate therapeutic strategies in adults born preterm to treat hypertension or modify heart failure risk. 2. Ischemic heart disease • Provide insight into how novel myocardial phenotypes influence ischemic heart disease development. 3. Systemic hypertension • Understand how genetically inherited factors contribute to systemic hypertension risk related to altered organ and vascular development and function. • Explore the contributions of kidney performance, oxygen delivery, autonomic dysregulation, vascular stiffness, and RAS and HPA dysregulation to the etiology of systemic hypertension. 4. PVD • Understand the bimodal presentation of PVD and explore why a subset of premature infants are more likely to develop more severe PVD. • Further evaluate the physiological response of the right ventricle to increased afterload in preterm born infants. • Define healthy cardiopulmonary interactions (RV performance and PV hemodynamics) from infancy through adulthood in well-characterized populations. 5. Therapeutic interventions • Explore the roles of intervention strategies throughout the lifespan, including lifestyle modifications such as exercise and pharmacologic interventions, on improving cardiac remodeling and decreasing long-term cardiovascular risk. • Explore interventions (eg nutritional, exercise) to enhance cardiometabolic health later in life and develop best practices to mitigate obesity. • Investigate specific cardiovascular interventions in animal and human studies to improve cardiovascular health later in life. • Develop multidisciplinary teams of neonatal, pediatric and adult clinical researchers, physiologists, and developmental scientists to build academic bridges that enable the identification of important modulators of abnormal cardiopulmonary development and opportunities for therapeutic intervention.

HPA, hypothalamic-adrenal-pituitary; *RAS*, renin-angiotensin-aldosterone.

prematurity on cardiovascular disease. Several investigators have demonstrated a putative link between cardiovascular outcomes and nutritional and lifestyle modifications in the early neonatal period and young adulthood, respectively.[130] Specifically, recent evidence suggests that type of enteral nutrition may play a role in adverse cardiac programming during early preterm life.[130,131] Follow-up data of premature neonates enrolled in a nutritional intervention trial in the United Kingdom in the 1980s provides the most concrete evidence of a link between early nutrition and long-term cardiovascular health. Infants who received an exclusive human milk diet during their NICU stay had lower BP during adolescence and a more favorable cardiac structural profile during young adulthood compared with premature infants who received an exclusive formula milk diet.[131,132] Another study of infants born prematurely who received high vs low exposure to their mother's own milk during their neonatal stay demonstrated that, although cardiovascular function and morphology were similar at 32 weeks postmenstrual age, by 1 year of age the high exposure group demonstrated enhanced RV and LV function, larger RV and LV cavity dimensions, and lower pulmonary pressure, even after accounting for neonatal morbidities.[90] Although details of mechanistic pathways that explain the modulator role of breast milk on postnatal cardiac performance remain unknown, human milk appears to be a vital intervention during early preterm life, with long-lasting protective effects on cardiovascular health.[130] Recent studies have explored the emerging evidence and examined the potential mechanisms mediating the changes contributing to immediate and long-term cardiovascular benefits for the preterm infant.[130] Current research efforts now focus on investigating early nutritional approaches to improve cardiac remodeling and decreasing long-term cardiovascular risk, in addition to lifestyle modifications such as exercise and pharmacologic interventions.[16,73]

Conclusions: Next Steps and Future Initiatives

Normal human cardiovascular growth and development is subject to multiple influences, beginning with preconception exposures and continuing through conception and childhood into early adulthood (**Figure 1**). Health surveillance of surviving ELBW infants to adulthood, which includes a standardized and multidisciplinary approach to the evaluation of cardiovascular performance, is needed to guide preventative strategies. Several studies focusing on very premature neonates and long-term cardiac health profiles have highlighted the need to better delineate the trajectories and modulators of cardiovascular growth and development throughout the lifespan. Although evidence suggests important correlations between infant cardiac health and adult cardiovascular function, major knowledge gaps exist regarding the influence of the preconception, perinatal, and postnatal periods on general cardiac health throughout life (**Table**). Research priorities can be delineated into 3 areas of academic focus: (1) developmental vulnerabilities of ELBW infants, (2) cardiopulmonary phenotyping over the first year of life, and (3) long-term cardiovascular sequelae and burden of being born premature. Specifically, future studies should investigate the determinants of abnormal myocardial development from prospective epidemiologic datasets extending from birth through childhood and into adulthood. Long-term maternal–infant dyad cohort studies offer key opportunities to capture the influence of preconception and obstetric risk factors on cardiovascular health, development, and disease in preterm individuals. Best practice recommendations should include the development of standardized guidelines, increased emphasis on healthy lifestyle counseling, and implementation of longitudinal formative clinical evaluations for cardiovascular disease in all individuals born preterm.[133] Neonatal and adult clinical researchers, physiologists, and developmental scientists should build academic bridges that enable the identification of important modulators of abnormal cardiopulmonary development and opportunities for therapeutic intervention. Future studies will need to not only examine preterm myocardial development, but also include well-characterized perinatal data, maternal data, and comprehensive plans for prospective follow-up of the infants (and their mothers) from birth through infancy and childhood and into adulthood. Long-term maternal–infant cohort studies offer key opportunities to capture the important influence of preconception and obstetric risk factors on cardiovascular health, development, and disease in preterm-born individuals. ■

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