# Reengagement with Physiology in Neonatal Heart and Lung Care: A Priority for Training and Practice

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Despite advances in respiratory, nutritional, and neuroprotective strategies, improving short- and long-term outcomes for neonates with complex cardiorespiratory disease remains a challenge.[1-4] Neonates, especially those born prematurely, are highly vulnerable to end-organ injury due to developmental immaturity of the myocardium and vascular bed, altered hemodynamic or respiratory states, and unanticipated adverse effects of medications or other interventions. The consequences of abnormal lung–heart interactions may play a role in the long-term health of individuals born premature; specifically, early cardiovascular disease in the neonatal period has been shown to predict important outcomes, such as the need for prolonged invasive ventilation and hospitalization, bronchopulmonary dysplasia (BPD) and/or pulmonary hypertension (PH), sustained respiratory disease throughout childhood, and severe cardiovascular disease into adulthood.[5-8] Improving cardiorespiratory outcomes depends on our ability to understand the complex heart–lung interactions and hemodynamic changes throughout the early clinical course and develop evidence of neonatal determinants of risk to sufficiently guide and apply clinical strategies aimed at optimizing clinical care.[9]

Characterization of the varying phenotypes among neonates with cardiopulmonary disease and recognition of temporal changes in disease course over time have been hampered severely by the lack of cardiopulmonary physiology education, especially during pediatric residency, neonatal–perinatal fellowship, and additional subspecialty training. Underappreciation of the importance of physiology in neonatal heart and lung care complicates the navigation of bedside decision-making and often hinders the clinician's ability to achieve "precision medicine" and the application of the best therapy to match the underlying physiology of the most critically ill newborns. The lack of exposure to cardiopulmonary physiology is most pronounced when it comes to identifying important modulating factors in neonatal disease states, such as patent ductus arteriosus (PDA), acute/chronic PH, systemic hypotension, and heart dysfunction. The nonphysiologic approach to neonatal hemodynamic care has been primarily driven by arbitrary symptom thresholds rather than disease states.[10] This paradigm is exemplified in the care of the neonate with hypoxic–ischemic encephalopathy (HIE). A recent survey of infants born at term with HIE undergoing therapeutic hypothermia highlighted the marked variance between practitioners in adjudication of hemodynamic stability; specifically, 17 different definitions of hypotension were reported across 71 academic centers in the US.[10] In addition, only 40% of centers reported use of echocardiography in patients with hypotension, which is further evidence of the limited consideration of underlying pathophysiology.

Appreciation of the full complement of heart and lung physiology will promote recognition that contributions to overall outcomes need to expand beyond the organ of interests. For example, in neonates with HIE, emerging evidence of an association between right ventricular dysfunction and the composite outcome of death or abnormal neurodevelopmental outcome highlights the importance of interplay between neurologic outcomes and modifiable cardiopulmonary physiology.[11,12] Interestingly, in a subsequent study, resolution of hypotension was not associated with recovery in heart function, further emphasizing the need for clinicians to characterize the underlying disease state based on the physiology and the phenotypes. Additional examples that may require precision medicine exist with evidence in patients with BPD, congenital diaphragmatic hernia, and complex arteriovenous malformations, as right and left heart phenotypes may appear similar clinically but require a different approach to treatment.[13-19] Currently, routine clinical practices and daily workflow in the neonatal intensive care unit (NICU) de-emphasize problem-based physiologic thinking.

The goals of this Commentary are 2-fold: first, to remind the neonatology community of the importance of physiology, enhanced diagnostic precision, and judicious use of treatments according to the underlying phenotype; and second, there is an urgent need to reconsider how evidence is both generated and interpreted in the context of the individual patient. In particular, the emphasis on the pragmatic randomized trial design, which prioritizes data generalizability but de-emphasizes the importance of "population of

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| BP | Blood pressure |
| BPD | Bronchopulmonary dysplasia |
| CPAP | Continuous positive airway pressure |
| HIE | Hypoxic–ischemic encephalopathy |
| NICU | Neonatal intensive care unit |
| PBF | Pulmonary blood flow |
| PDA | Patent ductus arteriosus |
| PH | Pulmonary hypertension |
| PVR | Pulmonary vascular resistance |

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interest," is a concern. For example, many randomized trials study commonly used medications in disease states without considering mechanistic relevance or pharmacologic appropriateness. These considerations are further exaggerated in the setting of a meta-analysis or systematic review.

## Cardiorespiratory Vulnerability of Infants Born Premature

The approach to neonatal cardiovascular care often is based on arbitrary measurement thresholds (eg, blood pressure, BP). In most centers, clinicians are alerted to cardiovascular concerns when the mean arterial pressure falls below an arbitrary threshold, eg, less than the infant's gestational age. Rather than determining whether the change in BP is associated with systemic hypoperfusion and suboptimal tissue oxygenation, and without determining the underlying pathophysiology, many clinicians will initiate treatment based on arbitrary evidence. Although maintaining an optimal arterial pressure threshold is important to support end-organ perfusion pressure, this "symptom-based" approach lacks diagnostic precision and assumes that a vasopressor-centric approach (oftentimes the same first-line agent) is uniformly applicable.

The evolution of this approach is based on the lack of reliable bedside tools to enhance diagnostic precision and the lack of immediate and longitudinal access to bedside echocardiography. Of concern, scientific evidence to support a "pressure-centric" approach, as based on maintenance of a mean arterial pressure threshold greater than the gestational age equivalent, is limited to expert opinion, and, importantly, normative data to support this arbitrary threshold are limited. It is therefore not surprising that evidence from observational studies suggest that treatment of hypotension is not beneficial and may be harmful.[20] These data have prompted some commentators to suggest that treatment of BP may not be of value. An alternate explanation may be that the approach to appraising BP, characterizing diagnosis, and selection of cardiovascular treatment lacks precision. Unfortunately, this limited approach to cardiovascular care has become the standard of care not only in the NICU but also in pediatric and cardiac intensive care units and pediatric emergency departments. In addition, this practice actively disinhibits consideration of underlying cardiovascular disease state and the prevailing physiologic factors. There is, however, evidence that a subpopulation of infants born premature with hypotension and low cerebral oxygen saturation are at greater risk of adverse neurodevelopmental outcome.[21] These data suggest that more a comprehensive and physiology based hemodynamic assessment may facilitate enhance diagnostic and therapeutic precision (Table I).

## Ground Zero in NICU–Interface with Physiology, and Lessons from Trials

The past 30 years have witnessed tremendous advances in neonatal survival, which relates, at least in part, to in improvements in respiratory interventions (eg, antenatal steroids with premature delivery, surfactant replacement therapy, enhancements in mechanical ventilator design, inhaled nitric oxide), neonatal nutrition (eg, exclusive breast milk use), and neuroprotective strategies. On the contrary the approach to common neonatal hemodynamic disease states remains controversial.[22] Of these, opinions related to treatment of a PDA are the most polarized in neonatology, ranging from "absolute nonintervention" in some centers to "universal treatment" in others. This is highly surprising, since the first report was made in 1956 by Mostyn Powell that infants born premature with a PDA have progressive respiratory impairment[23] and as less-invasive strategies for PDA closure are available at most medical centers.[24] Contemporary statements from major pediatric societies and institutional clinical practice guidelines are driven by the results of randomized clinical trials and cumulative meta-analyses.[25] Although this may give the appearance of "best evidence," it also may lead to erroneous conclusions and misinterpretation of the data.

David Sackett, a pioneer of evidence-based medicine, describes it as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of the individual patient." Therefore, in reviewing the results from randomized trials of PDA treatment, clinicians must determine whether the patient they are treating is comparable with enrolled patients. Thoughtful interrogation of the methodology used in trials conducted to date may suggest otherwise. First, standardization of the underlying diagnosis is an essential prerequisite and should be based on whether following conditions are satisfied: (1) high likelihood of physiologic derangement and end-organ morbidity and (2) low likelihood of spontaneous PDA closure. Up to 40% of clinical trials have not used echocardiography to adjudicate hemodynamic significance.[26] In most trials, echocardiography adjudication of hemodynamic significance is limited to a single point estimate of transductal diameter, which is problematic, as this measurement has a high degree of interobserver reliability and may not uniformly be representative of shunt volume.[27] In addition, the role of the PDA may range from harmful, as seen in a high-volume systemic-to-pulmonary shunt, to beneficial in patients with severe heart dysfunction or PH.[28] Trials to date have failed to characterize these varying phenotypes. Second, more than 50% of patients in the control arm received treatment. Third, many of the trials that are included in meta-analyses or systematic reviews reflect clinical practice from a different era in neonatology. For example, in studies before 2000, almost no infants born less than 24 weeks of gestational age were randomized, and many contemporary practices, such as use of probiotics, inhaled nitric oxide, and more gentle ventilation, were not available.[29] Even more recent trials have not enrolled patients born less than 24 weeks of gestation despite their high vulnerability.[30] Fourth, there is increasing evidence that the sickest and most vulnerable patients are not randomized due to physician equipoise.[31] Finally, conclusions are erroneously drawn regarding the relationship of the problem (PDA) to neonatal morbidity (eg, BPD) based on the lack of benefit

**Table I. Essential governing principles of cardiopulmonary physiology and clinical relevance**

| Governing laws, relationships, equations, and mechanisms | Physiologic principle | Relevance in neonates | Selected examples of clinical applicability |
|---|---|---|---|
| Heart function | | | |
| Stress–velocity relationship | Impact of afterload on heart function. | Immature myocardium intolerant to increased afterload. | Definitive PDA closure.<br>Acute PH.<br>HIE. |
| Frank–Starling mechanism | Impact of preload on heart function. | Crucial for maintaining cardiac output in response to changes in venous return. No augmentation in cardiac output across a normal range of filling pressures. | Definitive PDA closure.<br>Chronic PH with left heart dysfunction. |
| Force–frequency relationship | Myocyte response to chronotropy with relationship between heart rate and contractility. | Myocardial dysfunction resulting from impaired contractility, rather than changes in loading conditions. | Sepsis.<br>Definitive PDA closure. |
| Ventricular compliance | Adaptation of myocardial performance with increased volume loading. | Alteration of the left ventricle function to increased systemic afterload. | Fetal–neonatal transition.<br>Cardiomyopathy.<br>Interventional PDA closure. |
| Ventriculoarterial coupling | Response of ventricle function according to changes in afterload. | Optimization of stroke work efficiency. | Acute PH.<br>Chronic PH.<br>HIE. |
| Blood flow | | | |
| Hagen–Poiseuille equations | Relationship between pressure difference, vessel radius, blood viscosity, and vessel length that affect blood flow. | Insights into factors influencing blood flow and vascular resistance. | PDA.<br>Congenital arterial vascular malformation. |
| Pressure–flow relationship | Changes in pressure influence blood flow. | Adaptation of pressure and resistance to maintain optimal cardiac output. | Fetal–neonatal transition.<br>Closure of the DA. |
| Bernoulli principle | Relationship between the velocity of blood flow and its pressure. | Quantitative estimation of pulmonary pressures.<br>Estimate pressure gradients across heart valves by assessing blood flow velocities. | PH.<br>PDA.<br>Fetal–neonatal transition.<br>Congenital heart disease. |
| Mechanical ventilation | | | |
| Laplace's law | Relationship between the pressure, radius, and wall tension in a spherical structure. | Surfactant and alveolar surface tension with mechanics of small alveoli and prevention of alveolar collapse. | Respiratory distress syndrome.<br>Surfactant replacement therapy. |
| Boyle's law | Relationship between pressure and volume at constant temperature that drives air flow in and out of lungs. | Contraction of diaphragm during inspiration increases thoracic volume and decreases intrapulmonary pressure. | Congenital diaphragmatic hernia. |
| Resistance and Poiseuille's law | Relationship between pressure, air flow, and resistance in the airways. | Increased airway resistance impact airflow. | BPD.<br>Tracheobronchomalacia.<br>Small airway disease. |
| Dalton's law | Total pressure of a gas mixture equals sum of the partial pressures of individual gases (eg, oxygen and carbon dioxide in the alveoli and blood during gas exchange). | Titration of oxygen therapy and ventilator management. | Hypoxic respiratory failure.<br>Retinopathy of prematurity prevention. |
| Henry's law | Solubility of gases in liquids. | Dissolving of air in the liquid lining of the alveoli and influence gas exchange with the bloodstream.<br>Determination of oxygen saturations. | Respiratory distress syndrome.<br>Use of CPAP. |
| Fick's law of diffusion | Rate of gas diffusion across a surface. | Efficiency of oxygen and carbon dioxide exchange in the alveoli and capillaries. | Respiratory distress syndrome |
| Hooke's law | Relationship between an applied and resulting changes in shape (deformation). | Alterations in compliance and elastance in respiratory disease. | Respiratory distress syndrome.<br>Management of ventilation strategies.<br>Pneumothorax. |
| "U" lung volume–PVR relationship | Inverse relationship between lung volume and pulmonary vascular resistance. | Adaptation of lung volume mechanics with changes in PVR. | PH.<br>Surfactant deficiency. |

*CPAP*, continuous positive airway pressure.

of treatment (nonsteroidal anti-inflammatory medications) when treatment is not effective in resolving the problem. Of note, there is increasing skepticism about the use of BPD as the most appropriate target end point. The definition of BPD is based on the need for respiratory treatment (oxygen, respiratory support), which may be explained by a multitude of reasons beyond true BPD (eg, pulmonary vascular disease, atrial level shunts, pulmonary vein disease, pulmonary venous hypertension due to diastolic left ventricular failure in the setting of systemic hypertension), many of which may coexist and have no relationship to the primary trial question.

The cumulative effects of a nonstandardized definition of the problem (PDA), ineffective treatment, and diverse phenotypic possibilities within the end point of interest contribute to the failure of clinical trials to demonstrate any meaningful benefit. Of these, the prioritization of the "pragmatic trial" at the expense of diagnosis purity represents the greatest limitation. It is unlikely that randomizing patients with a PDA of uncertain hemodynamic significance and high likelihood of spontaneous closure to medical therapy with limited efficacy will yield meaningful clinical data. The ethics of continuing to conduct randomized trials from both a patient outcome and fiscal perspective, without defining the population of interest, is therefore questionable. Consider randomizing adults with any form of chest pain to use of a thrombolytic such as streptokinase or tissue plasminogen activator—would this pragmatic approach be acceptable to cardiologists, medical internists, or the patient themselves?

How does the field move beyond the current state of polarized medicine? In the words of Albert Einstein, "If I were given one hour to save the world, I would spend 59 minutes defining the problem and one minute solving it." Unfortunately, many clinicians and institutions have drifted toward a noninterventional (nihilistic) approach to PDA care, often failing to recognize the limitations of published trials and the impurity of diagnostic methods. Of greater concern is the ambivalence to mounting evidence that such an approach in the most immature infants is associated with increased incidence of BPD,[32-34] pulmonary vascular disease,[35,36] and PH.[37] How much these perspectives relate to absolute trust and unquestioning belief in data from a randomized trial or a drift away from physiology-based care remains unclear.

## Current State of Cardiovascular Physiology Education in Neonatology

Early advances in neonatal cardiorespiratory care were driven by an enhanced understanding of ambient physiology and mechanisms of disease. As a trainee in neonatal medicine in the 1990s in Ireland, daily rounds were dominated by in-depth conversations related to physiologic precision, maintenance of a stable biologic milieu, and understanding disease (McNamara, personal experience). Yet, bedside neonatal rounds in the year 2024 look very different. Whether driven by the time constraints of having to see high volumes of patients, the need to review systematic "head-to-toe" checklists, or the need for more detailed medical documentation, there is often little time to engage in meaningful discussions related to cardiorespiratory physiology or mechanism of disease. The consequences of the lack of trainee exposure to bedside physiology or mechanistic discussions related to disease are unclear; however, it is plausible that they further promote a symptom-based, rather than disease-based, approach to neonatal care. For the 2024 trainee checklists, single-metric thresholds and algorithms are easy to follow but actively discourage the importance of understanding "why" and selecting treatments based on enhanced diagnostic or physiologic precision.

In an era in which trainee hours have fallen, faculty have less experience, and cardiology-performed echocardiography assessments are not usually physiology based, the approach to neonatal hemodynamic care has become less precise. Although neonatal hemodynamics research, conducted by neonatologists with echocardiography expertise, has increased, these neonatal hemodynamics programs are confined to a minority of US centers.[38] The ripple effect on trainee education and their approach to rationalizing acute and chronic medical situations is likely to further contribute to impaired diagnostic consideration. Of concern, trainees in neonatal–perinatal medicine report limited cardiovascular physiologic interaction or structured learning.[39] In one national survey, two-thirds of trainees were "not completely satisfied" with their education in cardiovascular physiology in programs without a hemodynamics service, whereas trainees in programs with a hemodynamic consultation reported increased exposure to cardiovascular physiology. More than one-half of trainees reported no training on differences between the preterm and term myocardium, and important cardiovascular physiologic laws such as the Frank–Starling law (preload and heart function), stress–velocity relationship (afterload and heart function), and the force–frequency relationship (heart rate and heart function) were rarely taught in formal structured or bedside learning sessions or considered in making decisions about the selection of cardiovascular medications.[40] These perspectives are alarming and question the efficacy of training in neonatal–perinatal medicine and the validity of cardiovascular care practices in the NICU setting.

## Importance of Characterizing Phenotypes

The biological contributors to neonatal cardiopulmonary disease are complex, and knowledge of disease phenotype can ensure precision medicine. Comprehensive clinical evaluations combined with physiology assessment help decipher etiopathologies in neonatal disease,[41] may identify cardiopulmonary compromise earlier,[1] and ultimately guide individualized treatment tailored by the specific phenotype of the disease. PVD, and its most severe form of PH, represent an ideal example for which to implement physiology-based approaches for the management its presenting phenotypes.[41] PVD and PH may be present at different stages after preterm

birth, representing a physiologic hemodynamic spectrum accounting for variance in acute, chronic, and sustained phenotypic signatures.[2,42] Previous classification systems have grouped neonatal PVD based on endotype of the pulmonary vasculature,[43] or placed them in categories according to clinical classifications (eg, World Health Organization[44,45]) Although the potential contributors to PH are commonly identified using these classifications, there is significant overlap between disease and less emphasis on the spectrum of the physiology that delineate the cardiopulmonary contributors to PH based on the phenotypic contributions within the acute, chronic, or sustained presentations.[2]

Phenotypic differentiation based on physiology holds the potential to provide a high index of suspicion for the cardiac, pulmonary, and pulmonary vascular contributions to disease (**Table II**). Although PVD and PH are defined by the degree of pathologic elevation of pressure in the pulmonary vascular bed, the heterogeneity of PH phenotypes is best delineated by considering the traditional etiologic categorization of the pulmonary vasculature within the framework of the phenotypical relationships between the major contributors to pressure in the lungs: mean transpulmonary pressure gradient, pulmonary blood flow (PBF) and pulmonary vascular resistance (PVR). For example, chronic PH in infants born premature is commonly associated with severe BPD due to pulmonary vasculature remodeling and elevated PVR. However, chronic PH also may present with 2 other important phenotypes: (1) systemic-to-pulmonary shunt (eg, PDA, atrial or ventricular septal defects); with high PBF leading to limited compliance, vascular remodeling, and interstitial edema (flow-driven phenotype) and/or (2) alterations in transpulmonary pressure gradient that results from a left heart phenotype (eg, systemic hypertension, left ventricular diastolic dysfunction, or pulmonary vein stenosis). The World Health Organization classifies the PH associated with BPD (BPD-PH) as Group 3 PH, but this does not fully consider pathologic changes that each variable of pulmonary pressure contribute to disease. Accordingly, since chronic PH also can result from exposure to high PBF, left heart failure, or even genetic loss-of-function mutations, combining the categorization based on clinical disease, endotype of the pulmonary vasculature, and the hemodynamic phenotype will actually assign BPD-PH to more than one PH group according to the World Symposium of PH (2018).[46] As such, comprehensive physiological and hemodynamic evaluations can help distinguish the phenotypical presentation of specific disease etiologies and provide critical insights into the mechanisms contributing to development and severity of disease.

## How Phenotypes May Define Treatment Paths

Careful delineation of the phenotype is essential to enable physiologically appropriate selection of therapy that optimizes the cellular homeostasis of blood flow and tissue oxygenation. Physiological evaluations that are comprehensive, quantitative, and thorough are not only valuable in identifying the physiology but may be critical in targeting treatment strategies for the lung, heart, or pulmonary vascular dysfunction, and ultimately monitoring therapeutic response. Both cardiovascular and lung parenchymal disease may present with hypoxemic respiratory failure, but the phenotype of each disease will affect the therapeutic choice. Clinical differentiation of cardiopulmonary phenotypes of disease is, however, challenging. Chronic PH as heterogeneous disease is an example that demands attention to the specific phenotypes for optimal diagnosis and management. The phenotypic variance of cardiopulmonary disease with the unique relationship between PVR, alterations in lung compliance from increased PBF, and heart function of each phenotype need to be considered when formulating an approach to clinical treatment pathways. The adaptive process for the impaired circulation is complex but can be particularly more challenging in specific conditions that alter transitional physiology in the early and later neonatal periods and require specialized treatments strategies. Using physiology, comprehensive hemodynamic evaluations (eg, neonatal echocardiography coupled with clinical examination) have the potential to guide therapeutic intervention

**Table II. Physiology–drive phenotypes of chronic PH**

| Phenotypes | Pathophysiology | Characteristic echocardiographic features | Physiological/hemodynamic approach to treatment |
|---|---|---|---|
| Classic | Pulmonary vascular remodeling, intermittent hypoxia (↑ PVR) | Dilated RV, septal flattening in systole, predominantly R→L shunts, ↑PVRi, PA Doppler notching | Optimal lung parenchyma and recruitment, pulmonary vasodilators<br>Phenotyping BPD (see **Table III**) |
| Shunt-mediated | High volume of blood in a circuit with limited compliance, vascular remodeling, edema (↑ PBF) | Dilated RV or LV, discrepant ventricular outputs with either ↑RVO, ↑LVO or both septal flattening in diastole if ASD/VSD | Manage shunt; maintain ↑PVR, avoid selective pulmonary vasodilators<br>Close shunts |
| Left-heart mediated | High LV afterload leads to ↑LVEDP, LA hypertension, pulmonary venous congestion | Dilated LV, LV diastolic dysfunction (↓transmitral passive (e-wave) velocity, ↑IVRT, ↓PV velocities), MR and/or AI | Manage systemic hypertension<br>Pulmonary vein stenosis management<br>Long-term follow-up |

*AI*, aortic incompetence; *ASD*, atrial septal defect; *IVRT*, isovolumic relaxation time; *LA*, left atrium; *LV*, left ventricle; *LVEDP*, left ventricular end-diastolic pressure; *LVO*, left ventricular output; *MR*, mitral regurgitation; *PA*, pulmonary artery; *PV*, pulmonary vein; *PVRi*, pulmonary vascular resistance index; *R-L*, right to left; *RV*, right ventricle; *RVO*, right ventricular output; *VSD*, ventricular septal defect.

**Table III. Pathophysiologic lung specific phenotypes of BPD**

| BPD phenotypes | Mechanism of disease | Therapeutic approaches tailored to phenotype |
|---|---|---|
| Alveolar disease | Interruption of alveolarization<br>Airway inflammation<br>Structural changes | High tidal volumes<br>Long exhalation time/low rate<br>Optimization of nutrition Evaluate for aspiration |
| Small airway disease | Airway inflammation | Bronchodilators<br>Inhaled corticosteroids<br>Systemic steroids for exacerbations |
| Large airway disease | Tracheobronchial malacia<br>Structural changes in proximal or distal airways | Dynamic bronchoscopy with PEEP titration<br>Tracheopexy and/or bronchopexy if disease is primarily in proximal airways<br>Evaluate for aspiration |
| Pulmonary vascular disease | Interruption of vasculogenesis<br>Flow-mediated (V/Q mismatch)<br>Left heart mediated | Screening echocardiogram and determine phenotype (see Table II)<br>± Cardiac catheterization<br>Optimize ventilation/oxygenation<br>Evaluate for aspiration<br>Correct metabolic derangements<br>Pulmonary vasodilators |
| Lymphatic disease | Interruption of lymphatics<br>Anasarca<br>Immune dysfunction | Maintenance of fluid balance<br>Diuresis<br>Optimization of nutrition |
| Interstitial lung disease | Interruption of alveolarization<br>Airway inflammation<br>Interruption of vasculogenesis | Genetic evaluations |
| Infectious | Airway inflammation | Respiratory culture<br>Consider prophylaxis |

*PEEP*, positive end-expiratory pressure; *V/Q*, ventilation–perfusion.

based on valuable insights into the phenotypical presentation of disease.

Phenotypic differentiation is also critical in guiding the development of screening algorithms to detect chronic PH in infants born preterm. The current consensus guidelines and expert opinions vary as to the appropriate patient population to screen, identification of additional risk factors and comorbidities, timing of screening, screening modalities, management, follow-up, and appropriate subspecialty consultation.[41,44,45,47,48] Although each set of guidelines was developed by multidisciplinary panels of experts, the major limitations are lack of clear diagnostic definitions that use the physiology to decipher the phenotypical presentation and guide therapeutic intervention. For example, if a neonate screens positive for PH, it may not initially be evident if the PH is due to the underlying lung disease ("classic BPD"), excessive PBF from systemic-to-pulmonary shunting, or impact from left heart disease. The etiology of the hypoxemia in these children is multifactorial, and treatment must be tailored to the biological phenotype contributing to the PH. Specifically, a pulmonary vasodilator may be an appropriate agent for the treatment of classic BPD with elevated PVR but would be inappropriate in the BPD-PH due to increased PBF or left heart disease. Phenotypic delineation will further provide insight into the ventilatory strategies to optimize lung recruitment, consider small and large airway, and even assess for infectious. As such, the treatment pathway for chronic PH must rely on the physiological delineation with the clinical, echocardiography, and biochemical clues. Deciphering pulmonary vascular phenotypes and its physiological impact are critical for diagnostic evaluation, selection and implementation of therapeutic strategies, and identification of infants born preterm at risk for late cardiopulmonary disease.[2]

## Interface between Targeted Neonatal Echocardiography and Phenotype Characterization

TnECHO refers to the use of comprehensive hemodynamics evaluation, which incorporates physiologic data acquired through echocardiography, to obtain accurate, reliable, and real-time information on developmental hemodynamics in sick newborns.[49] This approach has allowed earlier recognition of cardiovascular compromise and allows for precise, timely, and longitudinal management. The distinction from point-of-care ultrasonography, which provides limited and brief one-time assessments, is important.[50]

Current definitions of BPD are based on the amount of oxygen or respiratory support provided, rather than underlying pathophysiology.[51] Clinical assessment is therefore challenging, as there may be overlap between several contributing disease phenotypes (Table III). Among some infants, lung parenchymal disease, characterized by fibrosis with large and simplified alveolar development, leads to reduced lung surface area for gas exchange and may, on its own, present with respiratory failure and chronic dependence on mechanical support.[52,53] This may be referred to as classic

BPD without PH. Among infants with severe BPD, however, the reported incidence of contemporaneous classic BPD with PH is between 15% and 58%.[54-56] Additional phenotypes include chronic PH secondary to excessive PBF seen in patients with prolonged intracardiac (eg, atrial communication) or transductal shunts and PVD secondary to diastolic heart failure with preserved ejection fraction seen in the setting of systemic hypertension. The optimum approach to screening for chronic PH, regardless of primary etiology, among patients with BPD is unknown. Its presenting features often are subtle, and the timing of onset is insidious and also likely variable, with findings reported as early as 28 weeks of postmenstrual age in some patients.[55] Due to the marked variance in underlying pathophysiology and the potential negative impact of incorrect treatment selection, early diagnostic echocardiography and close surveillance are recommended, especially in evolving BPD. There are important management considerations that highlight the importance of phenotypic characterization. For example, the non-judicious use of selective pulmonary vasodilators (eg, inhaled nitric oxide) may aggravate pulmonary edema in patients with diastolic left heart failure and pulmonary venous hypertension due to left ventricular diastolic dysfunction or pulmonary vein stenosis. Rather, recent evidence suggests that angiotensin-converting enzyme inhibition may represent the optimal treatment strategy for PH of left heart origin.[15]

Finally, increasing evidence that adults born premature are at increased risk of systemic hypertension, exercise-induced heart dysfunction, ischemic heart disease, heart failure, and PH, which negatively influence adult heart disease, further emphasizes the importance of characterizing phenotypes in the neonatal period.[6-8,57] In the words of the ancient Greek philosopher Phaedrus, "Things are not always what they seem; the first appearance deceives many; the intelligence of a few perceives what has been carefully hidden." Increased access to longitudinal echocardiography, through the establishment of neonatal hemodynamics programs, will enhance the extent of surveillance and quality of phenotypic characterization.

## The Intersection between Physiology and Clinical Trials in Neonatology

There are very few well-conducted randomized trials of cardiorespiratory therapies in neonatology. Too often trials are designed based on "what we do" rather than "whether there is sufficient mechanistic and pharmacologic insight to support the scientific merits of conducting the trial," which has major implications from both a financial sustainability and clinical relevance perspective. One example would be conducting trials of diuretic therapy in infants with BPD without determining the specific target population in which this treatment may be biologically relevant. Although diuretics may have a beneficial role in patients with pulmonary edema secondary to systemic hypertension associated left ventricular diastolic dysfunction or moderate- to high-volume atrial level shunts, they may little benefit in patients with straightforward BPD where the need for ongoing respiratory support is secondary to lung inflammation, fibrosis, or impaired alveolarization. Our intent is not to dissuade neonatologists away from conducting randomized trials but to call attention to the need for incorporation of the dynamic nature of cardiorespiratory physiology to optimize study design. An additional objective is to shift the focus of trial design toward disease-specific states and populations of interest where pathophysiological mechanism is understood and treatment pharmacology is characterized. Funding agencies must carefully review whether a trial reflects appropriate mechanistic understanding of the disease state, sufficient appreciation of pharmacologic relevance of the study medication, and patient selection based on concrete evidence of the disease state. The importance of phenotypes and diagnostic precision must be prioritized in neonatal clinical research, and randomized clinical trials would benefit from research teams that include physiologists and hemodynamic and respiratory scientists to optimize methodology. One example is the National Institutes of Health–funded Percutaneous intervention Versus Observational Trial of Arterial ductus in Low-weight infants (PIVOTAL) trial, which has embraced the importance of standardization of patient enrollment through the incorporation of an ECHOCORE, whereby all echocardiography studies of hemodynamic significance of the PDA are performed according to a standardized protocol and sent to the core laboratory for independent adjudication of hemodynamic significance before randomization. Unlike all previous PDA trials, verification of the population of interest will help optimize the enrollment process. This concept has broader applicability to other randomized trial designs in neonatology.

## Opportunities to Enhance Cardiorespiratory Physiology Education

One of the potential drivers of the attrition in cardiorespiratory physiology education has been the reduction in exposure of neonatal trainees and faculty to neonates with major cardiac malformations. Similarly, training of pediatric cardiologists and pulmonologists has been limited by the lack of exposure to bedside care and discussions provided by critical interactions among the disciplines. In some centers, these patients are managed primarily by neonatologists, in collaboration with the cardiac and pulmonary teams, but this is now the exception.[58] The need for such interdisciplinary programs for comprehensive care of infants with severe BPD has been described,[47] but the development of strategies that enhance training and education within the fields warrants further work. Bodies that oversee neonatal education, like the Accreditation Council for Graduate Medical Education, should appraise whether the current clinical exposures and educational framework related to them ensure neonatology trainees are sufficiently trained for independent practice. One recommendation would be to mandate formal rotations for neonatal trainees in cardiovascular intensive care units or

neonatal hemodynamics. Similarly, greater exposure and rotations of pulmonary and cardiology trainees in NICUs would likely enhance exposure, teaching and the development of skill sets that will enrich important clinical strengths for the next generation of clinicians and clinician–scientists. The clear limitation is that some programs what do not have these rotations on-site. Nevertheless, neonatal cardiorespiratory physiology education and, in particular hemodynamic physiology, should be recognized as a blind spot in contemporary neonatal education.

## Conclusions

Despite improvements in clinical care, a greater emphasis on applying and teaching bedside heart and lung physiology in the care of critically ill neonates is necessary to develop the next generation of care providers and clinician–scientists to improve short- and long-term outcomes. This should be considered a priority for pediatric residency and neonatal fellowship programs to offset the significant attrition in physiology-based thinking in daily neonatal care. Integrating the application of such as targeted neonatal echocardiography, LUS and other novel technologies to better define and apply greater precision based on physiologic-based targets will likely improve clinical care, research and enhancing the development of drug and medical devices in the future. ■

## CRediT Authorship Contribution Statement

**Patrick J. McNamara:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **Steven Abman:** Writing – review & editing, Writing – original draft. **Philip T. Levy:** Writing – review & editing, Writing – original draft.

## Declaration of Competing Interest

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## References

1. Giesinger RE, Rios DR, Chatmethakul T, Bischoff AR, Sandgren JA, Cunningham A, et al. Impact of early hemodynamic screening on extremely preterm outcomes in a high-performance center. Am J Respir Crit Care Med 2023;208:290-300.
2. Mirza H, Mandell EW, Kinsella JP, McNamara PJ, Abman SH. Pulmonary vascular phenotypes of prematurity: the path to precision medicine. J Pediatr 2023;259:113444.
3. Arjaans S, Haarman MG, Roofthooft MTR, Fries MWF, Kooi EMW, Bos AF, et al. Fate of pulmonary hypertension associated with bronchopulmonary dysplasia beyond 36 weeks postmenstrual age. Arch Dis Child Fetal Neonatal Ed 2021;106:45-50.
4. Lagatta JM, Hysinger EB, Zaniletti I, Wymore EM, Vyas-Read S, Yallapragada S, et al. The impact of pulmonary hypertension in preterm infants with severe bronchopulmonary dysplasia through 1 year. J Pediatr 2018;203:218-24.e3.
5. Bates ML, Levy PT, Nuyt AM, Goss KN, Lewandowski AJ, McNamara PJ. Adult cardiovascular health risk and cardiovascular phenotypes of Prematurity. J Pediatr 2020;227:17-30.
6. Goss KN, Beshish AG, Barton GP, Haraldsdottir K, Levin TS, Tetri LH, et al. Early pulmonary vascular disease in young adults born preterm. Am J Respir Crit Care Med 2018;198:1549-58.
7. Lewandowski AJ, Raman B, Bertagnolli M, Mohamed A, Williamson W, Pelado JL, et al. Association of preterm birth with myocardial fibrosis and diastolic dysfunction in young adulthood. J Am Coll Cardiol 2021;78:683-92.
8. Lewandowski AJ, Augustine D, Lamata P, Davis EF, Lazdam M, Francis J, et al. Preterm heart in adult life: cardiovascular magnetic resonance reveals distinct differences in left ventricular mass, geometry, and function. Circulation 2013;127:197-206.
9. Lewandowski AJ, Levy PT, Bates ML, McNamara PJ, Nuyt AM, Goss KN. Impact of the vulnerable preterm heart and circulation on adult cardiovascular disease risk. Hypertension 2020;76:1028-37.
10. Giesinger RE, Levy PT, Lauren Ruoss J, El Dib M, Mohammad K, Wintermark P, et al. Cardiovascular management following hypoxic-ischemic encephalopathy in North America: need for physiologic consideration. Pediatr Res 2021;90:600-7.
11. Giesinger RE, El Shahed AI, Castaldo MP, Breatnach CR, Chau V, Whyte HE, et al. Impaired right ventricular performance is associated with adverse outcome following hypoxic ischemic encephalopathy. Am J Respir Crit Care Med 2019;200:1294-305.
12. Giesinger RE, El Shahed AI, Castaldo MP, Bischoff AR, Chau V, Whyte HEA, et al. Neurodevelopmental outcome following hypoxic ischaemic encephalopathy and therapeutic hypothermia is related to right ventricular performance at 24-hour postnatal age. Arch Dis Child Fetal Neonatal Ed 2022;107:70-5.
13. Reyes-Hernandez ME, Bischoff AR, Giesinger RE, Rios DR, Stanford AH, McNamara PJ. Echocardiography assessment of left ventricular function in extremely preterm infants, born at less than 28 weeks' gestation, with bronchopulmonary dysplasia and systemic hypertension. J Am Soc Echocardiogr 2024;37:237-47.
14. Stanford AH, Reyes M, Rios DR, Giesinger RE, Jetton JG, Bischoff AR, et al. Safety, feasibility, and impact of enalapril on cardiorespiratory physiology and health in preterm infants with systemic hypertension and left ventricular diastolic dysfunction. J Clin Med 2021;10:4519.
15. Sullivan RT, Tandel MD, Bhombal S, Adamson GT, Boothroyd DB, Tracy M, et al. Role of left atrial hypertension in pulmonary hypertension associated with bronchopulmonary dysplasia. Front Pediatr 2022;10:1012136.
16. Maia PD, Gien J, Kinsella JP, Zablah J, Morgan G, Ivy DD, et al. Hemodynamic characterization of neonates with congenital diaphragmatic hernia-associated pulmonary hypertension by cardiac catheterization. J Pediatr 2023;255:230-5.e2.
17. Patel N, Lally PA, Kipfmueller F, Massolo AC, Luco M, Van Meurs KP, et al. Ventricular dysfunction is a critical determinant of mortality in congenital diaphragmatic hernia. Am J Respir Crit Care Med 2019;200:1522-30.
18. Massolo AC, Paria A, Hunter L, Finlay E, Davis CF, Patel N. Ventricular dysfunction, interdependence, and mechanical dispersion in newborn infants with congenital diaphragmatic hernia. Neonatology 2019;116:68-75.
19. Giesinger RE, Elsayed YN, Castaldo MP, McNamara PJ. Targeted neonatal echocardiography-guided therapy in vein of Galen aneurysmal malformation: a report of two cases with a review of physiology and approach to management. AJP Rep 2019;9:e172-6.
20. Batton B, Li L, Newman NS, Das A, Watterberg KL, Yoder BA, et al. Use of antihypotensive therapies in extremely preterm infants. Pediatrics 2013;131:e1865-73.

21. Alderliesten T, Lemmers PM, van Haastert IC, de Vries LS, Bonestroo HJ, Baerts W, et al. Hypotension in preterm neonates: low blood pressure alone does not affect neurodevelopmental outcome. J Pediatr 2014;164:986-91.
22. Backes CH, Hill KD, Shelton EL, Slaughter JL, Lewis TR, Weisz DE, et al. Patent ductus arteriosus: a contemporary perspective for the pediatric and adult cardiac care provider. J Am Heart Assoc 2022;11:e025784.
23. Powell ML. Patent ductus arteriosus in premature infants. Med J Aust 1963;2:58-60.
24. Bischoff AR, Kennedy KF, Backes CH, Sathanandam S, McNamara PJ. Percutaneous closure of the patent ductus arteriosus in infants ≤2 kg: IMPACT Registry insights. Pediatrics 2023;152:e2023061460.
25. Hamrick SEG, Sallmon H, Rose AT, Porras D, Shelton EL, Reese J, et al. Patent ductus arteriosus of the preterm infant. Pediatrics 2020;146:e20201209.
26. Zonnenberg I, de Waal K. The definition of a haemodynamic significant duct in randomized controlled trials: a systematic literature review. Acta Paediatr 2012;101:247-51.
27. de Freitas Martins F, Ibarra Rios D, MH FR, Javed H, Weisz D, Jain A, et al. Relationship of patent ductus arteriosus size to echocardiographic Markers of shunt volume. J Pediatr 2018;202:50-5.e3.
28. Rios DR, Bhattacharya S, Levy PT, McNamara PJ. Circulatory insufficiency and hypotension related to the ductus arteriosus in neonates. Front Pediatr 2018;6:62.
29. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol 2010;30:241-52.
30. Hundscheid T, Onland W, Kooi EMW, Vijlbrief DC, de Vries WB, Dijkman KP, et al. Expectant management or early Ibuprofen for patent ductus arteriosus. N Engl J Med 2023;388:980-90.
31. Liebowitz M, Katheria A, Sauberan J, Singh J, Nelson K, Hassinger DC, et al. Lack of equipoise in the PDA-TOLERATE trial: a comparison of eligible infants enrolled in the trial and those treated outside the trial. J Pediatr 2019;213:222-6.e2.
32. Altit G, Saeed S, Beltempo M, Claveau M, Lapointe A, Basso O. Outcomes of extremely premature infants comparing patent ductus arteriosus management approaches. J Pediatr 2021;235:49-57.e2.
33. Relangi D, Somashekar S, Jain D, Vanbuskirk S, Bancalari E, Sosenko I, et al. Changes in patent ductus arteriosus treatment strategy and respiratory outcomes in premature infants. J Pediatr 2021;235:58-62.
34. Wang H, Jain A, Weisz DE, Moraes TJ. Trends in patent ductus arteriosus ligation in neonates and changes in outcomes: a 10-year multicenter experience. Pediatr Pulmonol 2021;56:3250-7.
35. Gentle SJ, Travers CP, Clark M, Carlo WA, Ambalavanan N. Patent ductus arteriosus and development of bronchopulmonary dysplasia with pulmonary hypertension. Am J Respir Crit Care Med 2022;207:921-8.
36. Philip R, Nathaniel Johnson J, Naik R, Kimura D, Boston U, Chilakala S, et al. Effect of patent ductus arteriosus on pulmonary vascular disease. Congenit Heart Dis 2019;14:37-41.
37. Wang C, Ma X, Xu Y, Chen Z, Shi L, Du L. A prediction model of pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. Front Pediatr 2022;10:925312.
38. Giesinger RE, Stanford AH, Rios DR, Bhombal S, Fraga MV, Levy VY, et al. Targeted neonatal echocardiography in the United States of America: the contemporary perspective and challenges to implementation. Pediatr Res 2019;85:919-21.
39. Friedmann I, McNamara PJ, Bhattacharya S, Cheng A. Educational impact of targeted neonatal echocardiography and hemodynamics programs on neonatal–perinatal medicine fellows. Am J Perinatol 2022;14:1-8.
40. Rowland DG, Gutgesell HP. Noninvasive assessment of myocardial contractility, preload, and afterload in healthy newborn infants. Am J Cardiol 1995;75:818-21.
41. Levy PT, Levin J, Leeman KT, Mullen MP, Hansmann G, Kourembanas S. Diagnosis and management of pulmonary hypertension in infants with bronchopulmonary dysplasia. Semin Fetal Neonatal Med 2022;27:101351.
42. Thébaud B, Goss KN, Laughon M, Whitsett JA, Abman SH, Steinhorn RH, et al. Bronchopulmonary dysplasia. Nat Rev Dis Primers 2019;5:78.
43. Ruoss JL, Rios DR, Levy PT. Updates on management for acute and chronic phenotypes of neonatal pulmonary hypertension. Clin Perinatol 2020;47:593-615.
44. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation 2015;132:2037-99.
45. Hansmann G, Koestenberger M, Alastalo TP, Apitz C, Austin ED, Bonnet D, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: the European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant 2019;38:879-901.
46. Levy PT, Jain A, Nawaytou H, Teitel D, Keller RL, Fineman J, et al. Risk assessment and monitoring of chronic pulmonary hypertension in premature infants. J Pediatr 2019;217:199-209.
47. Abman SH, Collaco JM, Shepherd EG, Keszler M, Cuevas-Guaman M, Welty SE, et al. Interdisciplinary care of children with severe bronchopulmonary dysplasia. J Pediatr 2017;181:12-28.e1.
48. Krishnan U, Feinstein JA, Adatia I, Austin ED, Mullen MP, Hopper RK, et al. Evaluation and management of pulmonary hypertension in children with bronchopulmonary dysplasia. J Pediatr 2017;188:24-34.
49. Hébert A, Lavoie PM, Giesinger RE, Ting JY, Finan E, Singh Y, et al. Evolution of training guidelines for echocardiography performed by the neonatologist: toward hemodynamic consultation. J Am Soc Echocardiogr 2019;32:785-90.
50. Jain A, Ruoss JL, Fraga MV, McNamara PJ. Clarification of boundaries and scope of cardiac POCUS vs. targeted neonatal echocardiography. J Perinatol 2023;43:1207-10.
51. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The diagnosis of bronchopulmonary dysplasia in very preterm infants. An evidence-based approach. Am J Respir Crit Care Med 2019;200:751-9.
52. Bonikos DS, Bensch KG, Northway WH Jr, Edwards DK. Bronchopulmonary dysplasia: the pulmonary pathologic sequel of necrotizing bronchiolitis and pulmonary fibrosis. Hum Pathol 1976;7:643-66.
53. Husain AN, Siddiqui NH, Stocker JT. Pathology of arrested acinar development in postsurfactant bronchopulmonary dysplasia. Hum Pathol 1998;29:710-7.
54. An HS, Bae EJ, Kim GB, Kwon BS, Beak JS, Kim EK, et al. Pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. Korean Circ J 2010;40:131-6.
55. Bhat R, Salas AA, Foster C, Carlo WA, Ambalavanan N. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. Pediatrics 2012;129:e682-9.
56. Khemani E, McElhinney DB, Rhein L, Andrade O, Lacro RV, Thomas KC, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics 2007;120:1260-9.
57. Crump C, Winkleby MA, Sundquist K, Sundquist J. Risk of hypertension among young adults who were born preterm: a Swedish national study of 636,000 births. Am J Epidemiol 2011;173:797-803.
58. Chaudhry PM, Sen S, Steurer M, Levy VY, Gowda S, Ball MK, et al. Perioperative care models for neonates with congenital heart disease: evolving role of neonatology within the cardiac intensive care unit. World J Pediatr Congenit Heart Surg 2023;14:481-9.