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Acute Respiratory Distress Syndrome, Mechanical Ventilation, and Neurological Vulnerability in Neonates with Congenital Heart Disease

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Abstract: ***Background****: The postnatal transitional period represents a phase of marked hemodynamic adaptation in neonates, particularly vulnerable in those with congenital heart disease (CHD). Acute respiratory distress syndrome (ARDS) in this population may reflect circulatory instability rather than primary pulmonary pathology.*
Objectives*: To evaluate respiratory outcomes in neonates with CHD, focusing on the relationship between hemodynamic phenotype, ARDS development, and predictors of invasive mechanical ventilation.*
Methods: *We conducted a retrospective single-center study including 138 neonates with confirmed CHD admitted within the first 28 days of life. Clinical, demographic, and respiratory data were analyzed. ARDS severity, symptom burden, and prostaglandin E1 administration were evaluated as potential predictors of invasive mechanical ventilation using multivariate logistic regression.*
Results: *ARDS developed in 62.3% of patients, most frequently within the first day of life. The number of clinical symptoms at presentation was the sole independent predictor of ARDS (OR 2.4; 95% CI 1.84–3.14; $p < 0.001$). Invasive mechanical ventilation was required in 38.4% of neonates and was strongly associated with ARDS severity (OR 3.19; 95% CI 2.16–4.69; $p < 0.001$). These findings suggest that respiratory failure often reflects underlying hemodynamic instability during the transitional period.*
Conclusions: *In neonates with CHD, ARDS appears closely linked to circulatory imbalance rather than isolated lung disease. A physiology-driven approach integrating early hemodynamic stabilization with lung-protective ventilation strategies may improve outcomes in this high-risk population.*

Keywords: *congenital heart disease; acute respiratory distress syndrome; ARDS; neurodevelopmental impairment.*

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1. Introduction

Congenital heart disease (CHD) represents the most common category of major congenital anomalies, affecting approximately 8–9 per 1,000 live births worldwide (Hoffman & Kaplan, 2002; van der Linde et al., 2011). Advances in prenatal diagnosis, perioperative care, and surgical techniques have substantially improved survival. However, the neonatal period remains a critical window of vulnerability, characterized by a high burden of cardiorespiratory instability (Gowda et al., 2024).

Respiratory failure is a frequent feature presenting in neonates with critical CHD and often necessitates admission to neonatal intensive care units. Unlike respiratory distress syndrome of prematurity, respiratory compromise in term or near-term neonates with CHD is rarely driven by primary pulmonary immaturity. Instead, it reflects complex cardiopulmonary interactions, including pulmonary over-circulation, systemic hypoperfusion, metabolic acidosis, and inflammatory lung injury (De Boode, 2020).

The pathophysiology of respiratory failure in CHD is heterogeneous. Large left-to-right shunts may cause pulmonary edema and impaired gas exchange, while duct-dependent obstructive lesions predispose to systemic hypoxia and respiratory fatigue secondary to low cardiac output (Bronicki et al., 2022). Acute respiratory distress syndrome (ARDS) has increasingly been recognized as a frequent complication in this population, particularly during the immediate postnatal transition, when rapid hemodynamic shifts occur (Himebauch et al., 2018).

The present study aimed to explore respiratory outcomes in neonates with CHD and identify associations between hemodynamic phenotype, ARDS and invasive mechanical ventilation.

2. Materials and Methods

Study Population. Neonates aged 0–28 days with a postnatal echocardiographic diagnosis of CHD were eligible. Inclusion required complete documentation of respiratory status and ventilatory support. Exclusion criteria included respiratory failure unrelated to cardiac physiology and incomplete records. A total of 138 neonates met the inclusion criteria.

Data Collection. Demographic data, gestational age, birth weight, and length were recorded. CHD was classified anatomically and by Bethesda complexity. ARDS was diagnosed according to modified neonatal ARDS criteria based on the Montreux definition (De Luca et al., 2017), including acute onset of respiratory failure, bilateral pulmonary infiltrates on chest imaging, absence of left atrial hypertension as the primary cause of pulmonary edema, and impaired oxygenation assessed using oxygenation index or oxygen saturation index. ARDS severity was categorized according to standard neonatal ARDS severity stratification. Mechanical ventilation, prostaglandin E1 administration, and major complications were documented.

Statistical Analysis. Continuous variables are reported as mean ± SD; categorical variables as n (%). Comparisons used t-test or χ^2 as appropriate. Logistic regression identified predictors of ARDS and mechanical ventilation. A p-value <0.05 was considered significant.

Study Design and Ethics. The study protocol received ethical approval from the Ethics Committee of Cuza Vodă Clinical Hospital of Obstetrics and Gynecology, Iaşi, Romania (approval number: 5/10.02.2025) and Grigore T. Popa University of Medicine and Pharmacy, Iaşi, Romania (approval number: 640/23.09.2025), before study initiation and manuscript submission. The study was conducted in accordance with the principles of the Declaration of Helsinki. The analysis was performed using anonymized data and written informed consent for the use of clinical data for research purposes was obtained from the parents or legal guardians at the time of hospital admission.

3. Results

3.1. Study Population and Baseline Clinical Severity

The study cohort consisted of 138 neonates diagnosed with CHD, with a balanced sex distribution (70 males, 50.72%; 68 females, 49.28%). A substantial proportion of patients originated from rural areas (68.84%), reflecting potential disparities in prenatal screening and access to specialized perinatal care.

Perinatal characteristics of the cohort are summarized in Table I. The mean gestational age was 36.9 ± 2.6 weeks, with male neonates born at a significantly higher gestational age than females. Prematurity affected approximately one-third of the cohort, predominantly in the late preterm category, without significant sex-related differences. Birth weight and length were within expected ranges, indicating relatively preserved somatic growth.

Table 1. Perinatal Characteristics of the study cohort

Parameter	Total cohort (n = 138)	Male (n = 70)	Female (n = 68)	p-value
Gestational age (weeks), mean ± SD	36.93 ± 2.59	37.47 ± 2.31	36.37 ± 2.75	0.0117
Prematurity, n (%)	49 (35.51)	20 (28.57)	29 (42.65)	0.368
Birth weight (g), mean ± SD	2692.55 ± 865.11	—	—	—
Birth length (cm), mean ± SD	47.70 ± 4.31	—	—	—

At admission, a large proportion of neonates presented with multiple clinical symptoms, reflecting a high baseline burden of systemic instability. This finding was particularly evident among patients with severe and duct-dependent CHD phenotypes, suggesting compromised postnatal cardiopulmonary adaptation from the earliest stages of life.

Genetic abnormalities were identified in 37 neonates (26.8%), of whom 29 (21.0%) were classified as syndromic. The distribution of genetic findings is detailed in Table 2.

Table 2. Genetic abnormalities

Genetic category	n	% of total cohort
Trisomies	**16**	**11.59**
Down syndrome	10	7.25
Edwards syndrome	3	2.17
Patau syndrome	3	2.17
Microdeletions	**8**	**5.80**
DiGeorge syndrome	5	3.62
Velo-cardio-facial syndrome	2	1.45
Williams syndrome	1	0.72
Situs anomalies	**4**	**2.90**
Situs inversus	1	0.72
Heterotaxy syndrome	1	0.72
Kartagener syndrome	2	1.45
Other syndromes	**1**	**0.72**
Morning Glory syndrome	1	0.72

The presence of a genetic syndrome was not independently associated with the development of ARDS or the need for invasive mechanical ventilation.

Cardiac Phenotype and Disease Complexity

Anatomically, CHD phenotypes were distributed as follows: right-to-left shunts (30.43%), complex CHD (28.99%), obstructive lesions (23.19%), and left-to-right shunts (18.12%). According to the Bethesda classification, the majority of cases were classified as severe (76.81%), while simple (13.77%) and moderately complex (9.42%) defects were less frequent.

This predominance of severe CHD provided an important clinical context for respiratory outcomes. Hypoxic–ischemic encephalopathy was uncommon, occurring in only two cases of hypoplastic left heart syndrome, precluding further statistical analysis of neurological predictors.

3.2. Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome developed in nearly two-thirds of the cohort. ARDS typically occurred early after birth and was most frequently characterized by proliferative or fibro-proliferative patterns, reflecting sustained pulmonary injury (Table 3).

Table 3. Frequency, onset timing, and severity patterns of ARDS

Parameter	**n (%)**
Patients with ARDS	86 (62.32)
Timing of ARDS onset	
< 24h birth	72 (83.72)
>24h birth	14 (16.28)
ARDS severity pattern	
exudative	14 (16.28)
proliferative	32 (37.21)
fibro-proliferative	40 (46.51)

3.3. Invasive Mechanical Ventilation and Predictive Factors

Invasive mechanical ventilation was required in 53 neonates (38.41%), all of whom had severe CHD. Ventilatory dependence was strongly associated with ARDS severity, symptom burden, and prostaglandin E1 administration, with odds ratios derived from multivariate logistic regression models (Table 4). Mechanical ventilation was typically initiated early during hospitalization, suggesting rapid clinical deterioration rather than progressive respiratory disease.

Table 4. Predictors of ARDS development and invasive mechanical ventilation

Outcome	**Predictor**	**OR**	**95% CI**	**p-value**
ARDS	Number of clinical symptoms	2.40	1.84–3.14	<0.001
Invasive mechanical ventilation	ARDS severity	3.19	2.16–4.69	<0.001
	Number of clinical symptoms	1.59	1.29–1.96	<0.001
	Prostaglandin E1 administration	1.85	1.20–4.62	0.002

3.4. Complications

Severe non-respiratory complications were relatively uncommon. Organ dysfunction, sepsis, or anasarca occurred in 7.25% of patients, while gastrointestinal or metabolic complications were rare (1.45%). Importantly, these complications were confined almost exclusively to neonates with severe CHD, indicating limited systemic reserve in this subgroup.

A reversible cardiorespiratory arrest occurred in 5.80% of cases, predominantly among neonates with hypoplastic left heart syndrome and severe tetralogy of Fallot variants. Two patients

developed post-resuscitation pneumothorax, reflecting the fragility of pulmonary mechanics in this population.

4. Discussion

This study provides an analysis of respiratory failure in neonates with CHD, demonstrating that hemodynamic severity and systemic instability are the primary determinants of respiratory compromise, with ARDS acting as a key intermediary between cardiac physiology and ventilatory dependence.

4.1. Transitional Hemodynamics as a Vulnerable Window

The postnatal transition represents a critical period of rapid cardiovascular adaptation, during which pulmonary blood flow increases dramatically, even up to 20-fold compared with fetal, primarily as a consequence of exposure of the pulmonary vascular bed to higher oxygen concentrations. This oxygen-mediated fall in pulmonary vascular resistance (PVR), together with vasoactive mediators, facilitates pulmonary vasodilation and lung recruitment. Increased pulmonary venous return raises left atrial pressure, leading to functional closure of the foramen ovale. Simultaneously, removal of the low-resistance placental circulation increases systemic vascular resistance (SVR), alters ductal flow patterns, and promotes closure of the ductus arteriosus (DA) within 24–48 hours in most term neonates (Hundscheid et al., 2019). The rapid decline in PVR and rise in SVR create a delicate equilibrium between pulmonary (Qp) and systemic (Qs) blood flow (Crossley et al., 2009; van Vonderen et al., 2014).

In neonates with CHD, even modest fluctuations in vascular resistance may destabilize this balance, resulting in pulmonary overcirculation or systemic hypoperfusion. In preterm infants, delayed ductal closure may further exacerbate shunting, particularly in the context of surfactant therapy or inhaled nitric oxide (Bronicki et al., 2022). During this transitional period, both ventricles increase output to meet metabolic demands. However, the immature myocardium remains relatively intolerant of afterload and has limited preload reserve, rendering the circulation highly sensitive to abrupt hemodynamic shifts (Azhibekov et al., 2015).

This early hemodynamic fragility may explain why, in our cohort, ARDS developed in 62.3% of neonates and most frequently within the first day of life, suggesting that respiratory deterioration often coincides with the immediate postnatal circulatory transition.

4.2. Hemodynamic Imbalance and the Development of ARDS

This transitional vulnerability provides a link to the development of ARDS in neonates with CHD. Pulmonary overcirculation increases capillary hydrostatic pressure and disrupts the alveolar–capillary barrier, promoting pulmonary edema and inflammatory activation, whereas systemic hypoperfusion contributes to metabolic acidosis, endothelial dysfunction, and secondary lung injury (De Boode, 2020; Jain et al., 2019). In this setting, ARDS may represent the pulmonary manifestation of hemodynamic instability rather than a primary respiratory disorder.

Consistent with this interpretation, the number of clinical symptoms at presentation emerged in our study as the sole independent predictor of ARDS (OR 2.4; 95% CI 1.84–3.14; $p < 0.001$), supporting the concept that cumulative systemic instability, rather than isolated pulmonary pathology, drives acute lung injury in this population.

Beyond respiratory consequences, hemodynamic instability in neonatal CHD may also carry significant neurological implications. Severe or ductal-dependent lesions are associated with reduced cerebral oxygen delivery even in utero, and evidence suggests that brain vulnerability may precede postnatal intervention (Limperopoulos et al., 2010; Miller et al., 2007). Early patterns of injury described in this population include delayed brain maturation, reduced total and regional brain volumes, white matter injury, and ischemic lesions detectable on neonatal neuroimaging (Licht et al., 2009; Miller et al., 2007). During transitional circulatory instability, fluctuations in

systemic output and oxygen delivery may exceed the limited autoregulatory capacity of the immature brain, increasing susceptibility to hypoxic–ischemic injury (Donofrio et al., 2003).

Importantly, these early structural and perfusion abnormalities have been linked to long-term neurodevelopmental consequences, including motor delay, executive dysfunction, attentional deficits, and impaired academic performance in survivors of complex CHD (Bellinger et al., 2003; Gaynor et al., 2015; Marino et al., 2012). While invasive mechanical ventilation can influence cerebral perfusion through changes in intrathoracic pressure and arterial carbon dioxide levels, it likely serves as a modifier of neurological risk in infants already hemodynamically compromised. Thus, the association observed in our cohort between ARDS severity and mechanical ventilation may identify a subgroup with heightened long-term neurodevelopmental vulnerability driven primarily by underlying cardiac physiology rather than respiratory support alone.

4.3. Heart–Lung Interactions in the Ventilated Neonate

Heart–lung interactions further influence this fragile physiology. Positive pressure ventilation (PPV) increases intrathoracic pressure and may reduce systemic venous return by decreasing right atrial transmural pressure and the gradient driving venous flow (Fessler et al., 1991). The magnitude of this effect depends on ventricular preload reserve, neurohormonal compensation, and lung and chest wall compliance (Gattinoni et al., 2004). Although increased intrathoracic pressure may reduce left ventricular afterload and transiently augment systemic output (Peters, Kindred, & Robotham, 1988), PPV can also increase right ventricular afterload through its effects on lung volume, oxygen tension, and pulmonary vascular resistance (Boissier et al., 2013; Bronicki et al., 2022; Himebauch et al., 2018; Vieillard-Baron et al., 1999). Because the right ventricle is particularly sensitive to afterload, excessive airway pressures or lung overdistension may impair right ventricular output, especially in the presence of pulmonary vascular disease or ARDS (Flores, Loomba, & Bronicki, 2020; Gattinoni et al., 2016).

In established ARDS, heterogeneous lung involvement leads to atelectasis in dependent regions and overdistension in nondependent regions, increasing pulmonary vascular resistance and predisposing to right ventricular dysfunction (Gattinoni et al., 2016). These interactions likely contribute to the strong association observed in our cohort between ARDS severity and invasive mechanical ventilation (OR 3.19; 95% CI 2.16–4.69; $p < 0.001$), as progressive pulmonary injury may further compromise right ventricular performance and systemic perfusion.

4.4. Ventilator-Induced Lung Injury in Neonates with CHD

While mechanical ventilation is often necessary, it carries the risk of ventilator-induced lung injury (VILI). The goals of ventilation in neonates with CHD include optimizing gas exchange, reducing the work of breathing and oxygen consumption, and maintaining comfort while minimizing lung injury (Bronicki et al., 2022). VILI may result from excessive oxygen exposure as well as from mechanical forces generated by positive pressure ventilation (Keszler & Sant'Anna, 2015). Oxygen therapy should aim for the lowest fraction of inspired oxygen compatible with adequate oxygenation, with commonly recommended saturation targets of 90%-95% in preterm infants (Cummings, Polin, & Committee on Fetus and Newborn, 2016).

Mechanical injury is more closely related to excessive tidal volume (volutrauma) than to pressure alone, as lung overdistension promotes cytokine release, inflammation, and structural disruption (Bronicki et al., 2022). Avoidance of excessive lung inflation and prevention of cyclic atelectasis through appropriate use of positive end-expiratory pressure (PEEP) are therefore essential (Bronicki et al., 2022; Cummings, Polin, & Committee on Fetus and Newborn, 2016). Given the association between ARDS severity and ventilatory dependence in our cohort, lung-protective strategies are particularly important in neonates with CHD, in whom ventilatory support may both stabilize and potentially exacerbate hemodynamic compromise.

4.5. Ductal Dependency and Circulatory Instability

Ductal-dependent lesions further amplify hemodynamic instability. In ductal-dependent systemic circulation, systemic perfusion relies on right-to-left ductal shunting, whereas in ductal-dependent pulmonary circulation, adequate pulmonary blood flow depends on left-to-right shunting across a patent ductus arteriosus. Prostaglandin therapy is therefore essential to maintain ductal patency until definitive intervention (Ball et al., 2023; Jain et al., 2019; Khare et al., 2021).

However, failure of ductal closure, particularly in preterm neonates, may result in a hemodynamically significant patent ductus arteriosus (PDA), with excessive left-to-right shunting leading to pulmonary overcirculation, left heart volume overload, and systemic hypoperfusion due to diastolic steal (Kumar et al., 2010; Mitra et al., 2023; Schneider & Moore, 2006). These mechanisms further reinforce the interpretation that respiratory failure in our cohort reflects a broader hemodynamic disturbance, rather than isolated pulmonary disease.

4.6. Limitations

This study is limited by its retrospective, single-center design. Detailed longitudinal hemodynamic measurements were not uniformly available, limiting direct physiologic correlations. The sample size may have reduced statistical power for subgroup analyses.

5. Conclusions

In neonates with CHD, respiratory failure is predominantly driven by hemodynamic severity and systemic instability, with ARDS emerging as a key intermediary between cardiac physiology and ventilatory dependence. These findings highlight the need for prospective studies integrating hemodynamic monitoring, biomarkers, and tailored ventilatory protocols to better define risk stratification and optimize outcomes in this population.

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