Congenital Diaphragmatic Hernia

Pulmonary Hypertension and Pulmonary Vascular Disease

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KEYWORDS

• Congenital diaphragmatic hernia • Pulmonary hypertension • Ventilation
• Cardiopulmonary interactions • Vasodilators • Inotropes

KEY POINTS

- The management of pulmonary hypertension and altered cardiac function are key in stabilization and long-term prognosis of infants with congenital diaphragmatic hernia.
- Pulmonary vascular disease, cardiopulmonary interactions, and cardiac dysfunction should all be addressed in the evaluation and management.
- The underlying physiology along with frequent reassessment allows for utilization of medical agents and ventilation strategies.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is characterized by a diaphragmatic defect, associated with abdominal contents herniating into the thorax, with bilateral maldevelopment of pulmonary parenchyma and vasculature.[1,2] Pulmonary hypertension (PH) and altered cardiac function have been associated with an adverse postnatal trajectory and increased mortality.[3–5] This review provides a comprehensive summary of the current understanding of PH in CDH, outlining the underlying pathophysiologic mechanisms, methods for assessing PH severity, optimal management strategies, and prognostic implications.

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PATHOPHYSIOLOGY

Diaphragmatic precursors develop at approximately 4 weeks of gestation with fusion completed by 12 weeks.[6] While a diaphragmatic defect leads to intra-abdominal contents herniating into the thorax, impeding pulmonary and cardiac growth, this phenomenon does not fully explain bilateral structural pulmonary findings. The current prevailing concept is the "2-hit theory,"[7] which postulates that CDH pathogenesis involves a dual sequence of insults. The first results in developmental arrest of both lungs, while the second primarily affects the ipsilateral lung subsequent to defective diaphragmatic development and compression. The airways, pulmonary vasculature, cardiac structures, and large vessels (pulmonary arteries and aorta) develop alongside in an orchestrated process. Experimental CDH models and postmortem studies demonstrate fewer and smaller caliber bronchioles,[8,9] as well as decreased lung weight, pulmonary arteriole numbers, size, and branching.[10,11] Some animal models demonstrate fetal structural alterations in cardiac dimensions and in the left to right ventricular (LV/RV) balance.[8] Beyond the absolute reduction in vascular surface territory implying a fixed effect in the pulmonary vascular capacitance, the developmental abnormalities include reduced vessel caliber, thickening of muscular media and adventitia, and aberrant functional reactivity.[2,12] These anatomic-histologic changes (variable contributions of abnormal vascular tone and reactivity, in combination with an underdeveloped vascular bed) impede the normal perinatal transition, with decreased pulmonary blood flow (PBF), increased pulmonary vascular resistance (PVR),[13] and persistence of PH (**Fig. 1**A).

Fetal markers of prognosis and mortality are the presence of other major congenital defects (particularly structural cardiac defects), genetic abnormalities, lung size, and liver herniation into the thorax. Specifically, the lung-to-head ratio (LHR) and observed to expected LHR (o/e LHR) have been validated as predictors of postnatal outcomes.[1,14] Prognostication relies predominantly on fetal imaging, with MRI often used in the assessment of lung volume and liver position, which are associated with postnatal survival and morbidity.[15] In severe fetal CDH (LHR or o/e LHR, below 0.6% and 25%, respectively), antenatal intervention can be considered, such as fetal tracheal occlusion (FETO).[1,16,17] Indeed, in severe left CDH, FETO increased survival (40% vs 15%; relative risk [RR] 2.67, confidence interval [CI] 1.22–6.11), despite resulting in preterm delivery.[18]

Fetal echocardiography has provided additional insight into abnormal cardiovascular development in CDH. Preferential streaming of umbilical venous return via the foramen ovale, for instance, is perturbed in CDH,[19] with a greater proportion of blood instead remaining on the right side of the heart. The combination of decreased PBF mediated by increased ductal flow, decreased left heart filling, and LV output, results in the development of a relatively smaller LV.[19–21] Impaired response to maternal hyperoxia is demonstrated in midgestation fetuses with CDH that have neonatal demise, while FETO is associated with improved LV growth and response to hyperoxia.[22–24] Together, these findings suggest that pulmonary vascular disease (PVD) is already present in the fetuses with CDH.

Postnatally, infants with severe CDH present with hypoxemic respiratory failure and shock. The remodeled pulmonary vasculature exhibits the physiology of PVD, with increased sensitivity to vasoconstricting stressors (eg, acidosis, hypoxia) and decreased capacitance with impaired vasorelaxation,[25] thus resulting in increased RV afterload. The failure to transition to normal increase in PBF compromises left atrial (LA) and LV filling and cardiac output, leading to impaired systemic oxygenation and perfusion.[26] This can be further exacerbated by the persistently high RV afterload

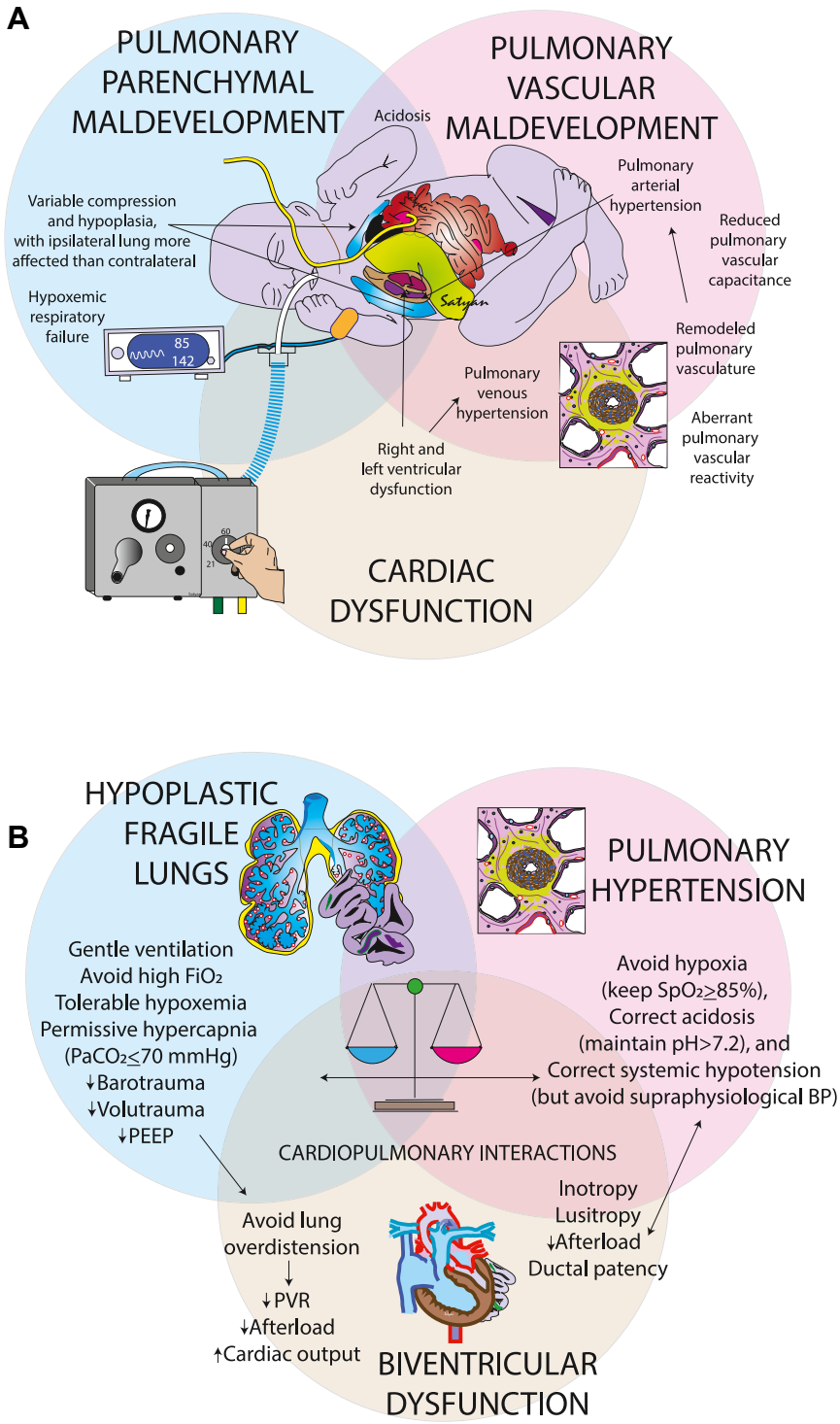

Fig. 1. Pathophysiology of congenital diaphragmatic hernia (CDH) and recommended targeted clinical management. (*A*) Pathophysiology: variable severity of pulmonary parenchymal

and RV dilation, which impedes LV filling through ventricular interactions, while right atrial pressure may be elevated. Systemic desaturation can be exacerbated by right-to-left shunting at the atrial level, with desaturated blood entering the systemic circulation. The increased pulmonary-to-systemic vascular resistance ratio, in the presence of a patent ductus arteriosus (PDA), allows for desaturated blood to enter the systemic circulation through the descending aorta, leading to a preductal/postductal saturation differential (**Fig. 2**). Systemic hypoxia, low mean arterial pressure, and reduced LV output may impair coronary perfusion, further exacerbating shock physiology. The role of the underdeveloped LV is not fully understood in this clinical scenario, as LV size normalizes postnatally in the majority of infants with abnormal fetal measures, although the LV remains small in the setting of elevated PVR with compromised filling.[21,27] Regardless, impaired ventricular function is an important marker for poor outcomes in CDH, including mortality and use of extracorporeal membrane oxygenation (ECMO), although the abnormal geometry of the compressed LV in the setting of PH makes conventional echocardiography measures of systolic dysfunction less useful.[28]

Elevated afterload due to pulmonary arterial hypertension may lead to RV-pulmonary artery (PA) uncoupling,[2] with compromised RV function.[4] LA hypertension due to LV restriction and dysfunction as a source of RV afterload is another concern.[29] The most common pathophysiology reported in infants with CDH is biventricular dysfunction, implicating ventricular interdependence as a mechanism that contributes to LV dysfunction. LV dysfunction alone has been less commonly described (5% LV alone, 15% RV alone, and 19% biventricular dysfunction).[28] Multiple echocardiographic measurements demonstrate decreased cardiac function in infants with CDH compared to unaffected controls (typically assessed in the first 48 hours),[27,30] while both decreased RV and LV myocardial performance index and cardiac output index have been associated with mortality within the CDH population.[31] Infants transitioning to ECMO had lower LV and RV function, both by conventional echocardiogram measures and by myocardial deformation analysis (strain, a surrogate for contractility).[3,30] Of interest, systolic eccentricity index (EI), a marker of LV deformation due to RV pressure overload, was associated with lower survival, lesser RV systolic function and output (velocity time interval), and more impaired RV global strain while LV strain measures were not correlated with EI.[27] In fact, by strain, only a minority (7/24) had measurements within the normal range, while the rest have biventricular or univentricular dysfunction.[30] Systolic and diastolic dysfunctions have been documented in both ventricles using tissue doppler imaging and speckle tracking echocardiography at<48 hours, while values significantly improved on repeat echocardiogram at 3 to 5 days of age.[27,30] Of note, LV diastolic dysfunction may be underestimated by echocardiography and is associated with high PVR.[32] RV septal strain is more affected than RV free wall or either LV parameter and RV and LV measures correlate with each other.[27,33] Thus, RV afterload is an important factor in cardiac dysfunction in CDH and interventricular interactions are critical.

FETO has become a major antenatal intervention, thought to enhance fetal pulmonary parenchymal development by increasing and maintaining transpulmonary

and vascular maldevelopment and dysfunction, accompanied by univentricular or biventricular cardiac dysfunction. (*B*) Management: mechanical ventilation strategy focused on protecting the vulnerable lung while decreasing pulmonary vascular resistance and supporting cardiac function. (Copyright Satyan Lakshminrusimha)

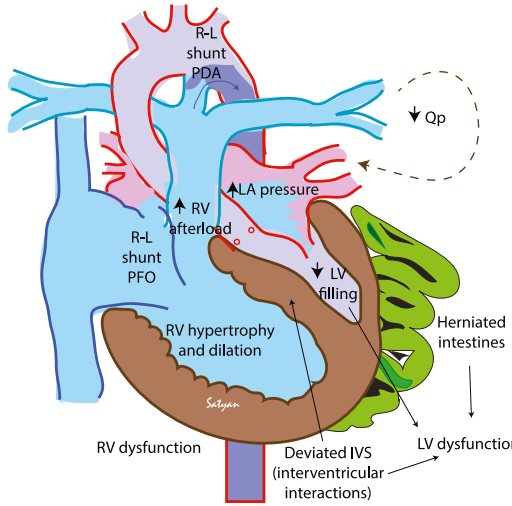

Fig. 2. Cardiac schematic in the setting of pulmonary hypertension due to suprasystemic pulmonary vascular resistance. Right-to-left shunting occurs at level of patent ductus arteriosus (PDA) and atrial septum (patent foramen ovale, PFO) with decreased pulmonary blood flow and pulmonary venous return to the left atrium. Interventricular septum (IVS) is deviated into the left ventricle (LV) due to right heart pressure overload, with both low pulmonary blood flow and deviated IVS contributing to decreased LV filling. Systolic and diastolic cardiac dysfunctions are common. (Copyright Satyan Lakshminrusimha)

distending pressure in utero.[34] As noted, a randomized control trial demonstrated significantly improved survival of FETO over expectant care in severe CDH, although similar benefit was not shown in moderate CDH.[18,35] The physiologic benefits of FETO are not well delineated, although neonatal assessment shows improved lung function, oxygenation, and measures of LV size, compared to newborns with expectant fetal management.[24,36] Improvements in later resolution of PH by echocardiography have also been described in both moderate and severe CDH.[37,38] Experimental models of FETO generally show favorable lung histopathology with respect to lung growth and vascular remodeling,[34] although a recent ovine model of tracheal occlusion recapitulating the contemporary practice of late release of the tracheal balloon prior to delivery did not demonstrate improved perinatal gas exchange despite improved lung function and increased PBF.[39]

MANAGEMENT

Published guidelines[40,41] provide a comprehensive perspective on approaches to postnatal management in CDH, employing a lung-protective, gentle ventilation strategy, including permissive hypercapnia with limitation of ventilator pressure and decreased exposure to hyperoxia using preductal oxygenation for supplemental oxygen titration while allowing for a preductal/postductal oxygen saturation differential (see **Fig. 1**B). Effective ventilation and airway management are crucial for these infants, emphasizing adequate lung recruitment without causing under-inflation or over-inflation. This balance is essential to prevent significant ventilator-induced lung injuries. Maintaining this equilibrium demands consistent bedside attention, including managing airway secretions, monitoring the ventilator's pressure-volume loops, and carefully adjusting the mean airway pressure based on auscultation, clinical response, and

radiographic findings (refer to section on "*Ventilation concepts and cardiopulmonary interactions")*. Strategies to reduce ventilator and oxygen-associated lung injury and inflammation are critical for survival due to lung hypoplasia in CDH, with the implementation of these protective strategies resulting in improved survival over time at several institutions.[42,43] This contrasts with historical approaches aimed toward maximal acute pulmonary vasodilation (ie, targeting hyperventilation, alkalosis and hyperoxia). Without randomized trials regarding optimal cardiovascular management, echocardiography-based evaluation, and comprehensive assessment of adequacy of cardiac output [clinical perfusion, vital signs, urine output, near infrared spectroscopy, blood lactate levels and metabolic acidosis, serum creatinine, blood urea nitrogen and B-type natriuretic peptide (BNP) as a marker of ventricular stress] promote a physiology-guided approach. Echocardiography allows for anatomic and functional cardiac and pulmonary vascular assessment and has been recommended early in the course (<24 hours of life) for all infants with CDH.[40,44] Quantitative echocardiography parameters of RV and LV function, as well as estimates of pulmonary arterial pressure due to elevated PVR are important to establish the baseline condition and monitor changes over time. Assessment of the degree and direction of any shunt at the atrial, ventricular, and ductal levels (including gradients measurement) can further inform regarding PVR to systemic vascular resistance (SVR), as well as relative function and compliance of the ventricles. RV-LV interactions are important to appreciate; a poorly filled LV with low output due to high right heart pressures with displacement of the interventricular septum and low PBF (at times with retrograde ductal flow in the transverse and ascending aorta) results in compromised systemic perfusion and oxygen delivery, even with a non-restrictive PDA. Serial echocardiograms can guide treatment from the initial transition to the chronic management phase in infants with CDH.[2,45,46] Of interest, PH at the initial echocardiogram (<48 hours) does not discriminate between infants that die or receive prolonged respiratory support versus survivors without prolonged respiratory support, while the persistence of PH by echocardiogram is associated with mortality and prolonged need for respiratory support.[47–49]

Ventilation Concepts And Cardiopulmonary Interactions

The Neonatal Resuscitation Program[50] and other published CDH-specific guidelines recommend immediate endotracheal intubation and avoidance of bag-valve or T-piece with mask ventilation at delivery for infants with CDH.[40,41,50](**Table 1**). Gentle ventilation, using peak pressures $\leq$25 cm H_2O, and positive end-expiratory pressure (PEEP) no higher than 5 cm H_2O are recommended[40,41] while allowing for permissive hypercapnia, targeting arterial partial pressure of carbon dioxide (P_{CO_2}) $\leq$70 mm Hg and pH>7.2, although some centers may allow for higher P_{CO_2} and lower pH, particularly if clinical perfusion and markers of adequate oxygen delivery are reassuring. Gas exchange markers tend to slowly improve if both shorter and longer- term effects of ventilator-associated injury can be minimized. Notably, no tidal volume targets are specified in published guidelines. In the setting of restrictive lung disease due to lung hypoplasia, lower tidal volumes are physiologically appropriate with higher respiratory rates to achieve ventilation targets. However, underdeveloped airways in the context of pulmonary hypoplasia may contribute to higher airway resistance and air-trapping, indicating the need for individualized ventilator strategies. In a small study of milder CDH, Lee and colleagues identified that tidal volume of 5 to 6 mL/kg while on mechanical ventilation was associated with lesser work of breathing than 4 mL/kg.[51] However, this study was not designed to evaluate later outcomes or lung injury, including time to successful extubation. Optimizing mechanical ventilation does not mandate lowering infant work of breathing if the trade-off is prolongation of invasive ventilation.

Table 1
Guidelines for respiratory management and oxygenation and ventilation targets

		Targets	Comments	References
Ventilator settings	CMV Consider HFOV for rescue		VICI trial: less ECMO use, shorter duration of ventilation, and more favorable hemodynamic outcomes with CMV	54,55
	PIP	$\leq$ 25 cm H_2O		40,41
	PEEP	2–5 cm H_2O	PEEP 2 superior to PEEP 5 with respect to lung compliance, oxygenation and pulmonary blood flow	40,41,56
Ventilation		$Paco_2$<70 mm Hg, pH>7.2	Higher $Paco_2$/lower pH may be tolerated during perinatal transition or if perfusion adequate	55
Oxygenation	Monitor preductal (right hand) Allow for preductal/postductal saturation differential	$\geq$85%	$\geq$ 80% during perinatal transition >90%–94% once Fio_2 at "safe" level of 0.4–0.5	40,41

Abbreviations: CMV, conventional mechanical ventilation; ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; PIP, peak inspiratory pressure; PEEP; positive end expiratory pressure.

Oxygenation targets are usually based on preductal (right hand) measures, with recommended goal oxygen saturations $\geq$ 85%. Some centers target higher saturation goals (>90–94%) if Fio_2 is at a "safer" level, commonly 40% to 50%, as this allows for the pulmonary vasodilatory effects of supplemental oxygen while limiting pulmonary exposure to hyperoxia. Conversely, saturation targets as low as $\geq$80% may be utilized to promote weaning of Fio_2 to limit hyperoxia.[40,41] Of interest, in an experimental ovine model of persistent PH of the newborn (PPHN), prior short exposure to Fio_2 of 1.00 decreased the vasodilator response to inhaled nitric oxide (iNO) in comparison to Fio_2 of 0.21 to 0.50, supporting utilization of lower saturation targets if needed to achieve safer Fio_2 exposure.[52] Guidelines and practice in some centers allow for initial transition over the first several hours, during which lower preductal saturations and higher Pco_2 may be tolerated. In general, oxygenation targets are accepting of a persistent preductal/postductal saturation differential, which would be expected, particularly in more severe CDH, given the prolonged course of resolution of PH.[14] A large preductal/postductal saturation differential (persistently>15–20%) raises concern for a lower mixed venous saturation, which occurs in the setting of decreased oxygen delivery due to increased tissue extraction. In this case, interventions to enhance cardiac output should be considered. Overall, even with adoption of oxygenation and ventilation guidelines, there can be substantial variability in practice and outcomes; among 4 high volume European centers over a 10-year period, survival ranged from 59% to 79%.[53]

The recommended mode of ventilation is conventional mechanical ventilation (CMV). The VICI-trial (High-Frequency Oscillation Versus Conventional Mechanical Ventilation in Newborns with Congenital Diaphragmatic Hernia: A Randomized Clinical Trial), which randomized newborns to CMV versus high-frequency oscillatory ventilation (HFOV), demonstrated increased use of ECMO, longer duration of ventilation, and more hemodynamic compromise with HFOV, with a nonsignificant increase in mortality.[54,55] The trial specified similar oxygenation and ventilation targets as described earlier, with pressure limitation for both CMV and HFOV. Increased hemodynamic compromise in infants randomized to HFOV highlights the importance of cardiopulmonary interactions. Hypoplastic lungs are not generally recruitable in the standard sense, as there is no parenchymal disease, and they are likely readily subject to overdistention, impeding venous return and increasing PVR, which can result in compromised cardiac output. Cardiopulmonary interactions also explain the improved hemodynamics demonstrated with low PEEP in a randomized crossover study of 2 versus 5 cm H_2O PEEP in infants with severe CDH and PH on CMV.[56] Infants had higher lung compliance on 2 cm H_2O PEEP with lower delta pressure and respiratory rate and better ventilation and oxygenation. The PDA had bidirectional flow in both conditions, while echocardiography on low PEEP showed increased PBF and improved left heart filling. Conversely, with appropriate higher ventilator rates in lung hypoplasia, even modest set PEEP may result in overdistention and elevated PVR due to "auto-PEEP."[57] Thus, rapid respiratory rates on the ventilator in the setting of restrictive lung disease are best employed with low-set PEEP ($\leq$3 cm H_2O) due to resulting elevated intrinsic PEEP, particularly in underdeveloped airways, as this can lead to gas trapping, potentially increasing PVR. These insights underscore the need for repeated cardiopulmonary assessment.

The VICI trial demonstrates the critical role of ventilator management in supporting newborns with CDH, with respect to mortality and hemodynamic status due to cardiopulmonary interactions. The trial required a prenatal diagnosis of CDH; however, eligibility was not restricted based on fetal assessment of the severity of lung hypoplasia, supporting use of consistent approaches across the spectrum of CDH severity.

Further, data suggest that the severity of fetal lung hypoplasia is associated with the resolution of persistent PH.[14] Thus, attention to the contribution of cardiac dysfunction due to increased afterload, interventricular interactions, and/or innate contractility is an important adjunct to respiratory management in CDH, as it directly impacts oxygen delivery.

Cardiac Output And Function

Decrements in innate contractility of 1or both ventricles are more common than not, and the necessity of contractility support should be assumed in infants with hemodynamic compromise (**Table 2**). As PH is predominant at the initial echocardiogram and RV afterload is important when considering RV dysfunction, serial assessments will guide management. In the context of significant PH with concern for compromised cardiac output and oxygen delivery, pulmonary vasodilator therapy should be considered. As noted, a decrease in mixed venous saturation (large preductal/postductal saturation differential) should be considered for additional intervention, as it may occur prior to the development of lactic acidosis. Since most infants likely have biventricular dysfunction, agents such as milrinone that provide vasodilatory, inotropic, and lusitropic (cardiac relaxation) support for both ventricles are favored. During perinatal transition, attention should be paid as the small fetal LV may not tolerate aggressive maneuvers to increase PBF, particularly in the setting of more profound acidosis, impairing ventricular function. Allowing for pulmonary transition, decreasing Fio_2 to safer levels as tolerated, and gentle volume loading, followed by pulmonary vasodilator therapy, is prudent. In isolated LV dysfunction, inotropic support and balanced volume loading may improve cardiac output. Given the importance of RV pressure overload to cardiac dysfunction, prostaglandin E1 (PGE) infusion to achieve or maintain ductal patency may allow for the maintenance of cardiac output when PVR is systemic-to-suprasystemic. This approach allows for lower RV afterload, as long as SVR is not manipulated to supraphysiologic levels. There may be a decrease in postductal (lower body) saturation, offset or overcome by increased oxygen delivery due to improvements in cardiac function and output. Data from a single center study support this, with BNP levels decreasing within 24 hours of PGE initiation.[58] It is important

Table 2
Cardiac phenotype and suggested management strategy

Key Physiology Element	Strategy	Targets
Normal cardiac function, mild or no PH	Lung protection strategy (for all physiologies)	See **Table 1**
RV dysfunction, significant PH	Pulmonary vasodilators, PGE	Maintain unrestrictive PDA
Biventricular dysfunction	Balance vasodilators, inotropes, and/or PGE. Frequent reassessment	Support contractility, maintain unrestrictive PDA while bilateral or right to left shunt, avoid excessive afterload burden
LV dysfunction	Inotropes to support cardiac output	Support contractility, avoid excessive afterload; avoid iNO in primary LV dysfunction with pulmonary venous hypertension until LV dysfunction is addressed

Abbreviations: LV, left ventricle; PDA, patent ductus arteriosus; PGE, prostaglandin E1; PH, pulmonary hypertension; RV, right ventricle.

to recognize that the physiology is dynamic and ductal patency may be particularly important during transient elevations in PVR with mucous plugging, loss of functional residual capacity during suctioning, and more extended episodes of manipulation such as during CDH repair, even when a preductal/postductal saturation differential is not present at other times.[58,59] Above all, the maintenance of a nonrestrictive PDA allows time for the anticipated decrease in PVR and improvement in cardiac function; interval echocardiograms at 2 to 7 days after PGE initiation show improved LV relaxation, diastolic volume, and myocardial performance index as well as signs of decreased PVR and RV pressure overload with decreased right-to-left ductal flow and displacement of interventricular septum.[30,47,58,59] In addition to lowering RV afterload through communication with the systemic circulation, PGE can function as a pulmonary vasodilator, and importantly, with severe LV dysfunction, allow for circulatory support by the RV. Timing of PGE discontinuation needs to be carefully considered as reversal of ductal shunting with PVR fall may result in excessive PBF and systemic steal, worsening pulmonary mechanics and systemic perfusion. Thus, careful clinical and echocardiographic monitoring are needed, and continuous preductal and postductal saturation monitoring can identify periods when ductal flow shifts.

Pulmonary Vasodilator Therapy

iNO activates guanylate cyclase, leading to the production of cyclic guanosine monophosphate (cGMP) in smooth muscle cells, allowing for selective pulmonary vasodilation and improved ventilation-perfusion matching. However, in a randomized trial, iNO failed to improve oxygenation, avert ECMO, or increase survival in infants with CDH, although management during this period was not focused on gentle ventilation and weaning of Fio_2, and randomization occurred when oxygenation index was in the 40s—conditions which may impact pulmonary vasculature potential for vasodilation.[60] In contrast, contemporary single center retrospective studies have shown that 30% to 40% of infants with CDH have a positive and enduring oxygenation response to iNO.[61,62] Further, iNO responders were less likely to transition to ECMO compared to nonresponders.[61] In consecutive studies from the multicenter CDH Study Group (CDHSG) registry, early iNO initiation (<3 days of age) was associated with increased mortality, although data collection and the statistical approaches in these analyses likely fail to differentiate iNO use as rescue therapy.[63,64] Some have postulated that this may be secondary to pulmonary venous congestion and edema in infants with LV dysfunction, leading to decreased lung function.[45] Left-to-right atrial shunting especially in the setting of right-to-left shunting at the PDA has been proposed as an indirect marker of LV diastolic dysfunction (relative to the RV), leading to cardiopulmonary compromise in the setting of vasodilator therapy. However, Lawrence and colleagues found no differences in pre-iNO echocardiographic LV diastolic measurements in iNO responders versus nonresponders, while abnormal LV systolic function (by shortening fraction, 19% of cohort) was associated with lack of response to iNO.[61] Infants with LV systolic dysfunction were more likely to transition to ECMO support and overall had poorer outcomes, with delayed time to CDH repair and higher mortality, supporting early LV dysfunction as a marker for poor outcome in CDH regardless of iNO therapy. Although Kumar and colleagues found that iNO nonresponders were not more likely to transition to ECMO support, nonresponders had higher mortality.[62] Elevated RV pressure estimates did not decrease in iNO-treated infants by interval echocardiogram on day 3, and despite overall more favorable outcomes in iNO responders, RV pressure estimates increased from pre-iNO echocardiogram, suggesting that iNO may not substantially decrease PVR even among

responders, or its effect on PVR may not persist.[62] Guidelines advocate for iNO as a first-line pulmonary vasodilator in those thought to have pulmonary arterial hypertension, with concomitant normal LV function.[40,41] Without clinical improvement, weaning and discontinuation of iNO could be considered.

Other pulmonary vasodilators have been described in the management of infants with refractory PH in the context of CDH. Sildenafil acts in the NO pathway as a selective phosphodiesterase-5 (PDE-5) inhibitor, inhibiting the breakdown of cGMP. Thus, it can potentiate the effect of endogenous or exogenous NO. Small retrospective studies describe variable improvement in oxygenation and cardiac output with sildenafil administration.[65,66] The prostacyclin pathway is another targeted pathway.[40] A CDHSG registry study described increased mortality in infants administered parenteral epoprostenol post-CDH repair, with effects attenuated by adjustment for severity of CDH, suggesting the relationship was due to residual confounding by indication.[67] Treprostinil is a more stable parenteral prostacyclin analogue which can be administered intravenously or subcutaneously. Two single-center retrospective studies described outcomes with initiation of treprostinil at a median of 12 and 19 days of age.[68,69] Over the first month of therapy, branch PA flow, interventricular septal displacement, and measures of RV function improved. Of note, although some improvements were identified within days of treprostinil initiation, these studies describe a time frame over which PH is improving/resolving and BNP is decreasing in infants with CDH without this intervention.[48,70] A recent CDHSG registry study with propensity-matching demonstrated decreased use and duration of ECMO with prostacyclin therapy initiated in the first week of life, although there was no effect on in-hospital mortality.[71]

The final pathway targeted for the treatment of PH is the endothelin pathway. Endothelin-1 is a potent pulmonary vasoconstrictor which is dysregulated in CDH.[47] Bosentan, a receptor antagonist, has been used as therapy for chronic CDH-related PH.[72]

Milrinone

Milrinone is a phosphodiesterase-3 (PDE-3) inhibitor which prevents the breakdown of cyclic adenosine monophosphate (cAMP), leading to pulmonary and systemic vasodilatation and positive inotropic and lusitropic cardiac support. Milrinone effectively dilates PA resistance vessels from an experimental model of PPHN.[73] Further, these vessels exhibit perinatal increases in PDE-3 activity with decreased cAMP levels, an effect rescued by milrinone administration.[74] These effects make milrinone a compelling agent for use in CDH, given elevated PVR and frequent ventricular dysfunction. Two small single-center retrospective studies provide supporting evidence in this respect.[62,75] When initiated in infants on iNO, milrinone was associated with improved oxygenation at 12 to 24 hours, improved diastolic and systolic function, decrease in RV pressure estimate, increase in LV ejection fraction, and maintenance of systemic blood pressures 2 to 3 days after initiation.[75] There is an ongoing randomized phase 2 trial of milrinone in infants with CDH and hypoxic respiratory failure, with target dose of 0.33 to 0.66 mcg/kg/min.[76] Optimal dosing is not established, but in postoperative infants with congenital heart disease, higher dose (0.75 mcg/kg/min) was more effective than low dose (0.25 mcg/kg/min).[77] PDE-3 distribution, abundance, and activity in the neonate may differ from older children, particularly in the setting of hyperoxia; addiotionally, milrinone clearance is decreased and half-life prolonged. In the authors' experience, milrinone initiation at 0.25 mcg/kg/min with titration up to 0.75 to 1 mcg/kg/min is well tolerated with changes every 2 to 6 hours and gentle volume loading at initiation if hypotension occurs.

Postnatal Glucocorticoids

Low cortisol levels (<15 mcg/dL) are common in newborns with CDH (20/34, 59% in a single-center retrospective study).[78] Infants with low cortisol were more likely to have liver herniation, but 88% of infants received steroid supplementation in this cohort, and outcomes and clinical course did not differ by cortisol level. In another single-center study, duration of stress dose steroids was associated with greater mortality in multivariate analysis; steroids did not improve survival with low baseline cortisol levels (<10 mcg/dL), while infants with higher cortisol levels who received steroids had a nonsignificant increase in mortality.[79] Nonetheless, in a lamb PPHN model, hydrocortisone improved oxygenation and ventilation, increased soluble guanylate cyclase, decreased PDE-5 activity, and increased cGMP levels in PA resistance vessels compared to lambs receiving Fio_2 1.0 alone.[80] Hence, in infants with CDH and refractory shock, a judicious course of stress hydrocortisone may be considered as an adjuvant therapy to support hemodynamics. Baseline cortisol level should be obtained prior to steroid administration, recognizing that stress steroids may be harmful when cortisol level is not low.

Inotropes and Vasopressors

Inotropes and vasopressors, while supporting cardiac function and vascular tone, may also be detrimental due to their side-effect profile (**Table 3**). Initiation and titration should be guided by hemodynamics, with close monitoring of clinical perfusion, markers of adequate oxygen delivery, and serial echocardiography. The choice of agents is based on presumed pharmaceutical effects and underlying pathophysiology. Epinephrine, dobutamine, and dopamine act on beta-adrenergic receptors providing some positive inotropic effect. Inotropic support may be best achieved with low doses of intravenous epinephrine or dobutamine, while being mindful of unwanted extreme chronotropy. A fast heart rate may impede filling and diastolic function, as well as increase cardiac oxygen demand. Activation of alpha-receptors (eg, dopamine, epinephrine, or norepinephrine) may result in peripheral systemic vasoconstriction, although lower dose dopamine and epinephrine usually spare this effect. While increased systemic perfusion pressure can improve blood flow to various vascular beds, increases in SVR will increase LV and RV afterload (via the PDA), which may worsen cardiac output and systemic oxygen delivery. When PGE is used in

Table 3
Inotropes and vasoactive agents

Agent	HR	Contractility	SVR/SBP	PVR/PBP	Suggested Use
Dobutamine	++	++	=	=	Ventricular dysfunction
Epinephrine	+	+++	+++	++	Ventricular dysfunction with low SBP
Dopamine	+	++	++	+++	Caution when significant PH
Norepinephrine	+	=	+++	+	Low SBP without significant ventricular dysfunction
Vasopressin	=	=	+++	↓/=	Low SBP without significant ventricular dysfunction
Milrinone	=	++	↓↓	↓↓	Severe PH with high/normal SBP

Abbreviations: HR, heart rate; PBP, pulmonary blood pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; SBP, systemic blood pressure; SVR, systemic vascular resistance.

severe PH to unload/protect the RV, systemic vasoconstricting agents should be used with caution, given the high proportion of infants with CDH and hemodynamic compromise who have some degree of RV dysfunction. In this situation, milrinone would be favored for its direct effects on the myocardium and pulmonary vasodilation.

In addition to the systemic circulation, direct effects of vasoconstricting medications on the pulmonary circulation should be considered. Vasopressors, such as norepinephrine and phenylephrine have been considered at low doses to restore the pulmonary-to-systemic pressure ratio and normalize cardiac septal configuration; however, biventricular function, as noted, may be compromised with this strategy and these medications provide limited inotropic support.[2] Vasopressin (adrenergic-independent) has been considered as an agent for the treatment of PPHN, with some advocating that it acts as both a pulmonary vasodilator and a systemic vasoconstrictor; it is not an inotrope. Although there may be developmental regulation in the pulmonary vascular response to vasopressin, experimental data suggest that it acts solely as a systemic vasoconstrictor, without pulmonary vascular effects.[81,82] Further, in a PPHN model, echocardiography demonstrated worsening of functional parameters for both ventricles during vasopressin infusion.[81] In a small single-center study of 11 infants with CDH and catecholamine-resistant hypotension being considered for ECMO support, supraphysiologic systemic blood pressures were achieved with vasopressin infusion, although 5 infants went on ECMO for hypoxemia and/or acidosis, including 3 with severe LV dysfunction.[83] Hyponatremia occurred in infants who received vasopressin infusion for>24 hours. Although there is concern that dopamine can vasoconstrict the pulmonary circulation, a comparative study in asphyxiated newborn piglets of high-dose versus combination moderate-dose dopamine plus low-dose epinephrine showed no benefit of the combination approach, and some high-volume CDH centers continue to use low-to-moderate dose dopamine for circulatory support.[84] Levosimendan, a calcium-sensitizing agent with positive inotropic, lusitropic, and vasodilating effects, was associated with improved oxygenation and stable blood pressure within 24 hours of initiation and improved severity of PH, RV, and LV function after 7 days in an observational cohort.[85] Negative inotropes should be avoided, such as beta-blockers.

Extracorporeal Membrane Oxygenation

ECMO is a rescue strategy for cardiac and/or respiratory failure. Overall mortality is higher in infants that transition to ECMO support, though a recent registry study showed decreased mortality with ECMO in high-risk CDH.[86] Both veno-arterial and veno-venous support can be used, without differences in short-term outcomes at the registry level, although individual institutional experiences may vary.[87]

PROGNOSIS—LATE PULMONARY HYPERTENSION AND CARDIORESPIRATORY PROFILE

The majority of infants with CDH will resolve their PH between 1 to 3 weeks of age, with favorable outcomes despite this delayed perinatal transition.[88] However, infants with evidence of persistent, protracted PH often require prolonged respiratory support and possibly chronic PH therapy.[89] These infants are at higher risk for mortality. Rates of late and chronic PH in this population vary significantly depending on the time of follow-up and PH definition. In a retrospective cohort of 140 infants with CDH, severity of PH at 2 weeks of age predicted mortality, prolonged invasive ventilation beyond 28 days of age, and need for prolonged respiratory support.[48] Rates of chronic PH in CDH survivors in preschool ages vary between 4.5% to 38%.[90] When comparing

cardiac catheterization results of CDH infants to infants undergoing PDA closure at 6 to 36 months of age, pulmonary arterial pressure and PVR were significantly higher in those with CDH, and PBF was significantly lower. Only half of these patients had PH signs on echocardiography.[91] This suggests an important role for cardiac catheterization in the long-term follow-up of CDH infants that are dependent on respiratory support.

The effect of fetal intervention on long-term prognosis is not yet described. A recent cohort of children surviving after FETO and a non-FETO comparison group with follow-up to 4 to 6 years demonstrated similar cardiopulmonary and gastrointestinal morbidity across groups.[92]

SUMMARY

PH remains a significant factor dictating management and outcomes in infants with CDH. Respiratory management critically interacts with pulmonary circulation and hemodynamics. Cardiopulmonary status and PH are dynamic, with various types and combinations of cardiac dysfunction contributing to the overall clinical condition, which may fluctuate within the same patient throughout postnatal stabilization. Altered right, left, or biventricular function, with both systolic and diastolic components, arterial disease, and left heart restriction may all contribute. Future studies should evaluate optimal strategies based on the combination of findings, prenatal and postnatal interventions, and the impact on short-term, long-term, and family-driven outcomes.

Best Practice Box

Recommendations for the assessment and management of PH in infants with CDH:

- PH in CDH has a dynamic and shifting clinical phenotype with variable contributions of vascular hypoplasia and arrested growth, abnormal tone and vasoreactivity, and vascular remodeling with possible contribution of pulmonary venous hypertension from left heart dysfunction.
- The authors emphasize the need for frequent reassessment of clinical parameters (perfusion and hemodynamics and changes with interventions), laboratory values (blood gases, lactate, renal function), and imaging (chest radiographs and echocardiography) to guide use of vasoactive and inotropic medications.
- To optimize outcomes of these challenging infants, one should balance gentle ventilation, avoiding hyperoxia with improving cardiopulmonary interactions and treatment tailored to the management of cardiac dysfunction.
- PGE1 infusion to maintain ductal patency can achieve RV afterload reduction, pulmonary vasodilatation, and augmentation of systemic blood flow.

DISCLOSURE

No conflicts of interest to declare.

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