

# Hemodynamic management of congenital diaphragmatic hernia: the role of targeted neonatal echocardiography

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## ABSTRACT

Congenital diaphragmatic hernia (CDH) is a major congenital anomaly, resulting from the herniation of abdominal contents into the thoracic cavity, thereby impeding the proper development of the lungs and pulmonary vasculature. CDH severity correlates with a spectrum of pulmonary hypoplasia, pulmonary hypertension (PHT), and cardiac dysfunction, constituting the pathophysiological triad of this complex condition. The accurate diagnosis and effective management of PHT and cardiac dysfunction is pivotal to optimizing patient outcomes. Targeted neonatal echocardiography is instrumental in delivering real-time data crucial for the bespoke, pathophysiology-targeted hemodynamic management of CDH-associated PHT.

## INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a major congenital malformation, characterized by the herniation of abdominal organs into the thoracic cavity, occurring in approximately 1 in 4000 to 5000 live births.<sup>1</sup> A recent report from the Congenital Diaphragmatic Hernia Study Group (CDHSG), analyzing over 5000 patients spanning 25 years, has demonstrated an improvement in both risk-adjusted mortality rates and observed-to-expected mortality rates for CDH, which are presently estimated to be between 26% and 31%.<sup>2</sup> Notably, a significant proportion of CDH mortality occurs between day 2 and 6 of life.<sup>3</sup>

The pathophysiological complexities associated with CDH principally arise from pulmonary hypoplasia and pulmonary hypertension (PHT), characterized by diminished alveolarization and an increased muscularization of the pulmonary arterioles.<sup>4</sup> The severity of PHT and the accompanying ventricular dysfunction serve as a pivotal determinant of clinical outcomes. The prompt identification of hemodynamic patterns and their potentially modifiable causes is paramount in guiding therapeutic interventions, including the potential application of extracorporeal

life support (ECLS) for infants with refractory cardiorespiratory failure.<sup>5</sup>

This review aims to provide an overview on the pathophysiological changes associated with CDH, emphasizing the imperative role of timely bedside hemodynamic evaluation with echocardiography in refining the management of these critically ill patients.

## DEVELOPMENTAL AND CIRCULATORY PATHOPHYSIOLOGY

CDH is a congenital anomaly with pathogenesis and etiology that remain incompletely understood. Rivas *et al.* proposed the “Retinoid Hypothesis,” stating that the underlying cause of abnormal diaphragm development in CDH was related to altered retinoid signaling.<sup>6</sup> Retinoid-related genes like STRA6, LRAT, CRBP1, CRBP2, and CRABP1 have been implicated in retinoic acid metabolism, which may have impact on normal diaphragm development.<sup>7</sup> Using the well-known nitrofen model, Keijzer *et al.* proposed the “Dual-hit Hypothesis,” suggesting an initial insult affecting both lungs before diaphragm development, followed by the second insult affecting the ipsilateral lung after defective diaphragm development and resulting extrinsic compression.<sup>8</sup>

The severity of CDH is notably linked with a variable degree of pulmonary hypoplasia, PHT, and cardiac dysfunction, constituting the triad of pathophysiological hallmark features of this complex disorder.<sup>8</sup>

## Pulmonary hypoplasia and PHT

In individuals with CDH, lung underdevelopment is evident, marked by thickened alveolar walls, increased interstitial tissue, diminished alveolar spaces, and consequently the surface area for gas exchange.<sup>9</sup> Early in gestation, there is a pronounced increase in the muscularity of arterioles and capillaries, along with a reduction in their diameter, leading to decreased angiogenesis, and



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diminished vasoreactivity.<sup>10 11</sup> An increase in the thickness of the adventitia in pulmonary arteries is also noted, accompanied by aberrant expression in the endothelin (vasoconstrictor) and prostacyclin (vasodilator) pathways, which are pivotal in early development.<sup>10 12</sup> Vascular growth is more adversely affected than alveolar growth.<sup>9 13</sup> The altered pulmonary vasoreactivity and pathological vascular remodeling, secondary to the reduced lung size and changes in pulmonary microarchitecture, are central to the pathophysiology of CDH-associated PHT.<sup>14</sup> Hemostasis of the pulmonary vascular bed is compromised, leading to altered endothelial signaling and resultant endothelial dysfunction, smooth muscle cell proliferation, impaired apoptosis, and vasoconstriction, clinically manifesting as PHT.<sup>15 16</sup>

Pulmonary hypoplasia, PHT, and cardiac dysfunction, along with concomitant cardiac and/or chromosomal anomalies, intersect in the high-risk neonate with CDH, creating a variety of unique phenotypes of CDH.<sup>17</sup> A significant portion of the mortality and morbidity in CDH is attributed to PHT, particularly when it persists beyond the neonatal period and is resistant to conventional treatments.<sup>13</sup>

### Redistribution of cardiac flow in utero

In normal fetal circulation, blood is directed from the ductus venosus toward the left atrium, through the patent foramen ovale (PFO), toward the left ventricle (LV), presumably “shaping” its cavity and size.<sup>18</sup> Human and animal studies demonstrate the necessity of fetal pulmonary artery blood flow for the normal development of pulmonary vascular, bronchial, and alveolar structures, yet the blood flow to the hypoplastic lung is reduced as much as half with severe lung hypoplasia.<sup>19 20</sup> Preferential streaming of the ductus venosus toward the right heart is found in left-sided CDH because of the rightward displacement of the heart that changes the orientation of the vena caval and ductus venosus flow toward the right atrium (rather than the PFO), leading to chronic underfilling of the LV. Since the growth of the LV is volume-dependent, decreased blood flow through the LV due to altered ductus venosus streaming and increased right-to-left ductal shunting leads to LV hypoplasia in severe cases of fetal CDH.<sup>17 18 21</sup> Altered fetal hemodynamics, leading to decreased left ventricular output (LVO), occurs in both right-sided and left-sided CDH, but the additional compressive effect on the left heart is seen only when the hernia is left-sided.<sup>22</sup>

Right-sided CDH is not associated with LV hypoplasia, but fetuses have reduced right ventricular dimensions and smaller pulmonary valve diameter and reduced right ventricle (RV) stroke volume and cardiac output.<sup>23 24</sup>

### Cardiac dysfunction

Following birth, the transition in circulation is dysregulated; the LV is compressed by intrathoracic abdominal organs, and the RV is dilated due to elevated pulmonary vascular resistance (PVR).<sup>25</sup> The vasoconstriction of the

pulmonary vascular bed, along with a delayed decrease in PVR postbirth, contributes to increased RV afterload. Moreover, the RV, which is more sensitive to arterial pressure, may undergo progressive dilation and dysfunction under sustained wall stress, leading to inadequate pulmonary blood flow.<sup>26</sup>

LV dysfunction can occur during the transitional period due to pre-existing developmental hypoplasia of the LV, decreased LV preload due to reduced pulmonary blood flow combined with acute increased LV afterload after the removal of the low-resistance placenta.<sup>27</sup> LV dysfunction may also occur secondary to RV dysfunction, via mechanisms of ventricular interdependence because of dysfunction of shared myocardial fibers and progressive bowing of the interventricular septum (IVS) into the LV secondary to RV dilatation.<sup>27 28</sup> Displacement of the IVS further restricts LV filling and preload, leading to decreased LVO.

The confluence of low ventricular output and PHT leads to hypoxemia, respiratory and metabolic acidosis, systemic hypotension, and shock.<sup>29 30</sup> Ductal shunting will either be bidirectional or right-to-left. However, in case of significant LV dysfunction, the pressure will increase in the left atrium leading to left-to-right inter-atrial shunt. An accurate understanding of an individual patient's real-time pathophysiological changes in circulation is essential for optimizing hemodynamic management.

### GENERAL APPROACH

Mortality is associated with early PHT, along with pulmonary hypoplasia and cardiac dysfunction. Many centers implement a CDH delivery bundle for initial monitoring and stabilization. This includes planned delivery at term in a tertiary center, intubation at birth in newborns with immediate respiratory distress, early gastric tube insertion to reduce stomach distension, use of T-piece to avoid a peak inspiratory pressure >25 cm H<sub>2</sub>O, supplemental oxygen titrated to achieve a preductal saturation of at least 85%, but not >95%, “gentle” intermittent mandatory ventilation as the initial ventilation mode, targeting an arterial pCO<sub>2</sub> between 45 and 60 mm Hg and a pH between 7.25 and 7.40. High-frequency jet ventilation can be considered both for conventional mechanical ventilation rescue and as a primary ventilation strategy in high-risk CDH. Crystalloid is infused judiciously in cases of poor perfusion, with selective use of inotropes, hydrocortisone, prostaglandins, and pulmonary vasodilators.<sup>31 32</sup> Avoiding excessive positive end-expiratory pressure may support cardiac function by reducing RV afterload, and, in turn, decrease LV compression and secondary dysfunction.<sup>33</sup> Early echocardiography is essential to rule out congenital heart disease, and to assess the degree of PHT and ventricular dysfunction, all of which are associated with increased risk of mortality or ECLS use.<sup>34</sup> The clinical presentation can evolve over time, and serial, timed functional echocardiographic monitoring allows targeted therapy and timely evaluation

of the response to therapies. The implementation of a CDH care bundle emphasizing frequent hemodynamic assessments by targeted neonatal echocardiography (TnECHO) has been shown to improve the short-term outcomes of CDH.<sup>35</sup>

## ROLE OF ECHOCARDIOGRAPHY

### Initial screening and diagnostic assessment

In a recent systematic review, up to 15% of live-born patients with CDH were found to have congenital heart disease, with the potential rate escalating to 28% if stillborn and terminated cases are included.<sup>25 36</sup> The most commonly associated cardiac lesions, ranked by frequency, are isolated ventricular septal defect, aortic arch obstruction, univentricular anatomy, and tetralogy of Fallot.<sup>37</sup> Echocardiography within the first 24–48 hours of life, or at least before surgery, is advised to look for cardiac anomalies not previously detected through fetal echocardiography.<sup>38</sup>

### Physiology-based treatment approach tailored to individual phenotype

The utility of TnECHO, conducted by trained neonatologists, has been shown to significantly improve the hemodynamic management of critically ill infants.<sup>35 39–41</sup> Serial echocardiographic assessments provide a longitudinal profile of cardiovascular performance, allowing hemodynamic management that is responsive to changes over time.<sup>42</sup>

Postnatal phenotypes observed in neonates with CDH range from normal ventricular size and function to impaired RV function with dilated RV, to a small, dysfunctional LV.<sup>43</sup> The clinical presentation of CDH may vary significantly during the early postnatal phase of hospitalization, through the perioperative period—distinguished by either improvement or worsening of PHT—and into the late postoperative phase, which in severe cases may be characterized by chronic PHT. The introduction, discontinuation, and precise modulation of therapeutic interventions must occur within the framework of a tailored hemodynamic management strategy, based on an on-demand, real-time assessment of hemodynamic status.<sup>38</sup>

TnECHO has been recommended to assess cardiac dimensions and ventricular function, estimate pulmonary arterial pressures (PAPs), and assess shunt physiology to guide cardiovascular support and provide prognostic information.<sup>35 44</sup> Early evaluation is particularly important in high-risk infants, such as those with unfavorable prenatal prognostic criteria including liver herniation or low observed to expected lung head ratio or total fetal lung volume or in cases of severe cardiorespiratory instability, as it may impact the optimal timing of surgery or the use of ECLS.<sup>38</sup>

### Role of TnECHO

The adoption of bedside TnECHO performed by neonatologists with specialized training marks a significant

evolution in neonatal intensive care, particularly in relation to CDH management.<sup>35</sup> The first echocardiogram performed by pediatric cardiology is crucial for assessing the severity of PHT and ventricular function, and for identifying congenital heart disease. After this initial assessment, a team of TnECHO-trained neonatologists provides serial reviews focusing on PHT, cardiac output, and ventricular dysfunction. These follow-up evaluations are conducted every 24–48 hours or in response to abrupt or unexplained hemodynamic or respiratory status changes, both prior to and following CDH surgery, continuing until PHT has resolved.<sup>35</sup> Assessments should align with the guidelines provided by leading echocardiography and pediatric cardiology associations such as the American Society of Echocardiography, the European Association of Echocardiography, and the Association for European Pediatric Cardiologists.<sup>45 46</sup> Using either a 6-MHz or 12-MHz high-frequency phased-array transducer probe, these protocols stipulate obtaining a comprehensive suite of images—including standard two-dimensional, M-mode, color Doppler, pulse-wave Doppler, and continuous-wave Doppler—for a thorough transthoracic echocardiographic analysis.

For LV systolic function, LV fractional shortening (FS)/ejection fraction (EF) and LVO are used as surrogate markers. The isovolumic relaxation time, the interval between aortic valve closure and mitral valve opening, and the E/A ratio are measured to assess diastolic dysfunction.<sup>40</sup> For RV systolic function, tricuspid annular plane systolic excursion (TAPSE) is measured, describing the apex-to-base shortening. RV-focused apical three-chamber view is acquired to measure RV areas at end-diastole and end-systole to calculate the fractional area change (FAC).<sup>35</sup> Right ventricular output (RVO) is calculated.

Function is classified as normal, RV dysfunction (indicated by, in order, global or regional cardiac hypokinesia, peak systolic velocity (S') wave <5.0 cm/s on tissue Doppler imaging (TDI), TAPSE <0.7 cm or RV FAC <25%), LV dysfunction (indicated by global or regional cardiac hypokinesia, FS <25%, EF <45%), or biventricular dysfunction (combination of LV and RV dysfunction). Ventricular disproportion, defined as an abnormal ratio of the RV diameter to the LV diameter ( $RV_D/LV_D$ ), can also be assessed for prognostic implications.<sup>43</sup>

To assess PHT, RV ejection time (RVET) and pulmonary artery acceleration time (PAAT) are measured to calculate the PAAT/RVET ratio. Interventricular septal curvature at the end-systole is assessed at the papillary muscle level. Pulmonary artery Doppler flow profile (near-isosceles triangle vs notching) characterizes screening and monitoring of PHT.<sup>47</sup> The presence of pulmonary insufficiency or tricuspid regurgitation is also used to estimate mean PAP and RV systolic pressure (RVSP), though both can be underestimated by RV dysfunction and may be unreliable in the presence of shunts.<sup>48</sup>

The presence or absence of patent ductus arteriosus (PDA) and PFO/atrial septal defect and their flow



**Table 1** Hemodynamic phenotypes in CDH: TnECHO characteristics and management

Phenotype	No PHT and normal cardiac function	PHT and normal/ solely RV Dysfunction	PHT with LV or biventricular dysfunction
TnECHO characteristics	PDA flow direction: left-to-right; PFO/ASD flow direction: left-to-right	Impaired RV systolic & diastolic function PDA flow direction: Bidirectional/ right-to-left; PFO/ ASD flow direction: Bidirectional/ right-to-left RV dilatation	PDA flow direction: Bidirectional/ right-to-left; PFO/ASD flow direction: left-to-right Decreased LV size (fetal hypoplasia and paradoxical IVS movement) Impaired LV (and/or RV) systolic & diastolic functions
Hemodynamic Treatment options/ precautions	Close monitoring of haemodynamic status, particularly during peri-operative period – blood pressure, lactate level, serial TnECHO	Use of dobutamine/ milrinone (if normotensive)/ low-dose epinephrine infusion <u>to augment RV systolic function</u> Use of iNO <u>to reduce RV afterload</u> Use of PGE <sub>1</sub> <u>to improve systemic flow in case of right-to-left shunting and closing ductus</u> Use of vasopressin/ norepinephrine as vasopressors <u>to improve SVR/ PVR ratio</u>	Use of dobutamine/ milrinone (if normotensive)/ low-dose epinephrine infusion <u>to augment systolic function</u> Use of PGE <sub>1</sub> <u>to improve systemic flow in case of right-to-left shunting and closing ductus</u> AVOID high-dose dobutamine due to its chronotropic effects which may reduce ventricular filling and exacerbate diastolic dysfunction PRUDENT use of vasoconstrictors to avoid excessive LV afterload AVOID sole use of pulmonary vasodilator like iNO which may cause pulmonary venous congestion

ASD, atrial septal defect; IVS, interventricular septum; LV, left ventricle; PDA, patent ductus arteriosus; PFO, patent foramen ovale; PGE, prostaglandins; PHT, pulmonary hypertension; PVR, pulmonary vascular resistance; RV, right ventricle; SVR, systemic vascular resistance; TnECHO, targeted neonatal echocardiography.

directionality are recorded. Pulsed TDI of the tricuspid annulus is obtained, measuring peak systolic (S'), early diastolic (E'), and late diastolic (A') velocities.

Severe PHT is associated with reduced LVO and RVO, a low PPAT/RVET index (<0.25), paradoxical IVS movement, low TAPSE value, notching in the pulmonary artery Doppler pattern, right-to-left ductal shunting and atrial shunting. Left-to-right atrial shunting in severe PHT can indicate LV dysfunction, contributing to systemic hypotension, metabolic acidosis, and reduced coronary flow.<sup>49 50</sup>

**Table 1** summarizes key findings of TnECHO of the various CDH phenotypes to guide treatment options.

## OVERVIEW OF THERAPEUTIC STRATEGIES FOR ACUTE MANAGEMENT OF PHT

With elevated PVR and increased RV afterload, RV failure can develop, resulting in right-to-left shunting through both PFO and PDA, aggravating hypoxemia. Decreased pulmonary flow reduces LV preload, compromising LV geometry and function, leading to low systemic cardiac output, impaired organ perfusion, and lactic acidosis. The recommended therapeutic strategy for this relatively common CDH pathophysiology is to address the primary problem of low pulmonary blood flow by reducing PVR, augmenting RV performance if required, normalizing

systemic blood flow, and optimizing RV coronary perfusion pressure.<sup>51</sup>

Common categories of medication use include pulmonary vasodilators, systemic vasoconstrictors, inotropic agents, and prostaglandins.

## Pulmonary vasodilators

### Inhaled nitric oxide (iNO)

Endothelial nitric oxide synthase (eNOS) is the primary isoform responsible for NO production in the perinatal lung.<sup>52</sup> The expression of eNOS within lung tissue increases throughout gestation, a regulatory mechanism crucial in sustaining basal vascular tone and ensuring a smooth transition characterized by a drop in PVR after birth.<sup>53</sup> As a selective pulmonary vasodilator, while sparing systemic circulatory effects, iNO has been used in neonates with hypoxemic respiratory failure (HRF) associated with PHT.<sup>54</sup> It functions by diminishing PVR, culminating in enhanced pulmonary blood flow, a reduction in the RV afterload, and an attenuation of right-to-left cardiac shunts via the PDA and PFO.<sup>51</sup>

A trial of iNO is frequently used in patients with CDH exhibiting persistent HRF, despite optimal ventilatory strategies and echocardiographic evidence of supra-systemic PHT.<sup>42</sup> A review of prospectively collected patient data within the CDH Study Group registry,

encompassing 3367 patients across 70 centers, indicated that 61% of infants received iNO therapy for a median duration of 8 days, including 36% of patients without PHT who also received iNO therapy.<sup>55</sup> However, the evidence supporting the broad application of iNO in infants with CDH remains limited, as highlighted by a Cochrane Review.<sup>56</sup> In the Neonatal Inhaled Nitric Oxide Study Group trial, which included 53 term and near-term infants with CDH and HRF unresponsive to conventional therapy, immediate short-term improvements in oxygenation were observed in some treated infants; however, iNO therapy did not significantly reduce the necessity for ECLS or mortality.<sup>57</sup> Another multicenter cohort study examining the impact of early iNO usage within the first 3 days of life showed that 48.6% of infants received early iNO treatment. Early use of iNO was associated with increased mortality (adjusted odds ratio (aOR)=2.06, 95% confidence interval (CI) 1.05 to 4.03,  $p=0.03$ ) and increased ECLS usage (aOR=3.44, 95% CI 2.11 to 5.60,  $p<0.001$ ), after adjusting for confounders such as lower birth weight, larger defect size, more severe PHT, and abnormal ventricular size and function.<sup>58</sup> Propensity score analysis has revealed that infants with CDH undergoing ECLS treatment have a significantly increased likelihood of renal complications (OR=1.52; 95% CI 1.14 to 2.01).<sup>59</sup>

It is important to note that use of iNO in the presence of LV dysfunction may intensify the strain on left heart structures (LV dysfunction, left atrial enlargement, small left-sided structures), potentially causing harm by compromising the RV-dependent systemic circulation. It is therefore important to confirm reasonable LV function before initiating iNO therapy.

### Sildenafil

Sildenafil, a potent and highly selective inhibitor of phosphodiesterase type 5, functions by reducing the degradation of cyclic guanyl monophosphate, leading to nitric oxide-mediated vasodilation.<sup>60 61</sup> Patel *et al.* conducted a retrospective case review involving nine infants administered intravenous sildenafil at doses ranging from 100  $\mu\text{g}/\text{kg}/\text{h}$  to 290  $\mu\text{g}/\text{kg}/\text{hour}$  following CDH repair but prior to the commencement of enteral feeding. This study observed a significant reduction in both Oxygenation Index (OI) and fractional-inspired oxygen ( $\text{FiO}_2$ ) after 72–96 hours of treatment.<sup>62</sup> Similarly, Noori *et al.* reviewed seven patients treated with oral sildenafil for PHT refractory to iNO, noting an increase in right cardiac output, and a trend toward increased left cardiac output within 1.5–4 hours of sildenafil initiation, which was sustained over a nearly 2-week study period.<sup>63</sup> A recent systematic review and network meta-analysis has identified a median concentration of 10–20 parts per million iNO in conjunction with orally administered sildenafil at a dosage of 1–3  $\text{mg}/\text{kg}/\text{dose}$  every 6–8 hours as the most effective treatment regimen for PHT.<sup>64</sup> The Congenital Diaphragmatic hernia Nitric Oxide versus Sildenafil (CoDiNOS) trial, an international randomized

controlled trial comparing intravenous sildenafil against iNO for treating PHT in neonates with CDH, is currently in progress. The primary outcome of this trial is the absence of PHT on day 14 without the need for pulmonary vasodilator therapy and/or survival beyond the first 28 days of life.<sup>65</sup>

Several animal studies have explored the role of antenatal sildenafil in pulmonary lung hypoplasia models, akin to those observed in CDH, in rats and rabbits.<sup>66 67</sup> However, these studies have yet to progress to clinical trial phases to ascertain their impact on PHT management postdelivery.

### Other pulmonary vasodilators

Prostacyclin ( $\text{PGI}_2$ ) is a relatively understudied pulmonary vasodilator in CDH-associated PHT. A recent study from the CDHSG which used propensity score matching to estimate the effect of early (within the first week of life)  $\text{PGI}_2$  administration on ECLS avoidance and duration found that patients with CDH who received  $\text{PGI}_2$  were less likely to receive ECLS (aOR=0.39; 95% CI 0.22 to 0.68), and if required, mean ECLS duration was shorter ( $8.6\pm 3.7$  days vs  $12.6\pm 6.6$  days;  $p<0.001$ ) in  $\text{PGI}_2$ -exposed patients.<sup>67</sup> Treprostinil, a synthetic analog of prostacyclin ( $\text{PGI}_2$ ), is employed in the management of PHT in adults.<sup>68</sup> A pivotal study aiming to elucidate the impact of continuous treprostinil administration in neonates presenting with CDH-related severe PHT was conducted, which included 17 patients who underwent treprostinil therapy for a median period of 54.5 days. The administration of treprostinil was correlated with a notable improvement in the severity of PHT, per echocardiographic evaluations, accompanied by a diminution in brain natriuretic peptide (BNP) levels.<sup>69</sup>

The efficacy of other pulmonary vasodilators, including surfactant, other prostacyclin analogs, or endothelin receptor antagonists (e.g., Bosentan), in addressing refractory or recurrent PHT among infants with CDH has not been adequately evaluated in clinical research settings. This indicates a significant gap in the literature and underscores the necessity for comprehensive studies to assess their therapeutic potential and safety profiles.

### Vasopressors

The utilization of vasopressors plays a critical role in managing high PVR, a defining characteristic of persistent PHT. Significant pulmonary vasoconstriction contributes ventilation–perfusion (V/Q) mismatch and diminished LVO. In instances where infants develop severe hypotension, including a diastolic component, vasopressors can be used to enhance coronary perfusion pressure and/or right ventricular preload. The treatment philosophy in general is to alter the systemic arterial pressure (SVR):pulmonary arterial pressure (PVR) ratio to augment net pulmonary blood flow to improve hypoxemia. Commonly used non-selective vasopressors such as dopamine and epinephrine may increase SVR, but not necessarily improve PVR due to their potential

vasoconstrictive effects on a labile pulmonary vascular bed.<sup>30 70</sup>

In the systemic circulation, vasopressin acts via V1 receptors in the vascular smooth muscle to cause potent vasoconstriction, leading to the improvement of SVR/PVR ratio and hypoxemia. It also acts on endothelial cells in the pulmonary vascular bed to potentiate NO release leading to vasodilation. In a retrospective chart review of 13 patients with CDH treated with vasopressin for refractory hypotension, vasopressin therapy increased mean arterial pressure, increased SVR:PVR ratio, and was associated with a decrease in heart rate and FiO<sub>2</sub>. Improvement in LV function and OI after vasopressin initiation was associated with a decreased need for ECLS.<sup>71</sup> Capolupo *et al.* reported a cohort of 27 patients with isolated CDH and found that early initiation of vasopressin improved OI and near-infrared spectroscopy after 12 and 24 hours of infusion.<sup>72</sup>

Norepinephrine has been employed to improve the SVR/PVR ratio and oxygenation in infants with severe PHT.<sup>73</sup> Research conducted by Tourneux *et al.*, encompassing a group of 18 neonates with severe PHT, demonstrated an increase in systemic pressure and LVO, alongside a 20% rise in mean left pulmonary artery blood flow velocity.<sup>73</sup> The wide application of norepinephrine in patients with CDH with severe PHT remains comparatively underexplored.

Hydrocortisone is widely used for the hemodynamic stabilization of neonates with CDH, serving as an adjunctive therapy to elicit useful increases in both SVR and cardiac output.<sup>19</sup> Adrenal insufficiency frequently complicates the clinical course of infants with HRF and can be associated with increased severity of illness.<sup>74</sup> Adrenal insufficiency has been shown to be prevalent among patients with CDH; one study demonstrated that two-thirds had low cortisol levels (a cortisol level <10 µg/dL when drawn during the period of stress and before steroid supplementation).<sup>75</sup> In a retrospective study of 58 infants with CDH admitted to the Children's Hospital at Denver, 67% of the study infants had a random stressed cortisol level <15 µg/dL, the commonly used threshold for relative adrenal insufficiency treatment in the neonatal literature.<sup>76</sup>

### Inotropic agents

Milrinone, by inhibiting phosphodiesterase III, manifests both inotropic and lusitropic effects on cardiac muscle, while concurrently acting as a pulmonary vasodilator. Its efficacy in enhancing oxygenation has been documented in neonates with PHT, including those demonstrating only partial responsiveness to iNO.<sup>77</sup> Patel *et al.* observed in a cohort of six infants with CDH and severe PHT, that milrinone infusion led to a significant increase in early diastolic myocardial velocities in the RV, as well as significantly reduced oxygen index, 72 hours after therapeutic initiation.<sup>78</sup> However, such benefits were not demonstrated in OI-matched untreated neonates presenting with mild-to-moderate CDH.<sup>49</sup> Currently, milrinone is

used in 17% of CDH cases within the Neonatal Research Network. Ongoing research (NCT02951130) aims to assess whether milrinone infusion can enhance oxygenation in neonates with CDH ≥36 weeks postmenstrual age.<sup>79</sup> A critical consideration for milrinone application pertains to its vasodilatory impact on systemic circulation, necessitating the potential use of vasopressin or norepinephrine to maintain systemic blood pressure.

Dobutamine, characterized as a positive inotrope, exerts minimal influence on PVR and is known to enhance cardiac function and pulmonary blood flow. Conversely, epinephrine, a potent inotrope, escalates SVR and PVR at higher dosages, potentially aggravating RV dysfunction without favorably altering the SVR:PVR ratio.

### Prostaglandins

By its direct effect on pulmonary artery smooth muscle, Prostaglandin E1 (PGE<sub>1</sub>) increases intracellular cyclic adenosine monophosphate leading to vasodilation and decreased PVR, reducing RV afterload and potentially improving coronary perfusion to the RV.<sup>80 81</sup> A restrictive ductus arteriosus may result in RV failure and low systemic blood flow in infants with RV-dependent systemic circulation, and PGE<sub>1</sub> can improve cardiorespiratory failure through reopening of the ductus.<sup>82</sup> Maintaining ductal patency with right-left ductal shunting reduces RV afterload by allowing runoff into the lower resistance systemic circulation, thus preserving systemic blood flow, particularly in cases of severe LV dysfunction. In a series of 75 infants treated with PGE<sub>1</sub>, improvements were noted in B-type natriuretic peptide levels and echocardiographic indices of PHT, without inducing post-ductal hypoxemia or systemic hypoperfusion.<sup>83</sup> No prospective studies have been conducted to date comparing the use of PGE<sub>1</sub> alone or in combination with other therapies targeting PHT in neonates with CDH.<sup>84</sup>

### PROGNOSTIC VALUE OF ECHOCARDIOGRAPHY IN CDH

In addition to identifying CDH phenotypes as a strategy in goal-directed hemodynamic therapy, early postnatal echocardiographic findings also enable some prognostication of outcome. A retrospective cohort study of 778 "low-risk" patients from the CDHSG registry who had a first postnatal echocardiogram performed within 24 hours from birth, demonstrated LV dysfunction, RV dysfunction, and severe PHT in 10.8%, 20.5%, and 57.5%, respectively. On all multivariable adjustment methods, LV dysfunction and severe PHT remained significant predictors of adverse outcome (death, ECLS utilization, oxygen requirement on day 30 of life, or hospitalization of at least 8 weeks). Persistence of PHT (defined as ≥2/3 systemic blood pressure) at 14 days by echocardiography predicted mortality and adverse respiratory outcomes.<sup>85</sup> In a single-center retrospective study, early (<48-hour age) Doppler echocardiography of 58 neonates with CDH was analyzed: RV TAPSE, PAAT/PET, TAPSE/PAAT, and TAPSE/RVSP ratios were



all significantly lower in the death/ECLS group.<sup>50</sup> On regression analyses, LV Myocardial Performance Index (MPI) and Cardiac Output Index were independently associated with mortality in infants with CDH.

Using data from the CDHSG registry, ventricular function was assessed by echocardiography within the first 48 hours of life. The adjusted risk of death for cases with LV dysfunction only was 1.96 (95% CI 1.29 to 2.98;  $p=0.020$ ) and for cases with combined RV and LV dysfunction was 2.27 (95% CI 1.77 to 2.92;  $p=0.011$ ).<sup>86</sup> Elevated proBNP was associated with high-risk defects (CDHSG stage C/D), ventricular dysfunction, and mortality.<sup>87</sup> In a systematic review to determine the prognostic value of various echocardiographic markers, pulmonary artery size, presence of ventricular dysfunction, and severe PHT were all found to be useful in prognosticating survival and the decision to offer ECLS treatment.<sup>5</sup>

Of studies utilizing TDI techniques, averaged RV early diastolic myocardial velocity on days 1 and 2 of  $<4.6$  cm/s predicted duration of respiratory support  $>21$  days, with 100% sensitivity and life 88% specificity.<sup>88</sup>

### MANAGEMENT OF PERSISTENT/CHRONIC PHT

As survival rates for individuals with CDH have improved, a chronic phenotype of PHT has become increasingly recognized. Distinct from the acute variant observed early in life, this chronic form of PHT presents a considerable clinical challenge in terms of management and treatment.<sup>89–90</sup> Estimating the accurate prevalence and duration of PHT postdischarge is challenging. Echocardiographic studies have shown that 2%–11% of patients continue to exhibit signs of PHT at the time of discharge, with a gradual resolution typically observed within the first 12 months.<sup>85–91</sup> However, a study using strain analysis and TDI has found that the survivors continue to have decreased RV function for years after CDH repair.<sup>92</sup> About 30%–50% of CDH survivors subsequently experience long-term pulmonary complications result of overarching pulmonary hypoplasia.<sup>93</sup> Within a cohort of long-term CDH survivors, lung perfusion and pulmonary function were reduced in 20% and 45%, respectively, without any significant cardiac or developmental sequelae.<sup>94</sup> Invasive hemodynamic study of early childhood CDH survivors showed elevated baseline pulmonary artery pressures and PVR in the face of low-normal pulmonary blood flow.<sup>95</sup>

The management of late or chronic PHT, and the weaning of anti-PHT treatment regimens postdischarge, currently lacks consensus, with various pharmacological protocols recommended to decrease right ventricular pressures and potentially improve RV function over time.<sup>96–97</sup> In a single institution study, Behrsin *et al.* reported that 17% of infants with CDH were discharged on a range of doses of sildenafil (2.91–5.78 mg/kg/day) and a weaning rate of 0.1 mg/kg/week (range 0.01–0.5 mg/kg/week).<sup>90</sup> This highlights the need for standardized assessment and treatment of PHT after

discharge to optimize the benefits and minimize the adverse effects of treatment.<sup>90</sup>

### CONCLUSION

The accurate diagnosis and successful management of PHT and cardiac dysfunction are crucial for enhancing the clinical outcomes in infants with CDH. Recognition of CDH-specific hemodynamic patterns or “phenotypes” by standardized echocardiographic assessment enables individualized targeting of therapies to encourage pulmonary and systemic vascular stabilization. There is an existing knowledge and practice gap for what constitutes best treatment for CDH-associated PHT (both acute and chronic) that must be addressed by future comparative effectiveness research. Implementing a protocolized CDH care bundle, with a focus on timely hemodynamic evaluation using TnECHO, is essential for improving the treatment and outcomes of infants with CDH.

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