Pulmonary hypertension complicates the course of many newborns with congenital diaphragmatic hernia. In the most severe cases, the fetal condition of markedly elevated pulmonary vascular resistance persists after birth and is associated with hypoxic respiratory failure and severe disturbances in cardiac performance. Late pulmonary hypertension (weeks to months after birth) is increasingly recognized in this population, and chronic pulmonary vascular abnormalities (months to years after birth) are now being discovered. In this review, we will discuss the pathophysiology of acute, late, and chronic pulmonary hypertension in patients with congenital diaphragmatic hernia. We will also review the role of currently available pulmonary vasoactive drugs in the management of pulmonary hypertension in this population.

Congenital diaphragmatic hernia (CDH) is a complex syndrome that causes severe hypoxic respiratory failure and is associated with a high mortality rate. In the most severely affected subset of newborns, CDH is characterized by pulmonary hypoplasia, pulmonary hypertension (PH) with structural and functional pulmonary vascular abnormalities, and disturbances in cardiac performance.

In the normal newborn, pulmonary vascular resistance (PVR) falls dramatically at birth with the onset of respiration. However, in infants with CDH, PVR often remains at suprasystemic levels, causing extrapulmonary right-to-left shunting and severe hypoxemia. High PVR in the newborn with CDH is related to the small cross-sectional area of pulmonary vessels that causes a fixed component of high resistance, structural vascular remodeling, and vasoconstriction with altered pulmonary vasoreactivity. Although in utero lung compression has long been implicated as the primary mechanism responsible for many of these changes, recent evidence suggests that decreased pulmonary blood flow alone causes lung parenchymal hypoplasia. Thus, if lung compression in utero decreases pulmonary blood flow, the subsequent hypoperfusion could, in turn, further compromise pulmonary vascular airway and parenchymal development.

Inhaled Nitric Oxide and Other Pulmonary Vasodilators

Although there are a number of agents that are available for the treatment of PH, much of the available information on pharmacotherapy for PH in infants with CDH is derived from observational studies rather than controlled, clinical trials. Indeed, there is a paucity of safety/efficacy data for most therapies in newborns with this condition. Blending low doses of nitric oxide gas with oxygen in the inspiratory limb of mechanical ventilators is an effective method for reducing pulmonary vascular resistance and decreasing extrapulmonary right-to-left shunting at the ductus arteriosus and foramen ovale in many patients with persistent pulmonary hypertension of the newborn (PPHN). Indeed, randomized, controlled trials have shown that inhaled nitric oxide (iNO) reduces the need for rescue therapy with extracorporeal life support in many newborns with PPHN. Thus, iNO was considered a promising therapy for the treatment of acute PH in CDH. The first report of the use of iNO in newborns with CDH suggested that early, acute improvement in oxygen-
tion was possible when adequate lung inflation was first achieved.\textsuperscript{8} However, the largest randomized, controlled trial of early iNO treatment in patients with CDH found no difference in the combined endpoint of death/ECMO utilization between iNO-treated and control infants.\textsuperscript{9} Moreover, in this trial, ECMO utilization was higher in the iNO treated group (Table 1). The failure of iNO to cause sustained improvement in newborns with CDH further demonstrates the complex nature of this syndrome.

In addition to pulmonary parenchymal and vascular hypoplasia, it is possible that the newborn with CDH may suffer from functional pulmonary vascular abnormalities of the NO-cGMP pathway that compromise the normal fall in PVR in the transitional circulation after birth. However, laboratory studies designed to characterize the NO-cGMP pathway in experimental CDH have yielded conflicting results. The predominant models for studying NO-cGMP function are the rat Nitrofen-induced CDH model and the surgically induced ovine CDH preparation. Studies in the rat model have demonstrated both decreased endothelial nitric oxide synthase (eNOS) expression\textsuperscript{10} and eNOS activity.\textsuperscript{11} However, in the lamb model of CDH, no reduction in NOS content or activity has been demonstrated.\textsuperscript{12,13}

In some patients with CDH, left ventricular mass is also diminished,\textsuperscript{14,15} which may contribute to PH and decreased left ventricular (LV) output. In clinical practice, we have found that decreased LV performance in patients with severe CDH syndrome is common and is perhaps the most important determinant of iNO responsiveness or lack thereof (ie, increased ECMO utilization). This markedly diminished LV performance causes a right-ventricular-dependent systemic circulation. That is, severe LV dysfunction may lead to dependence on the right ventricle for adequate systemic perfusion. In this setting, we have utilized both PGE\textsubscript{1} to maintain ductal patency to enhance the right-ventricular contribution to systemic blood flow, and pharmacologic LV afterload reduction (eg, milrinone).

It is also important to recognize that pulmonary immaturity and susceptibility to lung injury during mechanical ventilation can further complicate the care of patients who have CDH. Thus, in this setting, therapies that target only a single pathophysiologic component of the syndrome often will be ineffective (Fig. 1).

The success of iNO as a selective pulmonary dilator has prompted investigation into the efficacy of other agents modified for inhalational applications. Laboratory and small clinical pilot studies have been published using inhaled drugs such as PGI\textsubscript{2},\textsuperscript{16} PGE\textsubscript{1},\textsuperscript{17} ethyl nitrite,\textsuperscript{18} sodium nitroprusside,\textsuperscript{19} and sodium nitrite\textsuperscript{10} as potential therapies for PH. Pilot studies of some of these agents have yielded intriguing results, but none have been tested in controlled, clinical trials. More importantly, little is known about the inhalational toxicology of these drugs, and the LV dysfunction that characterizes the most severe cases of acute CDH may limit the efficacy of pulmonary vasodilator drugs in acute CDH, as seems to be the case with iNO.

Although iNO may be an effective therapy in some patients with CDH and PH, patients with CDH are poor responders as a group. Available evidence suggests that iNO therapy in patients with CDH should not be routinely used; rather, its use should be limited to patients with suprasystemic PVR after establishing optimal lung inflation and demonstrating adequate LV performance (ie, without ductal-dependent systemic blood flow). Moreover, there is a potential role for tNO therapy in the treatment of late PH in patients with CDH.

### Late Pulmonary Hypertension in the Newborn with CDH

Pulmonary hypertension not only complicates the early course of newborns with CDH, but many of them also have clinically evident protracted or late PH that can lead to prolonged mechanical ventilation, a second course of ECMO, or death.\textsuperscript{21-25} Indeed, mortality in CDH is most likely associated with the presence of other major malformations or genetic abnormalities, LV dysfunction, and prolonged PH, as opposed to pulmonary parenchymal hypoplasia per se.

Late pulmonary hypertension (LPH) in newborns with CDH is clinically evident when PVR becomes suprasystemic with right-to-left venoarterial admixture of blood across the foramen ovale and/or the ductus arteriosus causing hypoxemia. However, suprasystemic levels of PVR may be masked during treatment with ECMO or iNO, and sysystemic levels of PVR can only be determined by direct pulmonary artery measurements or echocardiography. Moreover, some newborns with CDH may have persistent pulmonary vascular abnormalities despite marked improvements in respiratory function, necessitating pulmonary vasodilator therapy to re-

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**Figure 1** Cardiopulmonary interactions that complicate the management of newborns with congenital diaphragmatic hernia.
duce PVR even when mechanical ventilation is no longer required. Thus, targeting LPH may be an effective approach to reducing mortality in a subset of newborns with CDH.

To determine the frequency of LPH and the potential role of noninvasive delivery of iNO, we recently reviewed our experience with CDH over a 6-year period, using a modified approach to the management of PH. This approach included treatment with low-dose iNO delivered by nasal cannula after extubation in newborns with CDH complicated by severe, protracted pulmonary hypertension. We examined a subset of patients with CDH who, despite marked improvement in gas exchange and resolution of their need for mechanical ventilation, still had clinically significant PH. Attempts to withdraw iNO (2-5 ppm) were performed during echocardiography to determine changes in pulmonary artery pressure on discontinuation of iNO. In patients who had hypoxemia, requiring increases in FiO₂ above 60%, and/or marked elevation of pulmonary artery pressure (PAP) to systemic or suprasystemic levels (as assessed by using the peak velocity of the tricuspid regurgitant jet or direction of shunting), iNO was immediately restarted. If on iNO withdrawal, PAP remained <2/3 of systemic arterial blood pressure, then iNO was not restarted.

Some patients with CDH had marked elevation of PAP on the discontinuation of iNO, despite meeting gas exchange criteria for extubation (FiO₂ < 0.40 and ventilator rate <15; Fig. 2). Infants who appeared to benefit from the selective pulmonary vasodilator effects of iNO, but no longer required mechanical ventilation for gas exchange (10/47, 21%) were extubated to hood oxygen in which iNO was blended, then transitioned to an oxygen/NO blended gas delivered by nasal cannula. Due to entrainment of room air during nasal breathing with a nasal cannula in place, the nasopharyngeal concentration of iNO was diluted approximately 50% (Fig. 3). Bedside ambient concentrations of NO and NO₂ were routinely monitored and did not change from baseline values during treatment with iNO by hood or nasal cannula. Of note is the fact that the severity of underlying PH was disproportionate to the respiratory status of these infants at the time of elective extubation (26 ± 3 days, mean ± SD), having a mean FiO₂ 0.34 ± 0.02 and a mean oxygenation index of 4 ± 1. Indeed, the median duration of nasal cannula iNO treatment for prolonged pulmonary hypertension was 17 days (range 5-60 days).

Thus, these observations suggest that, in some patients with CDH, sustained elevations of PVR may persist despite improvement in parenchymal lung disease such that mechanical ventilation is not needed for maintaining adequate gas exchange. In this setting, selective pulmonary vasodilation with iNO without mechanical ventilation may provide sustained improvement in oxygenation (by lowering pulmonary vascular resistance and decreasing extrapulmonary right-to-left shunting), without the potential adverse affects of tidal volume ventilation in the hypoplastic lung.

Pulmonary recovery in patients with CDH is typically measured by improvements in oxygenation based on arterial blood gas measurements. Although sustained PH is a common problem in patients with CDH, systemic hypoxemia only occurs when pulmonary vascular resistance becomes suprasystemic leading to extrapulmonary right-to-left shunting. Elevation of PVR alone (without extrapulmonary right-to-left shunting) does not cause severe hypoxemia in this setting. Indeed, in our patients who had near-systemic levels

![Figure 2](image2.png) Ratio of pulmonary artery pressure (PAP) to systemic arterial pressure (SAP) in newborns with CDH during treatment with iNO (N = 10) and during brief trial off of iNO.

![Figure 3](image3.png) Proximal and nasopharyngeal nitric oxide concentrations in newborns treated with iNO delivered by nasal cannula.

![Figure 4](image4.png) Phosphodiesterase inhibition with dipyridamole augments the response to iNO in a newborn with CDH.
of PH despite iNO therapy, inspired oxygen requirements were routinely below an FiO₂ of 0.35.

The use of iNO to treat pulmonary hypertension after ECMO treatment of CDH is a promising adjuvant therapy. Moreover, the observation that sustained pulmonary vasodilation can be achieved using nasal cannula delivery of iNO, suggests the potential for noninvasive chronic management of the most severely affected newborns with CDH and PH.

Recent studies suggest that endogenous vasodilator substances may not only modulate pulmonary vascular tone but also pulmonary vascular medial proliferation. Considering the important role of vascular remodeling in CDH, therapies which may favorably affect the structural basis of PH could have potential advantages beyond pulmonary vasodilation alone. There is limited experience in CDH with other pharmacologic pulmonary vasodilators. Prostacyclin is an established therapy for children and adults with primary PH; however, its use requires central venous access and dose-escalation may be associated with adverse systemic effects. Similar, bosentan is an endothelin antagonist that may prove useful as an adjuvant therapy in some patients with PH; however, its use may be associated with hepatic toxicity in infants and there are no published reports of bosentan use in infants with CDH.

One potentially promising approach is the use of phosphodiesterase inhibitors to reduce the degradation of cGMP produced by endogenous production of NO or exogenous NO delivery. It is possible that the use of phosphodiesterase inhibitors (eg, dipyridamole, sildenafil) may serve to augment the pulmonary vasodilator effects of iNO or cause sufficient vasorelaxation alone to allow the discontinuation of iNO in selected patients (Fig. 4). However, it is important to recognize that nonselective pulmonary vasodilators may increase intrapulmonary shunting and worsen oxygenation, despite lowering PAP.

### Chronic Pulmonary Vascular Abnormalities in CDH

In survivors with CDH, common late complications include gastroesophageal reflux, chronic lung disease with persistent ventilation/perfusion abnormalities, and PH. As described above, in the newborn period CDH is character-
ized by pulmonary hypoplasia and severe PH with structural and functional pulmonary vascular abnormalities. Moreover, a subset of newborns with CDH has prolonged PH that can be successfully treated with noninvasive iNO therapy, with resolution before hospital discharge. However, little is known of the long-term structural pulmonary vascular abnormalities that can complicate the course of patients with CDH surviving the neonatal period.

In this section, we describe the pulmonary vascular abnormalities demonstrated during cardiac catheterization of seven patients with CDH who survived the newborn period but had prolonged PH. Patients were referred to the Pulmonary Hypertension Clinic at the Children’s Hospital for evaluation of prolonged or recurrent PH diagnosed by echocardiography. These patients (median age: 4.0 years, range: 3 months to 12 years) underwent cardiac catheterization for evaluation of their PH. All of them had a history of severe hypoxemic respiratory failure and PH in the newborn period. Therapies in use at the time of cardiac catheterization included supplemental oxygen (N = 7), iNO (N = 2), prostacyclin (N = 2), and bosentan (N = 1). Demographic data and the major findings at cardiac catheterization are shown in Table 2. These included left pulmonary artery hypoplasia or stenosis in three patients and pulmonary vein stenosis or delayed venous return in six patients. One patient with right-sided CDH recovered and was discharged home. However, he suffered sudden death at 5 months of age. A postmortem examination revealed marked pulmonary vascular changes consistent with severe pulmonary hypertension (Fig. 5). Two patients who had a right-sided diaphragmatic defect had striking left-sided pulmonary venous abnormalities.

After median follow up of 12 months (range: 6-36 months) from the date of the cardiac catheterization, five patients (71%) are alive and discharged from hospital. The two patients with the most severe PH (Patients #1 and #3) died from complications of this entity at age 8 months and 19 months, respectively.

Significant but subclinical PH can persist beyond the newborn period into late childhood in patients with CDH, and may contribute to long-term morbidity and mortality. We found that cardiac catheterization yielded clinically important findings concerning both pulmonary arterial and venous abnormalities that were not apparent by echocardiography alone. Moreover, we found that three of the seven patients studied had significant pulmonary vascular abnormalities in the lung contralateral to the initial diaphragmatic defect. These findings suggest that the traditional view about the role of in utero cardiopulmonary compression on the pathophysiology of CDH may be too simplistic. It is possible that the injury associated with management of hypoxemic respiratory failure in newborns with CDH causes previously unrecognized long-term effects in susceptible individuals, or that the pulmonary circulation in patients with severe CDH is fundamentally altered in utero, leading to abnormal responses to injury that last far beyond the newborn period.

**Summary**

We describe the acute, late, and chronic pulmonary vascular perturbations that characterize CDH. The early, acute course of CDH is characterized by severe PH, pulmonary parenchymal abnormalities, and LV dysfunction. Pharmacologic pulmonary vasodilation using iNO may play an important role in a subset of newborns after adequate LV adaptation. However, the routine use of iNO should be discouraged without proper interrogation of right ventricular-dependent systemic circulatory requirements.

Pulmonary hypertension complicates the course of some newborns with CDH long after spontaneous respiratory sufficiency is achieved. Therapies that target pulmonary vasorelaxation after the discontinuation of mechanical ventilation may facilitate cardiopulmonary recovery and improved survival in this subset of high risk CDH infants.

Finally, we found that late pulmonary vascular abnormalities occur in a small subset of newborns with CDH, often initially presenting with signs of chronic lung disease alone. Understanding the impact of newer therapies on the long-term cardiopulmonary morbidity and mortality of CDH will require continued vigilance and collaboration among the subspecialists who evaluate this population.

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