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Pulmonary development considerations in the surgical management of congenital diaphragmatic hernia

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ABSTRACT

Congenital diaphragmatic hernia remains a clinical challenge for both neonatologists and pediatric surgeons. Advancements in mechanical ventilation strategies and neonatal intensive care have improved survival and transformed treatment of congenital diaphragmatic hernia from emergent surgery to early stabilization of the newborn followed by delayed repair of the diaphragmatic defect. Surgical technique has evolved and minimally invasive surgical approaches to close the diaphragmatic defect in these babies will likely improve with increasing experience. Finally, as more patients are diagnosed prenatally, attempts have been made to close the diaphragmatic defect prenatally. Unfortunately, this approach did not change the outcome of affected babies. Recently, progress has been made with prenatal tracheal plugging to improve prenatal lung development. In the near future experimental studies will start to explore new ways of treating affected babies prior to birth. This article reviews the evolution of the current treatment strategies in congenital diaphragmatic hernia and its future directions.

1. Introduction

Congenital diaphragmatic hernia (CDH) is a developmental defect of the diaphragm that allows herniation of abdominal viscera into the chest cavity. It occurs with an incidence of 1 in 2000 to 3000 live births [1]. Although the diaphragmatic defect can be repaired postnatally, substantial morbidity and mortality result from associated pulmonary hypoplasia and persistent pulmonary hypertension. Current therapy emphasizes early stabilization using gentle ventilation followed by delayed surgery. This approach has improved the survival of infants born with CDH to greater than 80% in modern series [2]. Despite major strides in neonatal intensive care and surgical management of CDH, many children born with this condition experience considerable long-term morbidity from pulmonary, gastrointestinal and neurodevelopmental impairment. These complications are more common among infants who require invasive therapies such as extracorporeal membrane oxygenation (ECMO).

2. Delayed surgery

Until 1980s, CDH was considered a surgical emergency. This was based on the assumption that herniating abdominal viscera were the underlying pathologic feature of the disease, causing respiratory and hemodynamic compromise through compression of lungs and mediastinum [3]. This thinking was challenged by clinical reports of worsening respiratory compliance and pulmonary hypertension following surgical repair [4]. Multiple factors can contribute to postoperative deterioration. These include pulmonary vasospasm secondary to stress, increased intra-abdominal pressure associated with reduction of herniating organs and abnormal respiratory mechanics. Justification for delayed surgery has come from single-institution retrospective reviews demonstrating increased survival compared to historical controls [5]. Two prospective randomized trials comparing immediate versus delayed surgery did not observe a significant difference in survival. However, both trials were limited by their small sample size [6,7]. Despite a lack of conclusive prospective data, early stabilization followed by delayed surgery has been widely adopted based on the cumulative experience of high volume tertiary canters. In 1998 a review of the CDH registry revealed that the overwhelming majority of patients were undergoing elective repair [8].

In addition, experimental studies in animal models, such as the nitrofen rat model have provided new insights into the pathogenesis of pulmonary hypoplasia and CDH. For instance, pulmonary hypoplasia was identified to rather be the result of a defect inherent to the lungs and not only the result of herniated abdominal organs compressing on the lungs. As an example, our group postulated the dual-hit hypothesis in 2000. This hypothesis explains pulmonary hypoplasia by two developmental insults: the first affecting both the ipsilateral and contralateral lung prior to occurrence of the diaphragmatic defect as a result of so far unidentified genetic and environmental factors. The second insult affects only the ipsilateral lung after herniation of abdominal organs into the chest through the diaphragmatic defect due to interference with fetal breathing movements of the ipsilateral lung [9].

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3. Gentle ventilation

Patients born with CDH require immediate intubation to avoid the use of bag-masking. Traditionally these infants were routinely treated with paralysis and hyperventilation. This strategy intended to decrease the pulmonary vascular resistance by inducing respiratory alkalosis. However, hyperventilation is associated with significant barotrauma including pneumothorax. Preoperative air leaks are considered a strong predictor of mortality with 87.5% of such patients dying in one series. Wung et al. described gentle ventilation with permissive hypercapnia for the first time in the management of infants with severe respiratory failure [10]. In this manner, airway pressures are minimized while tolerating a certain degree of respiratory acidosis. Similar to delayed surgery, historical controls have been used to compare permissive hypercapnia with hyperventilation. Kays et al. performed a retrospective review of CDH cases at the University of Florida from three eras: hyperventilation, the introduction of ECMO and the use of permissive hypercapnia. The survival rate improved over time from 15% to 44% and 78% respectively. In addition, the rate of pneumothorax decreased dramatically from 83% to 43% and 1.9% respectively. Despite the limitations of using historical controls, these data demonstrate the value of a combined strategy of gentle ventilation and delayed surgery.

4. High frequency ventilation

High frequency ventilation achieves oxygenation through an open lung strategy. The ventilator keeps the lungs open by delivering a continuous airway pressure. Ventilation is then achieved through small tidal volumes delivered at high frequency. High frequency oscillatory ventilation (HFOV) is by far the most common type of high frequency ventilation in use. Animal models have shown that HFOV is associated with improved oxygenation as well as reduced lung injury compared to conventional ventilation.

HFOV is an attractive option in the management of patients with CDH, given the concerns regarding iatrogenic lung injury. Multiple single-institution retrospective reviews have reported good results with HFOV as the initial mode of ventilation for patients with CDH. Like many other aspects of treatment for CDH, a randomized controlled trial of HFOV versus conventional ventilation is lacking. However, the CDH Euro consortium is currently conducting a randomized controlled clinical trial comparing HFOV versus conventional mechanical ventilation as an initial ventilation mode for newborns with CDH. The trial is expected to be complete in 2012. Today, HFOV is more frequently used as a rescue therapy when conventional ventilation fails to achieve adequate oxygenation. The goal of this strategy is to minimize the number of infants who are placed on ECMO.

5. Inhaled nitric oxide

Persistent pulmonary hypertension in CDH results from abnormal development of the pulmonary vasculature. The total size of the pulmonary vascular bed is decreased. There is also marked hypertrophy of vessel walls resulting in a decreased luminal diameter. Nitric oxide is an endogenous regulator of vascular muscle tone. It is produced by an endothelial enzyme, nitric oxide synthase. Nitric oxide diffuses from the endothelial cells into the adjacent vascular smooth muscle and leads to vasodilation through production of cyclic guanosine monophosphate (cGMP). Inhaled nitric oxide (iNO) is a selective dilator of pulmonary vessels. It is inactivated in the circulation through production of nitrosylhemoglobin, which is metabolized to methemoglobin, and therefore has little effect on the systemic blood pressure.

A randomized controlled trial of iNO among infants with CDH did not find any significant improvement in oxygenation or survival [11]. The majority of infants in this trial were treated with neuromuscular blockade and alkalosis. Inhaled nitric oxide could potentially be of benefit as an adjunct to permissive hypercapnia. The optimal dosage and duration of iNO in CDH is unknown. Toxicity, including methemoglobinemia, is minimized if the dose is kept below 20 ppm. Weaning iNO may cause rebound pulmonary hypertension in some infants. A strategy of weaning iNO at 20% increments is considered to be safe.

6. Phosphodiesterase inhibitors

Another treatment for persistent pulmonary hypertension of the newborn is sildenafil, which is a selective inhibitor of phosphodiesterase 5 (PDE5). PDE5 is an enzyme that catalyses degradation of cGMP in smooth muscle cells. Sildenafil can therefore mediate pulmonary vasodilation in a manner similar to nitric oxide. Due to its lower costs and ease of administration, oral sildenafil is an attractive alternative to iNO in developing countries. There is a suggestion that sildenafil may in fact be more effective than iNO due to the lack of a rebound effect. Apart from a few case series there is a paucity of data on the use of phosphodiesterase inhibitors in CDH. Sildenafil can potentially interact with other phosphodiesterases found in the retina and other parts of the central nervous system. A case of severe retinopathy of prematurity was observed in a premature infant following treatment with sildenafil for pulmonary hypertension. Clinicians should consider this complication when using phosphodiesterase inhibitors in preterm infants.

7. Surfactant

Initial studies into the pathophysiology of CDH using animal models suggested a deficiency in surfactant. Alveolar lavage samples from lambs with a surgically created diaphragmatic defect were found to contain decreased levels of phospholipids. Administration of exogenous surfactant to these lambs improved pulmonary compliance and gas exchange. However, analysis of surfactant composition and kinetics in infants born with CDH did not reveal a primary surfactant deficiency. This was followed by two retrospective reviews that found exogenous surfactant to be associated with poorer outcome in patients with CDH [12]. Based on these findings routine use of surfactant in patients with CDH is not recommended.

8. Extracorporeal membrane oxygenation

ECMO was initially used in patients with CDH for refractory hypoxemia following emergency surgical repair. With the advent of delayed surgery, ECMO is now more commonly used in preoperative stabilization. Based on a 2004 report from the Extracorporeal Life Support Organization (ELSO), CDH is the second most common indication for ECMO in the neonatal age group. This is believed to be secondary to availability of rescue therapies such as iNO and HFOV despite the decreasing annual rate of neonatal ECMO. The efficacy of ECMO in CDH is still debated. A recent meta-analysis of neonatal ECMO concluded that while ECMO improves survival among newborns with severe respiratory failure, the benefit of ECMO in CDH is unclear [13]. Opponents of ECMO argue that the principle cause of death in severe cases of CDH is irreversible pulmonary hypoplasia, which does not improve with ECMO. Furthermore, ECMO is associated with considerable costs and long-term morbidity. A randomized trial of ECMO versus conventional treatment of CDH is not available.

Approximately one-third of neonates with CDH are treated with ECMO, for whom the short-term survival is near 50%. Institutions that employ ECMO for treatment of CDH use the general principle that ECMO should be reserved for patients who fail medical management. Some centers consider traditional criteria for ECMO too restrictive and start treatment earlier to avoid barotrauma. The type of ECMO used in CDH is evolving with increasing use of venovenous access. This mode of ECMO avoids ligation of the carotid artery and is