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Congenital diaphragmatic hernia: searching for answers

John R. Gosche, M.D., Ph.D.*, Saleem Islam, M.D., Scott C. Boulanger, M.D., Ph.D.

Division of Pediatric Surgery, University of Mississippi Medical Center, 2500 N. State St., Jackson, MS 39216, USA

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Abstract

Background: Pulmonary hypoplasia and hypertension are the primary causes of morbidity and mortality in infants with congenital diaphragmatic hernia (CDH). At present, the origin of CDH and the causes of pulmonary hypoplasia and hypertension are unknown.
Data Sources: This article reviews the available published data regarding the origin of CDH and the pathogenesis of the associated pulmonary hypertension and hypoplasia. These investigations have employed human tissues as well as two types of CDH animal models.
Conclusions: Investigations performed to date have not yet provided definitive answers regarding the pathogenesis of CDH. However, they have yielded many new and exciting discoveries and several opportunities for intervention. Ongoing research should open new possibilities to improve the outcome for these unfortunate babies with CDH.

Keywords: Branching morphogenesis; Congenital diaphragmatic hernia; Pulmonary hypertension; Pulmonary hypoplasia

A congenital diaphragmatic hernia (CDH) at the foramen of Bochdalek occurs in approximately 1/2,500 live-born infants. The defect in diaphragm development allows intra-abdominal viscera to enter the fetal chest cavity during the early stages of lung development. The resultant encroachment by the abdominal viscera on the developing lung buds is believed to cause altered lung growth and maturation. As a result, infants with CDH are afflicted with smaller-than-normal lungs (pulmonary hypoplasia [PH]) and an associated decrease in the cross-sectional area of the pulmonary vasculature (pulmonary vascular hypoplasia). Furthermore, CDH is also associated with delayed lung maturation and alterations in pulmonary vascular structure. These features, which lead to hypoxemia and persistent pulmonary hypertension, are the primary causes of the high morbidity and mortality associated with CDH. This review will focus on investigations into the pathogenesis of abnormal diaphragm development, lung growth and maturation, and pulmonary vascular control that characterize CDH.

Animal Models

As with any disease of unknown etiology, the ability to investigate the pathogenesis and pathophysiology of the disease process is dependant on the availability of appropriate animal models. In CDH research there are 2 principal types of animal models: surgically created and teratogen-induced diaphragmatic defects. Unfortunately, as with most animal models, potential drawbacks and questions about validity exist for both types of models.

Surgically created models

In 1962, de Lorimier et al [1] reported an animal model of CDH in which a diaphragmatic defect was surgically created in fetal lambs at 98 to 138 days of gestation. At term, most of the intestine was found to have herniated into the thoracic cavity. These investigators reported that this model was associated with early postnatal mortality, PH, decreased air capacity, and delayed lung development. These investigators also observed that the earlier the defect was created during gestation, the more severe were the resultant abnormalities.

In 1980, Harrison et al [2] reported a variation on the surgically created model of CDH. In this model, a conical silicon rubber balloon was gradually inflated in the thoracic cavity of fetal lambs beginning at 100 days of gestation. These investigators observed that inflating a balloon in the thoracic cavity of fetal lambs affected lung growth and resulted in high perinatal mortality. They also observed that deflating the balloon in the immediate neonatal period (simulating postnatal correction) did not improve survival. How-

* Corresponding author. Tel.: +1-601-984-5050; fax: +1-601-815-3734.
E-mail address: jgosche@surgery.umsmed.edu

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ever, in a subsequent report [3] they demonstrated that deflating the intrathoracic balloon during late fetal development (simulating prenatal correction) allowed lung growth and improved survival. This report provided the impetus for their subsequent work, which culminated in prenatal repair of CDH in human infants.

Many investigators have employed surgically created CDH models in lambs and rabbits. These models mimic many of the anatomic and clinical defects observed in human infants with CDH. Because of the larger animal size, this model is particularly suited to performing both prenatal and postnatal surgical manipulations and physiologic measurements. Drawbacks of this model include the increased cost and requirement for >1 surgical procedure. An important question of validity with this model is that the diaphragmatic defect is created relatively late in gestation, unlike the human disease.

Teratogen-induced models

Nitrofen (2,4-dichlorophenyl-ρ-nitrophenyl ether) is an herbicide used for pre- and post-emergent control of broadleaved weeds. Toxicologic studies of this herbicide revealed that prenatal exposure of rodents resulted in multiple teratogenic effects including diaphragmatic defects [4]. Iritani [5] and later Tenbrinck et al [6] and Kluth et al [7] exploited this toxicologic effect to develop a rodent model of CDH.

In this model, a single dose of nitrofen is administered orally to pregnant rats between days 9 and 11 of gestation. The initial descriptions of this model showed that CDHs developed in 24% of the offspring. Subsequent reports show much higher rates (approximately 80%) of CDH development. In addition, either right-sided or left-sided CDHs can be induced by varying the timing of nitrofen exposure.

This animal model is associated with PH, pulmonary vascular abnormalities [8], and pulmonary immaturity [9]. The teratogenic model of CDH has been used extensively to study the embryologic origins of defects in diaphragm and lung development as well as for studies of prenatal treatments designed to improve lung growth and function.

The teratogenic model of CDH has the advantages of being less expensive and easy to use. In addition, the diaphragmatic defect in the teratogenic model is produced during the early stages of lung development and in this regard may more closely reflect the human disease. Drawbacks include the small size of the animals, which makes performing prenatal or postnatal surgical manipulations difficult. The largest challenge to the validity of this model relates to the teratogenic effect itself. To date, no known teratogens have been consistently associated with CDH in humans.

However, nitrofen has recently been shown to inhibit retinal dehydrogenase, the final step in retinoic acid production [10], and retinoic administration has been shown to decrease the incidence of CDH in nitrofen-exposed rats [11]. Other compounds that inhibit retinal dehydrogenase have also been shown to induce diaphragmatic defects in rodents [10]. Interestingly, plasma retinol and retinol-binding protein levels have been shown to be 50% less than control values in newborn infants with CDH [12]. Thus, there may be a common origin for CDH in humans and in rodents.

Diaphragm Development

The anomaly underlying CDH is failure of normal diaphragm development during embryogenesis. Understanding the pathophysiology and the development of new therapeutic strategies to treat CDH have been areas of active research for many years. However, efforts to improve survival have been frustratingly difficult. Part of this frustration results from a lack of understanding of the cause of the diaphragmatic defect. In this section, the 5 common hypotheses regarding the mechanisms that contribute to CDH will be discussed. These investigations have by necessity principally used the teratogenic model of CDH.

One theory is that malformation of the diaphragm is linked to abnormal development of the adjacent lung. This theory is based on 3 observations. Contralateral lung development is impaired and appears to occur independent of compression by intrathoracic viscera. Iritani [5] reported abnormalities in the developing lung before development of the diaphragm. Finally, studies have shown that nitrofen can directly affect lung development [13–15].

Arguments against this theory include the following. Herniation of the abdominal viscera into the chest causes mediastinal shift, thus the contralateral lung is also compressed during development. Closer scrutiny of the Iritani study [5] shows that higher doses of nitrofen were used during a longer period of time, so it is possible that the effects on the lung were caused by higher doses of nitrofen. In fact, Kluth et al [13], using more conventional doses of nitrofen, found that the lung appeared normal before intrathoracic invasion by the abdominal viscera. In addition, Allen and Greer [16] found no quantitative difference in lung size and cell content until after development of a diaphragmatic defect. Finally, lung agenesis in humans and animals frequently is not associated with a CDH [17,18].

Another theory is that malformation of the diaphragm is the result of abnormal muscle innervation by the phrenic nerve. This theory is based on the following observations. The phrenic nerve innervating the herniated diaphragm is often smaller than the contralateral nerve, and it has fewer axons, and the dorsal horn on the affected site contains fewer phrenic motor neurons [16]. Thus, it has been hypothesized that abnormalities of the phrenic nerve cause abnormal diaphragm development.

An alternative explanation for these findings is that the size of the phrenic nerve reflects less muscle to innervate. It has been shown that motorneurons undergo a natural period of programmed cell death during embryogenesis [19]. The