Evaluation of Neonatal Lung Volume Growth by Pulmonary Magnetic Resonance Imaging in Patients with Congenital Diaphragmatic Hernia

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Objective To evaluate postnatal lung volume in infants with congenital diaphragmatic hernia (CDH) and determine if a compensatory increase in lung volume occurs during the postnatal period.

Study design Using a novel pulmonary magnetic resonance imaging method for imaging neonatal lungs, the postnatal lung volumes in infants with CDH were determined and compared with prenatal lung volumes obtained via late gestation magnetic resonance imaging.

Results Infants with left-sided CDH (2 mild, 9 moderate, and 1 severe) were evaluated. The total lung volume increased in all infants, with the contralateral lung increasing faster than the ipsilateral lung (mean ± SD: 4.9 ± 3.0 mL/week vs 3.4 ± 2.1 mL/week, $P = .005$). In contrast to prenatal studies, the volume of lungs of infants with more severe CDH grew faster than the lungs of infants with more mild CDH (Spearman's ρ=-0.086, $P = .01$). Although the contralateral lung volume grew faster in both mild and moderate groups, the majority of total lung volume growth in moderate CDH came from increased volume of the ipsilateral lung (42% of total lung volume increase in the moderate group vs 32% of total lung volume increase in the mild group, $P = .09$). Analysis of multiple clinical variables suggests that increased weight gain was associated with increased compensatory ipsilateral lung volume growth ($\rho = 0.57$, $P = .05$).

Conclusions These results suggest a potential for postnatal catch-up growth in infants with pulmonary hypoplasia and suggest that weight gain may increase the volume growth of the more severely affected lung. *(J Pediatr 2017;188:96-102).*

Multiple developmental and obstetric conditions inhibit fetal lung growth causing potentially life-threatening pulmonary hypoplasia in the infant, including congenital diaphragmatic hernia (CDH), congenital pulmonary airway malformations, mediastinal tumor, omphalocele, congenital dysplastic renal disease, renal agenesis, lower urinary tract obstruction, prolonged rupture of membranes causing oligo/anhydramnios, skeletal dysplasias, neuromuscular anomalies, and several chromosomal abnormalities.[1-3] Although the mechanism of fetal lung injury in each of these diseases is different, the prognosis of all of these conditions is highly dependent on the degree of pulmonary hypoplasia.[4-14]

CDH is one of the most common and well-studied causes of pulmonary hypoplasia and often serves as a paradigm by which pulmonary hypoplasia is evaluated in other diseases. CDH is a developmental condition affecting 1 in 3000 pregnancies in which the abdominal viscera herniates into the thoracic cavity and impedes lung growth in the second and third trimesters.[15] It carries significant morbidity and mortality because of pulmonary hypoplasia and pulmonary hypertension, and the degree of hypoplasia is one of the primary factors that predicts neonatal survival and morbidity.[4-14]

A commonly used marker to prenatally measure pulmonary hypoplasia is total lung volume (TLV) determined by magnetic resonance imaging (MRI).[10,16-20] TLV obtained at 32-34 weeks gestation correlates with neonatal outcomes in CDH such that extracorporeal membrane oxygenation use and mortality increase significantly with lower lung volumes.[21]

Although TLV correlates strongly with survival in CDH, the factors that decrease or increase fetal lung growth is uncertain. Coleman et al[6] used fetal MRI to examine lung volume and lung growth during early and late gestation, and found that survival correlated with the change in TLV during the third trimester. Phithakwatchara[22] reported that the degree of visceral herniation correlates inversely with lung growth, and lung growth is inhibited more on the ipsilateral side when compared with the contralateral side. Ruano et al[23] observed that fetal lung growth after 24 weeks

CDH	Congenital diaphragmatic hernia
LHR	Lung area to head circumference ratio
LLV	Left lung volume
MRI	Magnetic resonance imaging
NICU	Neonatal intensive care unit
O/E	Observed to expected
RLV	Right lung volume
TLV	Total lung volume

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was lower in more severe vs milder forms of CDH. In addition, autopsy studies have demonstrated that while both the ipsilateral and contralateral lungs in fetuses with CDH are abnormal, the ipsilateral side has a greater reduction in the number of terminal airways, arteries, and acinar units.[24,25] These studies suggest that the rate of fetal lung growth and the right-left asymmetry of fetal lung growth can be affected by both the severity of the CDH and the side of the CDH.

Although these studies have improved our understanding of prenatal lung growth in CDH, our understanding of postnatal CDH lung growth, including lung growth after surgical repair of the diaphragm, has been inhibited by the challenges of imaging infant lungs. Therefore, it is uncertain if the reduced lung growth observed in more severe CDH or on the ipsilateral side continues during the postnatal period. Because lung growth is inhibited by abdominal visceral herniation and this inhibition is removed following repair of the diaphragm, we hypothesize that there would be compensatory growth of the more severely compressed lung in patients with CDH. We have developed a novel method for infant pulmonary MRI in the neonatal intensive care unit (NICU), providing an opportunity to measure TLV in the postnatal population with CDH.[26,27] Therefore the objective of this study was to compare prenatal and postnatal lung volumes in infants with CDH and determine the factors that influenced lung volume in patients with pulmonary hypoplasia.

Methods

This study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board. The study population included all infants with CDH admitted to Cincinnati Children's Hospital Medical Center NICU from February 2014 to February 2016. Inclusion criteria included CDH diagnosis and infants born after 34 weeks' gestation. Gestational age was determined by last menstrual period and/or sonographic biometry in the first trimester. The infants received no prenatal interventions. Exclusion criteria included infants not considered viable at birth (ie, decision made not to provide life-saving therapies), infants that were not considered clinically stable enough for MRI, congenital heart disease (not including patent ductus arteriosus and hemodynamically insignificant ventricular or atrial septal defects), other congenital malformations affecting life expectancy or cardiopulmonary development, presence of an implanted device incompatible with MRI, and uncontrolled atrial or ventricular arrhythmia. Infants with a weight greater than 4.5 kg at the time of MRI were excluded due to inability to fit the infant within the 18 cm bore of the neonatal-sized MRI scanner at Cincinnati Children's Hospital Medical Center. There was concern that higher pressures associated with mechanical ventilation at the time of MRI might confound lung volume measurements. Therefore, infants that were still on mechanical ventilation at the time of MRI were excluded.

All infants that were prenatally diagnosed with CDH at the Cincinnati Fetal Center also received a fetal MRI. Fetal MRI was performed without maternal or fetal sedation in mid to late gestation (24-37 weeks gestational age) using a conventional 1.5-T scanner as previously described.[6,22] The fetal MRIs were reviewed and analyzed including TLV as part of the normal clinical reading by staff radiologists experienced in interpreting fetal MRIs.

All infants were managed by a team of CDH specialists at our institution following standard treatment protocols. After birth, the infants were intubated and stabilized with gentle ventilation and nitric oxide. The timing of repair of the diaphragm was determined by the clinical team.

The infants with CDH included in this study received a pulmonary postnatal MRI when the clinical team determined the infant was stable following repair of the diaphragm. The MRI was obtained using a small footprint 1.5-T orthopedic MRI scanner adapted for use within our NICU.[26,27] Standard 3-dimensional axial fast gradient echo images were acquired in all patients (repetition time/echo time ~7/1.9 ms; 10° flip angle; 18-20 cm field of view; 0.70-0.78 mm -in-plane resolution; 3 mm slice thickness; 26-32 partitions, 5-10 averages). No sedation or intravenous contrast was administered. Patients were fed, swaddled and equipped with ear protection before MRI. Respiratory support during MRI ranged from comfortably breathing on room air to nasal cannula oxygen to full ventilator support (although data from infants on mechanical ventilation were excluded as explained further in results). The postnatal MRIs were analyzed for research purposes by a blinded reviewer using Amira (FEI Visualization Sciences Group, Hillsboro, Oregon); lung volumes were determined via semi-automatic segmentation of the lungs (excluding major pulmonary vasculature) from the fast gradient echo images.

The following variables were collected from MRI analysis at prenatal and postnatal periods for analysis: TLV, right lung volume (RLV), and left lung volume (LLV). TLV was calculated as the summation of the RLV and LLV. The infants were assigned a CDH severity rating (mild, moderate, severe) based on their prenatal TLV measured by late gestation fetal MRI (mild disease: TLV >40 mL, moderate disease: TLV 20-40 mL, severe disease: TLV <20 mL).10 If the fetal MRI was acquired prior to 30 weeks gestational age, then the sonographically measured observed to expected (O/E) lung area to head circumference ratio (LHR) was used to determine CDH severity (mild disease: O/E >45, moderate disease: O/E 25-45, severe disease: O/E <25).[28] Severity was also determined by the CDH Study Group defect size classification system.[29,30]

The primary outcome measure was the rate of change in TLV. Secondary outcome measures were change in RLV, and change in LLV between the prenatal and postnatal MRIs. Lung growth rates were calculated by dividing the difference in postnatal and prenatal lung volumes by the number of intervening weeks (ΔTLV, ΔRLV, and ΔLLV, in mL/week). Clinical data retrospectively gathered included the following: gestational age at fetal MRI, corrected gestational age at postnatal MRI, estimated fetal weight on the same day as the fetal MRI (as determined by ultrasound without modification for the potentially lower abdominal circumference in CDH), birth weight, and weight at the time of postnatal MRI, days on the ventilator,