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Left Heart Structures in Human Neonates with Congenital Diaphragmatic Hernia and the Effect of Fetal Endoscopic Tracheal Occlusion

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Key Words
Congenital diaphragmatic hernia · Fetal echocardiography · FETO · Fetal tracheal occlusion · Fetal surgery

Abstract
Background: Small left heart structures are observed in fetuses with left-sided congenital diaphragmatic hernia (CDH). Fetoscopic tracheal occlusion (FETO) in mid-gestation promotes lung growth in fetuses with CDH, however cardiac effects of FETO are poorly described. We studied the effects of FETO on cardiac structure size at birth, hypothesizing that left heart structures would be larger in neonates who had undergone fetal intervention. ***Methods/Results:*** We performed retrospective measurements of atrioventricular and semilunar valve and pulmonary artery diameters, ventricular lengths, left ventricular end-diastolic volume indexed (LVEDVi) to body surface area. 35 patients were studied (9 FETO, 26 controls). All fetuses had liver herniation and a lung-to-head ratio <1 at fetal presentation. At birth the intervention group had larger LVEDVi (16.8 vs. 12.76 ml/m^2, $p < 0.05$), LV length Z-score (–2.05 vs. –4, $p < 0.01$), LV:RV length ratio (1.43 vs. 1.04, $p < 0.05$), LPA diameter Z-score (+1.71 vs. –1.04, $p < 0.05$), and better growth of aortic valve (–2.18 FETO, –3.3 controls, $p < 0.01$). There was a trend toward higher LV output in the FETO group. ***Conclusions:*** Left heart structures and LPA were larger postnatally in patients with CDH who underwent FETO than in those who did not. Hemodynamic alterations are introduced with tracheal occlusion that are associated with alterations in ventricular loading and may influence growth.

Introduction

Congenital diaphragmatic hernia (CDH) is a relatively common disorder, occurring in approximately 1 in 4,000 live births and accounting for approximately 8% of all major congenital abnormalities [1–3]. In over 60% of all cases, CDH is an isolated birth defect. Severe pulmonary hypoplasia and/or pulmonary hypertension are the cause of death in one third of these newborns [4, 5].

In human and experimental animal studies of fetuses and newborns with left-sided CDH, small left heart structures have been observed [6, 7]. The herniated abdominal organs compete for space with the developing lungs and may also directly compress the fetal heart [8]. Other cardiac structures may also become distorted due to abnormal orientation of the inferior vena cava and foramen ovale [6, 9, 10]. It has been speculated that reduced filling

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of the adjacent left ventricle (LV) leads to reduced flow through the mitral valve (MV), LV, and aortic valve (AoV), with redistribution to the right heart [6, 11, 12] resulting in the small left cardiac structures and that this may explain abnormal left heart size observed in CDH.

Several recent studies in animal models have focused on improving the survival of patients with CDH [13–15]. Currently, fetal endoscopic tracheal occlusion (FETO) with a balloon is a prenatal treatment showing promise and under active study in multiple countries [16–21]. During pregnancy, the fetal lungs secrete fluid into the airways, which drain to the amniotic cavity during fetal breathing movements [22]. In animal models and in human work, FETO prevents egress of pulmonary fluid leading to lung tissue stretch, thus triggering lung growth and inducing vascular changes [13–15, 23, 24]. Theoretically, inflation of this balloon also causes an increase in intrathoracic pressure while it also accelerates fetal lung growth, which may minimize the compression effect on the heart from the herniated abdominal structures [8].

Recently, several studies have investigated the role of pulmonary hypoplasia in CDH [17–19, 21]. However, the clinical implications of left heart hypoplasia and 'ventricular smallness' remain unknown [7, 8]. Therefore, measurement of cardiac dimensions may contribute to the complete understanding of the cardiopulmonary derangements seen in CDH. In this study, our objective was to document the size of cardiac structures in fetuses with isolated severe left-sided CDH prior to FETO, and to analyze the effects of FETO on the fetal and neonatal heart, before any postnatal surgical correction of the CDH. We hypothesized that increased lung size with FETO is associated with enhanced pulmonary blood flow, resulting an increased LV preload, which may ultimately lead to increasing size of left heart structures. While it has been previously shown that that left heart structures increase in size after birth in left CDH [7], we hypothesized that this increment would be higher in patients who underwent FETO compared to severe left CDH controls matched for severity.

Methods

This retrospective case-control study was performed at the Fetal Treatment Center and Fetal Cardiovascular Program at the University of California, San Francisco. Databases of the Fetal Treatment Center and Fetal Cardiovascular Program were searched for the period between June 2000 and June 2010 for fetuses diagnosed with left-sided CDH with normal karyotypes and without additional structural anomalies. We measured the heart structures before and after birth and compared those who underwent FETO with a matched group who were not treated with FETO.

The Fetal Treatment Center at the University of California San Francisco serves as a tertiary referral center that offers in utero therapy for selected cases with isolated severe CDH. During the study period, inclusion criteria for the intervention included confirmed left CDH with a portion of the liver herniated into the chest, lung-to-head ratio (LHR) determined by ultrasound [4, 25, 26] ≤1.0 measured between 24 and 26 weeks' gestation, normal karyotype, no other birth defects, singleton pregnancy, maternal age 18 years or older, fetus between 26 and 28 weeks' gestation, and meeting of psychosocial criteria as determined by social worker screening. Exclusion criteria include failure to meet all inclusion criteria, abnormal amniocentesis, other anomalies by ultrasound, maternal contraindication to abdominal surgery or general anesthesia, preterm labor, preeclampsia, uterine anomaly (e.g. large fibroid tumor), and family unable or refuses to stay near medical center for the duration of the tracheal occlusion period and for the duration of the pregnancy as medically necessary. For the fetal tracheal occlusion procedure, done under general endotracheal or spinal anesthesia, access to the fetus is gained as needed via percutaneous fetoscopy or maternal laparotomy and fetoscopy through the exposed uterus. The fetal bronchoscope is introduced into the airway and the detachable balloon deployed in the trachea under fetoscopic and ultrasound guidance. Approximately 6 weeks after deployment, the balloon is removed via repeat fetoscopy or EXIT (ex utero intrapartum treatment) procedure, as clinically indicated. Additional details of the procedure have been previously published by our group and others [8, 17, 18, 27].

Prenatal charts were reviewed for gestational age at the time of echo based on the last menstrual period or first-trimester ultrasound dating, pregnancy outcome, and associated cardiac anomalies. Obstetric ultrasounds were reviewed for liver position, side of herniated abdominal contents (hernia side), and LHR. LHR is a sonographically measured ratio of the contralateral lung size compared with the head circumference and it is an independent predictor of postnatal survival in fetuses with left CDH when measured at 24–34 weeks' gestation at our institution [4, 28]. Additional postnatal data collected included gestational age at the first evaluation and birth, additional structural and genetic anomalies, associated congenital heart disease, birth weight, gender, and postnatal survival. Subjects with significant structural congenital heart malformation on pre- or postnatal echocardiography were excluded. A patent foramen ovale, small atrial septal defect, and patent ductus arteriosus were not considered congenital heart defects.

Echocardiographic Data

Fetal echocardiograms were performed using ultrasonography systems (Acuson Sequoia C256 and C512; Siemens, Mountain View, Calif., USA) with a combination of curvilinear and phased-array probes operating at 6–8 MHz. All studies included a complete two-dimensional evaluation of cardiac structures and systolic ventricular function with complete pulsed-wave and color Doppler examinations including venous and umbilical cord investigations [29].

All fetal and neonatal echocardiograms were reviewed and the measurements were made off-line in a digital imaging system by a pediatric cardiologist (L.A.R.A.). We performed the measurements based on the two-dimensional images according to Schneider et al. [30].

– The MV and tricuspid valve (TV) diameters were measured in the 4-chamber view during the peak filling in early diastole at maximum excursion of the leaflets from inner edge to inner edge at hinge points of the leaflet attachments.

– The AoV and pulmonary valve (PV) diameters were measured in long axis views at the inner edge of the annular hinge points at maximal opening in systole.

– LV and RV major axis lengths (LV and RV lengths, respectively) were measured at end-diastole, defined as the frame at which the MV and TV closes, taking care not to foreshorten the ventricles, from the middle of the annulus level to the apical endocardium.

– LV short axis (LV minor) dimension and area were measured at end-diastole (maximal size) at the level of the papillary muscles.

– LV end-diastolic volume (LVEDV) was calculated using the 'bullet' method (formula V = 5/6 × short-axis basal area × LV length) [31] and indexed to body surface area.

– LV output was calculated from Doppler measurements using the equation: velocity time integral (VTI) × heart rate × semilunar valve area.

– The measurements of the main pulmonary artery (MPA) and left and right branch pulmonary artery (LPA and RPA, respectively) diameters were performed at the point of maximum expansion in para- or suprasternal short-axis views.

– The fetal *Z-scores* were normalized for gestational age [30, 32] and postnatal *Z-scores* for body surface area [33, 34].

As many patients had more than one echocardiogram study, we used the first most complete fetal and neonatal echocardiograms prior to CDH repair (and prior to cannulation for extracorporeal support, for those who required it) for our comparisons. All fetal measurements were repeated by a second observer (F.A.B.) for assessment of intra- and inter-observer variability via calculation of mean percent difference and intraclass correlation coefficient by one-way ANOVA.

Data Analysis

Statistical analysis was performed using the commercially available statistical software package (STATA). Fisher's exact test was used to compare unpaired nominal data between groups and the Student's t test to compare unpaired continuous data with a normal distribution. For non-normal distributed data, we used the Mann-Whitney test to compare unpaired data and Wilcoxon test to compare paired data. For any given parameter, statistical analysis was not performed if more than 50% of fetuses had missing data (inadequate or absent images available on previously stored digital studies); this applied to fetal measurements of MPA, LPA, and RPA.

The study was approved by the USCF Committee on Human Research (CHR approval No. H8215-18407-09A) with a waiver of consent.

Results

Clinical Findings

227 patients with fetal diagnosis of CDH were referred to the Fetal Treatment Center at the University of California San Francisco from 2000 to 2010. 216 of these fetuses had a comprehensive fetal echocardiogram. We excluded 2 fetuses with midline or bilateral CDH, 11 fetuses that did not have a recorded LHR, and 17 with right CDH, and 15 with significant congenital heart disease other than isolated left heart hypoplasia (diagnoses included aortic atresia, d-transposition of the great arteries, coarctation of the aorta, ventricular septal defect, pulmonary atresia with ventricular septal defect, tetralogy of Fallot, Ebstein anomaly, double outlet right ventricle, atrioventricular canal defect, and anomalous left coronary from the pulmonary artery). We excluded all fetuses with other anomalies or aneuploidy and those with LHR >1.0, and all pregnancy terminations as well as those who were not born at our center. The remaining group comprised the study population: 34 fetuses with left-sided CDH and LHR ≤1.0. Of these, 9 patients (26.5%) underwent FETO and the remaining 25 fetuses (73.5%) served as the controls. Eleven of the control group either declined FETO after having it offered or were randomized to postnatal therapy in the setting of a trial; the remainder were excluded from fetal therapy for a variety of reasons not related to the anomaly.

Table 1. Characteristics and outcomes in fetuses with left-sided CDH

Variable	Total (n = 34)	FETO (n = 9)	Controls (n = 25)	p
Mortality	18 (56)	6 (67)	12 (52)	NS
Male sex	26 (76)	7 (87)	18 (73)	
Gestation age at echo, weeks	23.6±3.2	23.2±2.7	23.7±3.5	NS
Lung:head ratio	0.87±0.11	0.85±0.14	0.87±0.11	NS
Gestation age at birth, weeks	36.7±2.5	35.1±3.1	37.2±2.1	0.03
Birth weight, g	2,942±597	2,540±853	3,081±417	0.1
BSA at echo, m^2	0.20±0.03	0.18±0.05	0.21±0.02	0.17

Data are given as n (%) and mean ± SD. Fisher's exact test used for categorical data and t test or rank sum for unpaired tests, as appropriate. NS = Not significant.

The study population was homogeneous, with no preprocedure differences between FETO and controls (table 1). Mean gestational age was 23.6 weeks; 76% of fetuses were male. Fetuses who underwent FETO were born at a lower gestational age (p = 0.03) with lower birth weight (table 1). There was no difference in neonatal survival (to 28 days) between groups in this small sample.

Echocardiographic Findings

There was no difference in any of the baseline pre-procedure fetal echocardiographic measurements between those who underwent FETO and the controls (table 2).

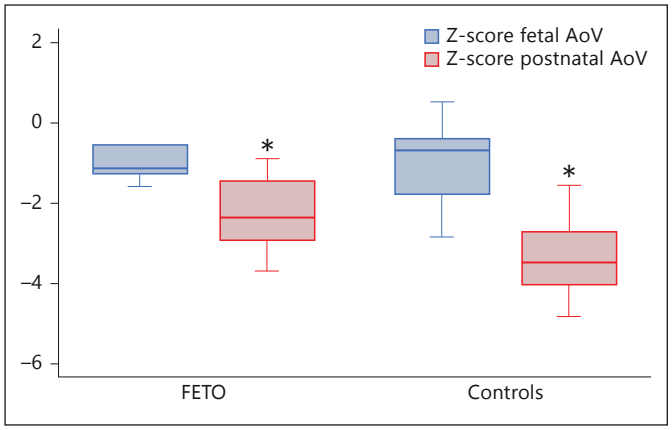

Fig. 1. Box-and-whisker plots of fetal and postnatal AoV diameter in FETO (n = 9) and control (n = 25) groups. Although baseline fetal measurements were not different between groups, postnatal measurements of AoV Z-score for the FETO group decreased to a lesser extent than in the controls (by pairwise comparison), suggesting that better growth of the valve occurred in the intervention group. Horizontal bars represent medians, boxes show upper and lower quartiles, whiskers show 1.5× interquartile range. * $p < 0.05$ for comparison of FETO vs. control.

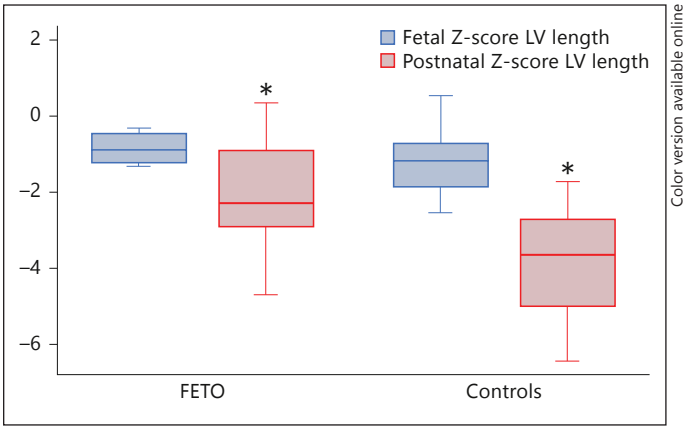

Fig. 2. Box-and-whisker plots demonstrating comparison of fetal and postnatal left ventricular length in FETO (n = 9) and control (n = 25) groups. Although baseline fetal measurements were not different between groups, postnatal measurements of left ventricular length Z-score for the FETO group decreased to a lesser extent than in the controls (by pairwise comparison), suggesting that better growth of the ventricle occurred in the intervention group. Horizontal bars represent medians, boxes show upper and lower quartiles, whiskers show 1.5× interquartile range. * $p < 0.005$ for comparison of FETO vs. control.

Table 2. Baseline fetal echocardiographic measurements

Measurements	FETO (n = 9)	Controls (n = 25)	p
MV Z-score	−2.96±1.01	−2.88±1.11	0.84
TV Z-score	−0.62±1.00	−0.19±0.91	0.25
AV Z-score*	−0.68±1.07	−1.04±0.96	0.68
PV Z-score	0.60±0.65	0.22±0.69	0.16
RV length	−0.69±0.74	−1.10±0.91	0.22
LV length Z-score*	−1.00±0.74	−1.20±0.89	0.39
MT:TV valve ratio	0.73±0.08	0.69±0.09	0.26
AV:PV ratio*	0.71±0.06	0.71±0.08	0.64
LV:RV ratio	1.06±0.16	1.09±0.13	0.46

Data are presented as mean ± SD. Student's t test was used to compare unpaired normally distributed data (*). Mann-Whitney test was used for all other comparisons.

Fetuses that underwent FETO experienced better subsequent/longitudinal growth of the AoV (fig. 1) and LV length (fig. 2) as evidenced by less of a difference in fetal (pre-procedure) versus postnatal measurement Z-scores in the FETO patients as well as postnatal measurements that were closer to the normal range in the FETO patients. Postnatal LPA diameter and LVED volume indexed to BSA after birth and before any surgical correction were also closer to normal and LV:RV ratio was larger in the FETO infants versus in the control infants at birth (table 3) (though these were not studied longitudinally due to inadequate data in the fetal groups). MV Z-scores were closer to normal in the FETO group, though this was not statistically significant. LV output indexed to body surface area was notably higher in the FETO infants postnatally (2,350 ± 1,149 $ml \cdot min^{-1} \cdot m^{-2}$) versus control infants (1,679.95 ± 718 $ml \cdot min^{-1} \cdot m^{-2}$) though this did not reach statistical significance, likely due to the small sample size and wide range of values obtained.

Inter-observer agreement (table 4) was good for length of both ventricles and AV and PV dimensions, good for LPA and fair for RPA, and fair for other measures (though intra-observer variability was generally good for all measurements).

Discussion

We hypothesized that small fetal left heart structures should increase to a greater extent in fetuses undergoing FETO if relative improvement in lung size results in increased LV preload and consequent increased pulmonary venous return. Indeed, in this study, we found a difference between the FETO and controls; the former group experienced enhanced growth of the AoVs, LV length,

Table 3. Postnatal echocardiographic measurements in intervention and control groups

Measurements	FETO (n = 9)	Controls (n = 25)	p
MV Z-score	–2.26 (1.06)	–2.80 (0.62)	0.07
TV Z-score	–0.19 (0.91)	–0.77 (0.95)	0.10
AoV Z-score	–2.34 (0.98)	–3.22 (1.10)	0.03
PV Z-score (n = 7)	0.733 (1.06)	0.19 (1.10)	NS
MPA Z-score	–0.17 (0.62)	0.69 (1.26)	0.07
LPA Z-score	–1.01 (1.33)	–2.31 (1.25)	0.02
RPA Z-score	–1.35 (1.05)	–1.79 (0.92)	NS
LV length Z-score	–2.05 (1.57)	–3.95 (1.41)	0.002
MV:TV ratio	0.69 (0.14)	0.70 (0.12)	NS
AoV:PV ratio	0.63 (0.14)	0.64 (0.14)	NS
LV:RV ratio*	1.42 (0.38)	1.04 (0.14)	0.001
LV output, ml · min^{-1} · m^{-2}	2,350 (1,149)	1,680 (718)	0.08
LVEDV indexed to BSA	16.8 (5.8)	12.8 (4)	0.039

Data are presented as mean ± SD. Paired t test was used to compare paired, normally distributed data (*). Wilcoxon test was used for all other comparisons. NS = Not significant.

Table 4. Inter-observer agreement for prenatal measurements of cardiac structures

Prenatal measurement	ICC (95% CI)	p	Mean difference, %	
			interobserver	intraobserver
MV	0.41 (0.12, 0.69)	0.008	16	9
TV	0.56 (0.32, 0.79)	0.0003	13	9
AV	0.74 (0.58, 0.90)	<0.0001	11	8
PV	0.85 (0.75, 0.95)	<0.0001	7	8
LV length	0.79 (0.67, 0.92)	<0.0001	12	12
RV length	0.92 (0.87, 0.97)	<0.0001	8	10
LVOT VTI	0.83 (0.70, 0.97)	<0.0001	15	5
RVOT VTI	0.46 (0.07, 0.86)	0.04	20	5
LPA	0.76 (0.56, 0.96)	0.0004	12	
RPA	0.48 (0.15, 0.82)	0.01	14	

ICC = Intraclass correlation coefficient, by one-way ANOVA; LVOT VTI = left ventricular outflow velocity time integral; RVOT VTI = right ventricular outflow velocity time integral.

LV:RV ratio, and LVED volume indexed to BSA versus controls. Our study documents changes in sizes of left heart structures in neonates who have undergone FETO in direct comparison with a cohort who had CDH of similar severity who did not undergo prenatal intervention. We demonstrate differences in left heart dimensions postnatally, prior to CDH repair, in the fetal intervention cohort that could potentially be important for postnatal hemodynamics and cardiopulmonary interaction.

There are relatively few studies examining cardiac structures in fetuses with CDH. Vogel et al. [7] evaluated the left-sided heart structures in both the fetal and neonatal period after surgical correction, and reported that mild or moderate left heart hypoplasia and reduced flow through the left heart is common in left-sided CDH, but left heart dimensions generally normalize after birth and surgical repair. Van Mieghem et al. [8] investigated left heart structures in fetal life prior to and following FETO and reversal of tracheal occlusion in the fetus. They demonstrated that the LV size in left-sided CDH is decreased and that FETO does not impair LV output or growth in a similar small number of patients. In the present study, we confirm that fetal left heart structures are small in a subset of fetuses with severe left CDH and no congenital heart

disease; the AoV and MV are smaller than the PV and TV in fetal and postnatal measurements. Further, we demonstrate that these left heart structures increase in size postnatally, prior to CDH repair.

In their study, Van Mieghem et al. [8] assumed that tracheal occlusion would increase the left heart structures and thus improve LV function. LV function did appear to improve with increased lung volumes, most likely because increased pulmonary blood flow is positively correlated with lung size [35]. In fetuses with severe CDH, there may be increased shunting through the ductus arteriosus and higher impedance to the LV outflow, due to their smaller lungs. Thus, larger lungs with greater pulmonary circulation may lead to improved LV preload [8, 36, 37]. This is analogous to the change in loading conditions in the postnatal circulation, with normalization of left heart structure measurements demonstrated post-CDH repair by Vogel et al. [7]. We suggest that with FETO, relatively increased fetal lung size is associated with enhanced fetal pulmonary blood flow, resulting an increased in utero LV preload, which may ultimately lead to larger left cardiac structures. However an alternate explanation is also possible: herniation of abdominal viscera including the liver may lead to impeded venous return and impede left heart filling [6, 10] in fetuses with severe left CDH. The effect of increasing lung volume during tracheal occlusion on both reduction of the herniated abdominal contents and possibly cardiac shift may improve venous flow patterns to the heart and left ventricular filling. Unfortunately the fetuses were not studied with echocardiography during tracheal occlusion in this retrospective cohort, therefore this possibility remains speculative. However, the improvement in left heart structures is seen in both FETO and control groups prior to CDH repair, when reduction of herniated contents occurs.

There are some limitations of our retrospective study. First, it was difficult to compare fetal PA sizes (MPA, LPA, and RPA) due to missing information for approximately half of those who underwent FETO. It is therefore possible that the two groups may have had differing fetal PA sizes, and the observed postnatal difference between the groups was not due to FETO. However, given the otherwise similar cardiac measurements and LHRs, we believe this is unlikely. We are also therefore unable to definitively state that PA growth was improved in those who underwent FETO due to a lack of longitudinal data. Second, there may be important intra-observer variability in fetal two-dimensional and Doppler measurements [38]. Our inter-observer variability was acceptable, though for a few measures variability was relatively high. This likely reflects the small sizes of the structures being measured and our reliance on retrospective analysis of captured images. Further, the normative datasets and methods of indexing for calculating fetal and neonatal Z-scores may differ, which can lead to relative inaccuracies or imprecisions. We used two-dimensional echocardiography to determine our measurements. However, three-dimensional echocardiography allows for more accurate evaluations, although it is more technically challenging. Third, we had a relatively small sample despite our study covering a 10-year period. However, this reflects the rarity of severe left-sided CDH and appropriate candidates for FETO. Finally, we performed our measurements before tracheal occlusion and compared these to neonatal measurements made before surgical correction. It has previously been shown in a more heterogeneous population of left CDH patients that the left heart normalizes after CDH repair [7]. It is possible that our comparisons may be modified if our measurements were made after birth and after CDH repair. Whether the observed difference in left ventricular dimensions in FETO patients was due to true structural growth, versus simply less compression and/or more pulmonary venous return, and consequently better left heart loading prior to repair, was not testable in this small cohort.

The potential benefits of fetal tracheal occlusion are currently under study in several European and North American centers of fetal medicine [39–43], and clearly must be weighed against the risks of prematurity and risk to the mother. Our preliminary results suggest, however, that future research should include an evaluation of the effect of FETO on cardiac and cardiopulmonary variables that might play a role in postnatal cardiac output and pulmonary hypertension in these patients.

In summary, a comparison of left heart measurements at birth shows that AoV growth, LV length, LV:RV ratio, and LVED volume indexed to BSA appear more favorable in neonatal patients who underwent fetal intervention with FETO than in those with a similar severity of left CDH who did not undergo fetal tracheal occlusion. Whether this will equate with improvements in postnatal outcomes will require further study.

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